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Development and biological evaluation of novel fluorinated ingredients for modern crop protection

Fallia Aribi

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Fallia ARIBI

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Development and Biological evaluation of novel fluorinated ingredients for modern crop protection

THÈSE dirigée par :

Dr LEROUX Frédéric R.

Directeur de recherche CNRS, Université de Strasbourg

RAPPORTEURS :

Dr TARAN Frédéric

Prof. PANNECOUCKE Xavier

Directeur de recherche, CEA de Saclay

Professeur, INSA de ROUEN

AUTRES MEMBRES DU JURY :

Dr BLANCHARD Nicolas

Dr PAZENOK Sergiy

Dr VORS Jean-Pierre

Dr JESCHKE Peter

Directeur de recherche CNRS, Université de Strasbourg

Bayer AG, Crop Science, Process Research, Monheim

Bayer S.A.S, Crop Science, Disease Control Chemistry, Lyon

Bayer AG, Crop Science, Pest Control Chemistry, Monheim

À Passidi, Mohamed RABAH,

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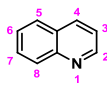
ABBREVIATIONS

4 Å MS: 4 Å Molecular Sieves	ee: Enantiomeric excess
AcOEt: Ethyl Acetate	<i>e.g.</i> : Example given
Acetone ^{d6} : Deuterated acetone	EtOH: Ethanol
AIBN: Azobisisobutyronitrile	Et ₂ O: Ether
Anh.: Anhydrous	Et ₃ N·3HF: Triethylamine trihydrofluoride
APTS·H ₂ O: <i>p</i> -Toluenesulfonic acid monohydrate	EWG: Electron-withdrawing group
B ₂ pin ₂ : Bis(pinacolato)diboron	FARs: Fluoroalkyl Amino Reagents
BF ₃ •Et ₂ O: Boron trifluoride diethyl etherate	GABA: Gamma Aminobutyric acid
Boc ₂ O: Di- <i>tert</i> -butyle dicarbonate	GCMS: Gas Chromatography Mass Spectrum
Bpin: Bis(pinacolato)diboron	Grd: Glycine like receptor of <i>Drosophila</i>
bpy: 2,2'-Bipyridine	HMDS: Hexamethyldisilazane
<i>n</i> -BuLi: <i>n</i> -Butyllithium	HOBt: Hydroxybenzotriazole
<i>t</i> -BuLi: <i>tert</i> -Butyllithium	HOMO: Highest Occupied Molecular Orbital
BuOH: Butanol	HRMS: High resolution mass spectroscopy
<i>t</i> -BuOH: <i>tert</i> -Butanol	IC ₅₀ : Inhibition concentration
<i>t</i> -BuOOH: <i>tert</i> -Butyl hydroperoxide	ICH ₂ B(O <i>i</i> Pr) ₂ : Diisopropyl iodomethylboronate
<i>t</i> -BuONO: <i>tert</i> -Butyl nitrite	<i>i</i> Pr: Isopropyl
<i>ca.</i> : circa	<i>i</i> PrMgCl: Isopropylmagnesium chloride
CACA: <i>cis</i> -4-aminocrotonic acid	<i>i</i> PrMgCl·LiCl: Isopropylmagnesium chloride lithium chloride complex (Turbo Grignard)
CDI: <i>N,N'</i> -Carbonyldiimidazole	<i>i</i> PrOBpin: Isopropoxy pinacolborane
CF ₃ TMS: Trifluoromethyltrimethylsilane	IR: Infra-Red
CNS: Central Nervous System	Ishikawa reagent: <i>N,N</i> -diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine
Co(OAc) ₂ : Cobalt (II) acetate	La(OTf) ₃ : Lanthanum(III) trifluoromethanesulfonate
CPA: Cyclopropylamide	Lcch3: Ligand-gated chloride channel homologue 3
Cu(OTf) ₂ : Copper (II) triflate	LDA: Lithium diisopropylamide
CV: Cyclic voltammetry	LiHMDS: Lithium bis(trimethylsilyl)amide
CyPA: Cyclopropylamine	LiTMP: Lithium tetramethylpiperidide
DAST: Diethylaminosulfur trifluoride	LUMO: Lowest Unoccupied Molecular Orbital
DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene	MeCN: Acetonitrile
DCE: Dichloroethane	MeI: Methyl iodide
DCM: Dichloromethane	MeLi: Methyllithium
DFMS: Zinc difluoromethanesulfinate	MeOH: Methanol
DIPEA: <i>N,N</i> -Diisopropylethylamine	MP: Melting Point
DMAC: <i>N,N</i> -Dimethylacetamide	Me ₃ SiCl: Trimethylsilyl chloride
DMAP: <i>N,N</i> -4-Dimethylaminopyridine	NaOtBu: Sodium <i>tert</i> -butoxide
DMF: <i>N,N</i> -Dimethylformamide	NEt ₃ : Triethylamine
DMSO: Dimethylsulfoxide	NFSI: <i>N</i> -Fluorobenzenesulfonimide
DNA: Deoxyribonucleic acid	
DPPA: diphenylphosphoryl azide	
EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide	
EDG: Electron-donating group	

NMR: Nuclear Magnetic Resonance
n.d.: Not determine
pI₅₀: Inhibition potential
PNS: Peripheral Nervous System
PPA: Polyphosphoric acid
r.t.: Room Temperature
Rdl: Resistance to dieldrin receptor
SDHI: Succinate dehydrogenase inhibitors
S_{NAr}: Substitution nucleophile aromatic
T: Temperature
t: time
T₃P: Propylphosphonic anhydride
TACA: *trans*-4-aminocrotonic acid
TBAT: Tetrabutylammonium
difluorotriphenylsilicate
TEMPO: 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TESCl: Triethylsilyl chloride
TFA: Trifluoroacetic acid
TFAE: Trifluoroacetaldehyde ethyl hemiacetal
TFEDMA: 1,1,2,2-Tetrafluoro-*N,N*-dimethylethan-1-amine
TMSCl: Trimethylsilyl chloride
THF: Tetrahydrofurane
Yarovenko reagent: 2-chloro-*N,N*-diethyl-1,1,2-trifluoroethan-1-amine

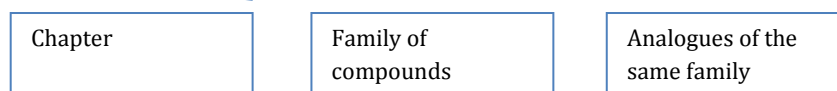
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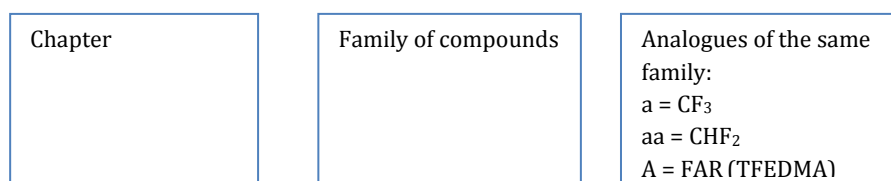


Designation of compounds:

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➔ Chapter III: **III.1.aA / III.1.aaA**



RESUME DE THESE

**Développement et évaluation biologique de nouveaux
ingrédients fluorés pour la protection des cultures**

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CHAPITRE I : INTRODUCTION

1 LE FLUOR UN SUBSTITUANT DE CHOIX

Le fluor fut isolé pour la première fois par Henri MOISSAN en 1886 sous la forme d'un gaz de fluor moléculaire (F₂) hautement réactif, toxique et corrosif. Cette découverte lui valut le Prix Nobel en 1906.

Le fluor est symbolisé par F, possède un numéro atomique Z = 9 et il est le premier élément du groupe des halogènes. L'isotope stable, le ¹⁹F, est le plus abondant sur terre tandis que le radio-isotope le plus stable est le ¹⁸F. Ce dernier est souvent utilisé en tomographie par émission de positons (TEP) pour l'imagerie médicale.

Le fluor est le 13^{ème} élément le plus abondant de la croûte terrestre, on le retrouve principalement sous forme minéral (fluorspar, fluoroapatite et cryolite). Cependant il est très peu présent dans les océans dû à la faible solubilité de ces derniers. Seulement douze métabolites contenant un atome de fluor ont été découverts, parmi lesquels huit correspondent à des chaînes d'acide gras dérivées de l'acide ω-fluoro oléique, métabolite présent dans la même plante. Le dernier métabolite contenant du fluor fut découvert en 1986, depuis lors, aucune nouvelle découverte ne fut reportée.

Nous pouvons donc nous demander ce qui lui confère un tel intérêt.

Parmi les halogènes, il est le plus petit des atomes avec un rayon de van der Waals (vdW) de 1.47Å et l'élément le plus électronégatif du tableau périodique (3.98 sur l'échelle de Pauling). La liaison C-F est la liaison de plus forte intensité (CH₃-F : 108.1 kcal/mol) parmi les liaisons carbone-halogènes et l'électronégativité de cet atome lui confère un fort caractère ionique. Le fluor est souvent utilisé pour remplacer les hydrogènes ou les groupements hydroxyles dû à leur taille comparable, ce qui peut engendrer un réel changement des propriétés biologiques des molécules.

Le fluor est considéré comme un élément électroattracteur par effet inductif, mais peut-être électro-donneur par résonance quand il est lié à un carbone sp². Les groupements fluorés sont quant à eux seulement électroattracteurs.

Les effets électroniques du fluor permettent de stabiliser un carbocation en α par effet mésomère donneur des doublets non-liant du fluor, appelé effet « push ». En revanche, un fluor positionné en β d'un carbocation aura tendance à le déstabiliser à cause de son effet inductif attracteur, appelé effet « pull » (Figure 1).



Résumé de thèse

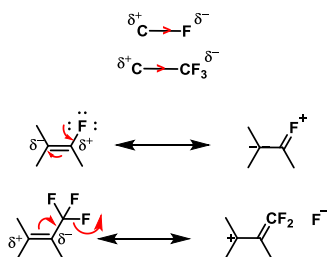


Figure 1: Effets électroniques des substituant fluorés

Un des aspects les plus importants lors de la conception de molécules bioactives dans l'industrie pharmaceutique consiste à rendre résistant le composé bioactif à pH physiologique afin que celui-ci puisse franchir les membranes cellulaires. Ce paramètre est aussi un point considéré dans l'industrie agrochimique. Cependant, d'autres paramètres peuvent intervenir tel que la résistance de la molécule à l'oxygène de l'air et de l'eau ainsi que leur dégradabilité.

L'introduction de fluor dans une molécule bioactive permet d'améliorer ses propriétés physico-chimiques et leurs caractéristiques pharmacologiques telles que : la stabilité métabolique, la biodisponibilité et les interactions existantes entre le ligand et la protéine.

Pour cela, différents paramètres peuvent être modulés lors de l'introduction d'un atome de fluor amenant à la formation d'une molécule « hit » tels que :

- La biodisponibilité (influencée par le pKa et la lipophilie).
- Le pKa des fonctions acide et basique voisines.
- La lipophilie (mesuré entre l'eau et l'octanol : logP).
- La capacité à former des liaisons hydrogènes (même faible) peut jouer un rôle dans les interactions entre un substrat et sa cible biologique.
- La stabilité métabolique : la liaison C-F confère une stabilité métabolique, oxydative et thermique aux molécules et empêche la désactivation du produit actif. Le ralentissement du métabolisme oxydatif est une méthode très utilisée pour bloquer des sites d'oxydation sur les molécules et est dû à la formation défavorable de la liaison C-OF (Figure 2).

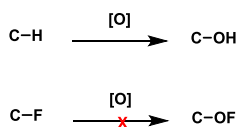


Figure 2: Processus de métabolisation oxydatif

Bien que les composés fluorés soient quasi inexistant à l'état naturel, les molécules contenant un atome de fluor sont de plus en plus présentes sur le marché et leur nombre ne cesse d'augmenter. Entre 1977 et 2014, la quantité de produits agrochimiques contenant du fluor est passée de 4% à 17.7%. Parmi les produits développés par l'industrie agrochimique présent sur le marché, 28% contiennent au moins un atome de fluor. Ils sont divisés en trois catégories d'ingrédients phytosanitaires : les herbicides (54%), les insecticides (27%) et les fongicides (19%) (Figure 3).

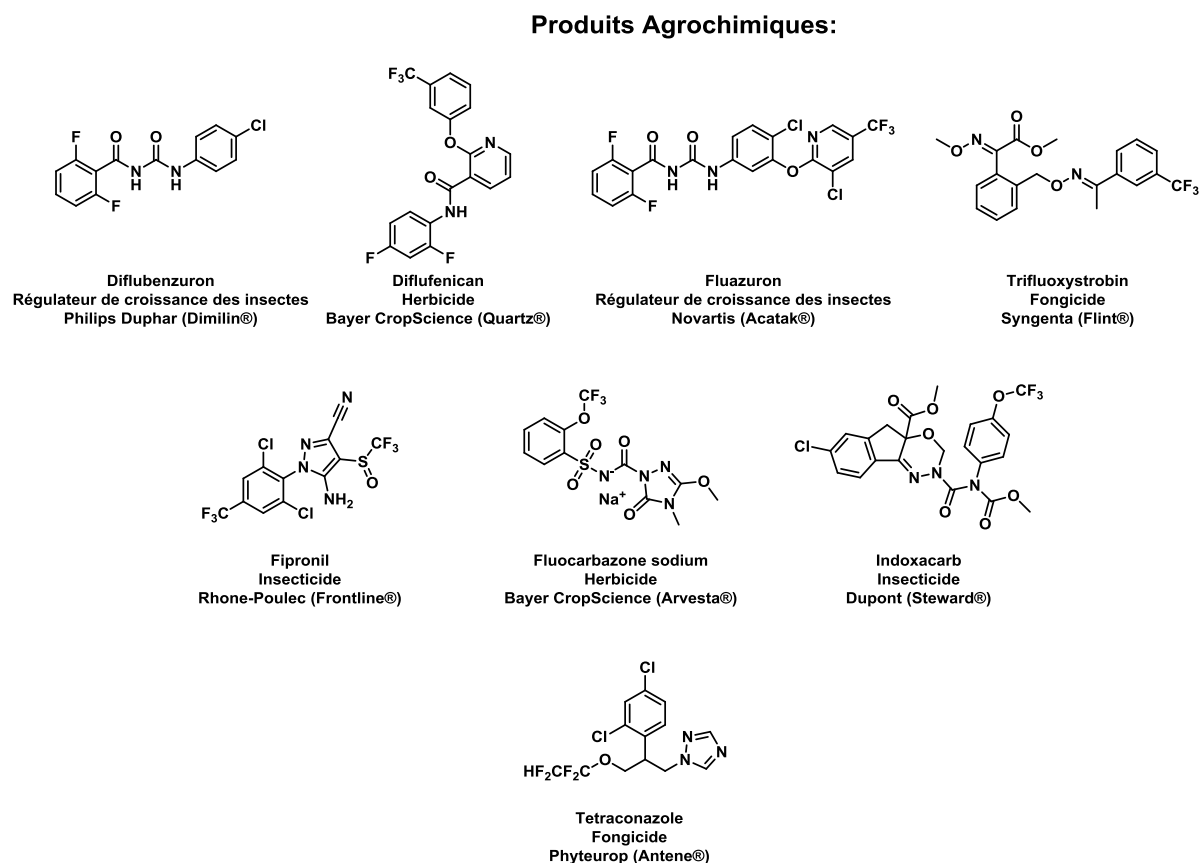


Figure 3: Exemples de produits agrochimiques fluorés

2 CONCLUSION

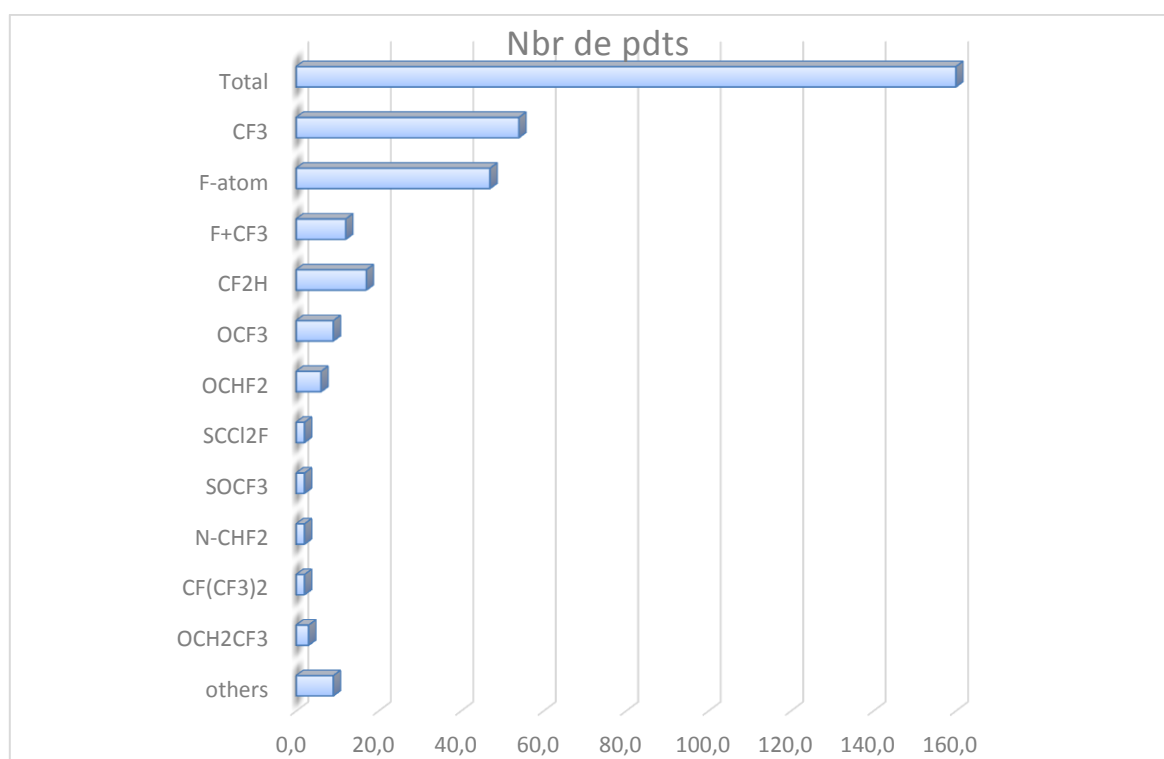
L'utilisation accrue du fluor a permis la synthèse de nouveaux composés bioactifs dans les domaines de la recherche pharmaceutique et agrochimique. L'atome de fluor ainsi que les groupements fluorés émergents ont prouvé leur efficacité en améliorant les propriétés physico-chimiques, les modes d'action et les interactions avec la cible des produits formés. Environ un tiers des blockbusters contiennent au moins un atome de fluor. De ce fait, cet incroyable élément pourrait permettre le développement de produits de manière économique, efficace et respectueux de l'environnement.

3 OBJECTIFS DU PROJET DE THESE

De nos jours, l'accès à une nourriture de qualité en quantité est un réel défi que les chimistes doivent relever en respectant les normes environnementales les plus strictes et ce à des prix abordables.

La protection des cultures est donc un point important à traiter dans lequel l'ajout de fluor sur des molécules bioactives peut faire la différence.

Le graphique ci-après (Graphique 1) représente la répartition des groupements fluorés en agrochimie. Les composés aliphatiques, aromatiques et hétéro-aromatiques substitués par des groupements F- ou CF₃- représentent la majeure partie des produits phytosanitaires fluorés utilisés (F: 28%; CF₃: 33%; F+CF₃: 7%). Le développement de nouvelles réactions de fluoration a aussi attiré l'attention des chercheurs sur le développement de nouvelles fonctionnalités telles que les CHF₂ (10%) et OCF₃ (5%).



Graphique 1: Répartition des groupements fluorés émergeant en agrochimie (2014)

Dans un contexte agrochimique, le sujet de ma thèse fut divisé en deux parties. La première fut le design et la synthèse d' α,α -difluoro- β -hydroxy cétones. Ces produits devraient agir en tant qu'agonistes des récepteurs GABA et cibler le système nerveux central (SNC) des insectes. La synthèse d'analogues a déjà été reportée dans la littérature, cependant aucune de ces publications ne décrit la synthèse d'ingrédients polyfluorés à des fins agrochimiques (Figure 4).

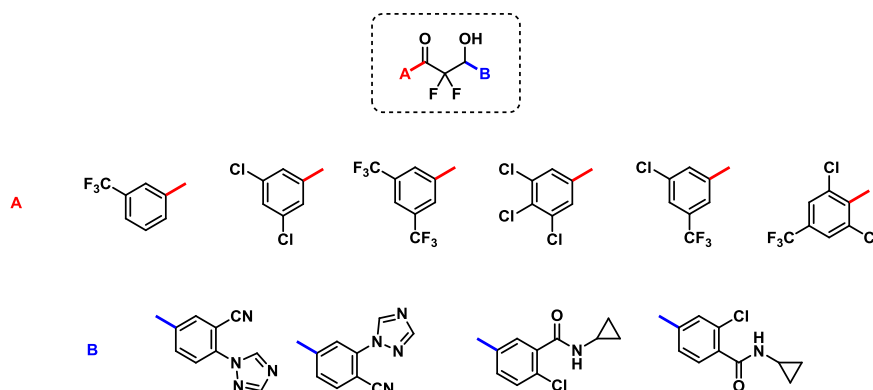
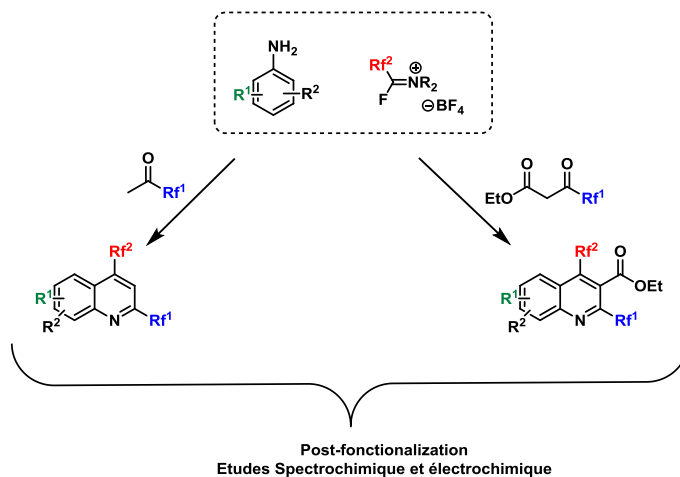


Figure 4: Synthèse du motif α,α -difluoro- β -hydroxy cétone pour le design de composés destinés à la protection moderne des cultures

Le second projet fut dédié à la synthèse de quinoléines 2,4-bis(fluoroalkyl)-substituées utilisant un sel d'iminium fluoré. En effet, les dérivés quinoléiques sont des éléments importants et utiles à des fins pharmaceutiques et agrochimiques en raison de leurs nombreuses propriétés biologiques. Le but a été de développer une nouvelle série d'hétérocycles bis-fonctionnalisés par des groupements fluorés émergents, plus spécifiquement des quinoléines, à partir d'une méthode industriellement applicable utilisant les Réactifs Fluoroalkyl Amines (FARs). Ces composés peuvent être accessibles avec de bons rendements, dans des conditions expérimentales douces et avec une complète régiosélectivité. Dans un second temps, nous voulions exemplifier cette série de nouveaux dérivés quinoléiques en réalisant des réactions de post-fonctionnalisation dans des positions diverses. En parallèle, des études électrochimique et spectrophotométrique ont été réalisées pour évaluer les propriétés physico-chimiques de ces composés (Figure 5).

Résumé de thèse



R = Me, Et
R¹ = H, F, OMe, Cl, NMe₂, OCF₃, CF₃, Ph, SPh, fused phenol
R² = H, Me
Rf¹ = CHF₂, CF₃
Rf² = CHF₂, CHFCl, CHFCl₂

Figure 5: Synthèse de quinoléines 2,4-bis(fluoroalkyl)-substituées

Tous les produits furent testés chez Bayer CropScience en tant que nouveaux ingrédients phytosanitaires. Les résultats biologiques ne sont pas tous reportés dans ce manuscrit pour des raisons de confidentialité.

CHAPITRE II : SYNTHÈSE D' α,α -DIFLUORO- β -HYDROXY CETONES

1 INTRODUCTION

Les insectes sont à l'origine des principales maladies causées chez l'Homme et chez l'animal, mais aussi aux cultures agricoles. Jusqu'à ce jour, quatre grandes classes de composés dominaient le marché mondial : les pyréthrinoïdes, les organophosphates, les méthylcarbamates et les néonicotinoïdes. Ce projet s'est concentré sur la synthèse d'insecticides et plus précisément ceux ciblant le système nerveux central (SNC). Ce type de composés peut interférer ou inhiber l'impulsion électronique permettant la transmission de message nerveux entre les synapses et les cellules nerveuses.

Le SNC des insectes est constitué d'un cerveau relié au ganglion ventral et d'une multitude de nerfs appartenant au système nerveux périphérique. Une quantité importante d'acide gamma-aminobutyrique (GABA) y est concentré. Ce sont des neurotransmetteurs inhibiteurs présents principalement dans le cerveau ainsi qu'à la jonction neuromusculaire.

Les récepteurs GABA peuvent être ciblés au moyen :

- D'antagonistes, qui bloquent l'ouverture d'un canal chlorure et empêchent l'introduction d'ions chlorures.
- D'agonistes, qui va permettre l'augmentation de la fréquence d'ouverture de ce même canal et augmenter la quantité d'ions chlorures s'y introduisant.

L'attaque des récepteurs GABA par des agonistes se traduira chez l'insecte par une hyperpolarisation de la membrane synaptique, ce qui diminuera l'excitabilité du neurone et ralentira l'activité cérébrale. Ces symptômes engendrent des convulsions, une paralysie et finalement la mort des insectes.

2 PRESENTATION DE LA STRATEGIE DE SYNTHESE

Le but de ce projet fut de développer de nouveaux insecticides agissant en tant qu'agonistes des récepteurs GABA. Pour cela, nous avons synthétisé une série de molécules combinant le motif α,α -difluoro- β -hydroxy cétone et deux cycles aromatiques poly-substitués. Ce motif particulier a déjà prouvé son efficacité dans le domaine de la chimie pharmaceutique et nous voulons étendre son champ d'action au domaine agrochimique (Figure 6).

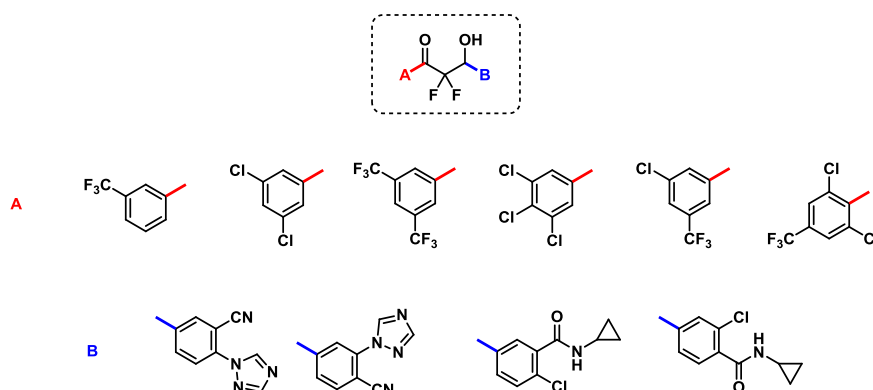


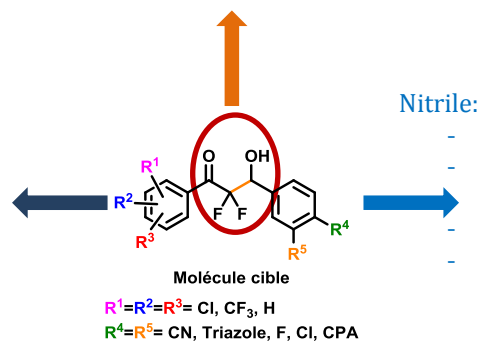
Figure 6: Design des molécules cibles à partir de substituants prédéfinis

Le design de ces molécules cibles fut réalisé selon l'activité spécifique présentée par les substituants (Figure 7) :

- Le motif α,α -difluoro- β -hydroxy cétone est reconnu pour ses nombreuses propriétés biologiques comme inhibiteur d'enzymes ou agoniste des récepteurs de la sous unité GABA_B.
- Le CF₃ : la présence de groupements fluorés améliore les propriétés physico-chimiques des molécules bioactives.
- Le groupement cyclopropyle est considéré comme un bioisostère des alcènes agissant selon le même mode d'action et possédant une forte stabilité métabolique. La fonction amide est une fonction inerte, limitant la photo-dégradation. Elle possède un large spectre de propriétés biologiques telles que: antifongiques, insecticides, et herbicides.
- Le triazole possède aussi un large spectre de propriétés biologiques.
- Le nitrile est une fonction robuste qui n'est pas facilement métabolisée ou hydrolysée. Elle peut facilement traverser les membranes cellulaires sans être altérée. C'est aussi un très bon groupe accepteur de liaison hydrogène.

1) Inhibiteur d'enzymes

- CF_3 : améliore les propriétés physico-chimiques des molécules
- Cl: précurseur pour l'introduction de nouveaux groupes fonctionnels



Nitrile:

- groupe inductif attracteur
- peut servir de précurseur pour d'autres fonctions
- bon accepteur de liaisons hydrogène
- bioisostère des fonctions hydroxyle et carboxyle

Triazole: possède un large spectre d'applications biologiques

Figure 7: Résumé des propriétés de chaque substituant

Les produits finaux sont obtenus par une méthode de synthèse convergente entre deux intermédiaires clés, couplés entre eux dans une étape de synthèse finale (Figure 8).

Les intermédiaires **1** sont obtenus en trois étapes qui consistent tout d'abord en un échange halogène-métal donnant accès à une cétone. Puis une réaction de condensation de Claisen et enfin une réaction de difluoruration produisent les produits désirés : les 1-aryl-2,2,4,4-pentafluoro-3,3-dihydroxy-butanones.

Les intermédiaires **2** ont été obtenus en utilisant différentes méthodes selon le composé final désiré.

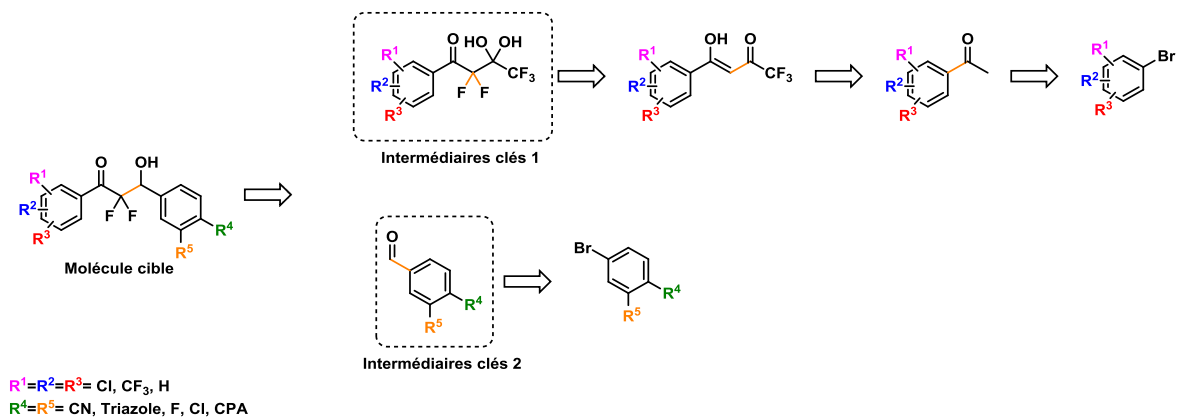


Figure 8: Schéma rétrosynthétique de la synthèse des α,α -difluoro- β -hydroxy cétones

3 SYNTHÈSE DES INTERMÉDIAIRES CLÉS 1

Trois étapes ont été nécessaires pour la préparation de ces intermédiaires (Figure 9).

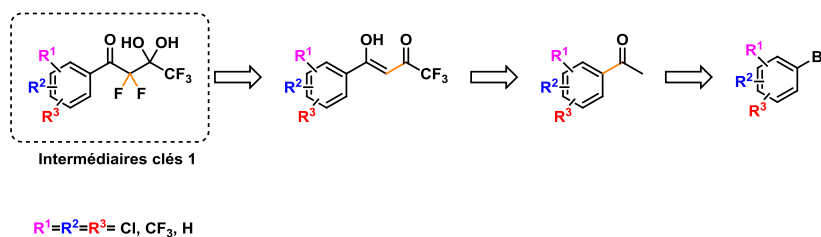


Figure 9: Rétrosynthèse des intermédiaires clé 1

3.1 Synthèse des cétones II.1

L'étape 1 correspond à une réaction d'échange halogène-métal en présence du « Turbo Grignard » et d'un amide de Weinreb, donnant accès aux cétones **II.1**. Les composés furent obtenus avec un rendement d'environ 60% après purification par colonne chromatographique (Schéma 1).

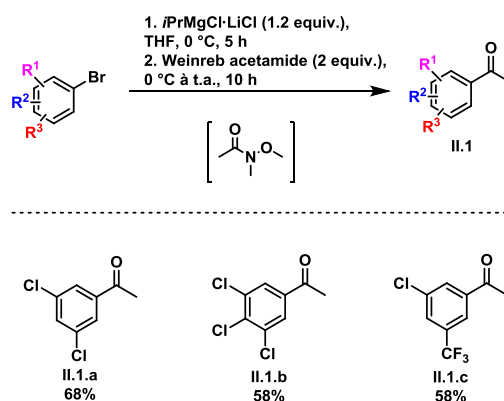


Schéma 1: Synthèse des cétones II.1.a-c

La cétone **II.1.d** fut quant à elle obtenue en deux étapes. Tout d'abord un échange halogène-métal en présence de *n*-BuLi et d'acétaldéhyde a permis l'obtention de l'alcool secondaire correspondant **II.2** qui a ensuite été oxydé en présence de dichromate de sodium donnant accès à la cétone désirée **II.1.d** avec un rendement de 75% (Schéma 2)

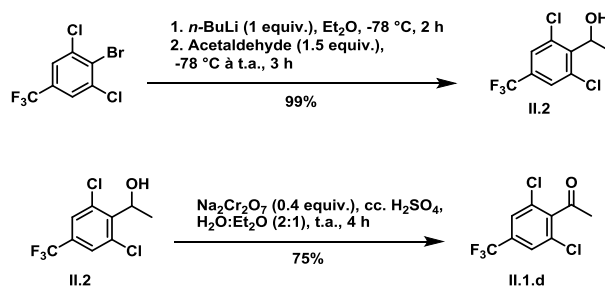


Schéma 2: Synthèse de la cétone II.1.d

3.2 Condensation de Claisen

En présence du trifluoroacétate de trifluoroéthyle, les cétones **II.1** réagissent quantitativement selon une réaction de condensation de Claisen permettant l'obtention des composés **II.3** (84-99%) (Schéma 3).

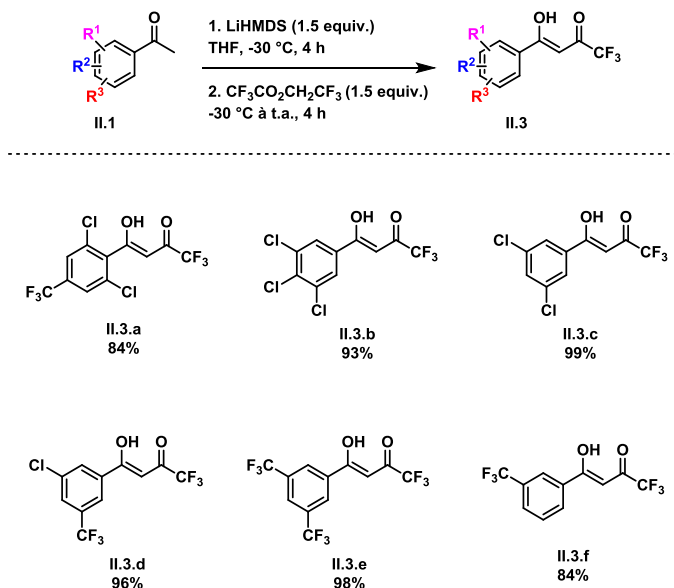


Schéma 3: Obtention des composés **II.3.a-f** grâce à la réaction de condensation de Claisen

3.3 Réaction de difluoration

La dernière étape de la synthèse de l'intermédiaire **1** fut une réaction de difluoration. Les composés **II.4** furent obtenus en mélangeant les α,α -difluoro- β -trifluoromethyldihydroxy cétones **II.3** précédemment synthétisées avec 2.5 équivalents de Selectfluor® (Schéma 4

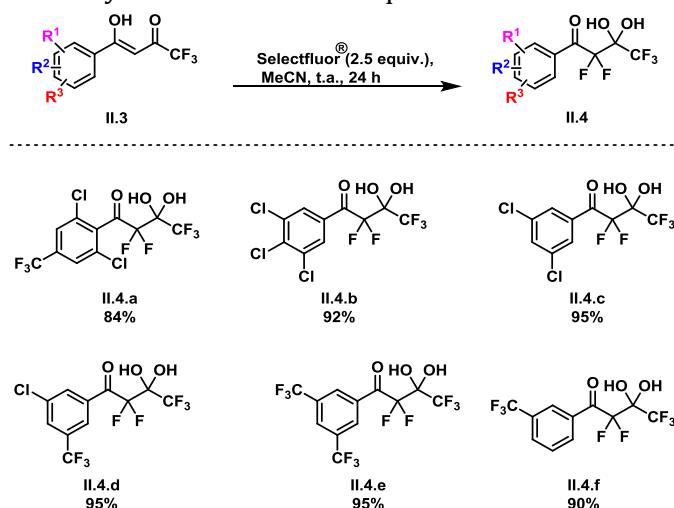


Schéma 4: Réaction de difluoration des composés **II.3** et formation des produits **II.4**

4 SYNTHÈSE DES INTERMÉDIAIRES CLES 2

La synthèse des intermédiaires **2** consistait en la formation de deux familles d'aldéhydes substitués par des groupements triazole et nitrile d'une part et des groupements chlorure et cyclopropylamide d'autre part (Figure 10).

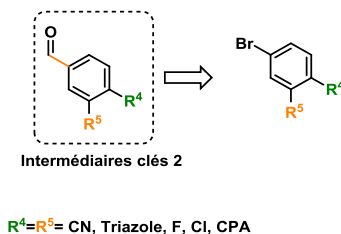


Figure 10: Rétrosynthèse des intermédiaires clé 2

4.1 Synthèses des 4- et 5-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitriles II.5

L'aldéhyde **II.5.a** fut obtenu à la suite d'une substitution nucléophile aromatique du fluor par le triazole dans l'acétonitrile. Le composé a été obtenu avec un rendement de 51%, conforme à la littérature (Schéma 5).

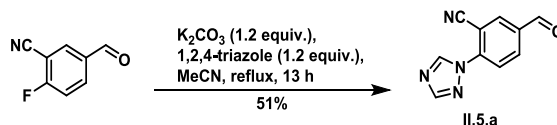


Schéma 5: Synthèse du 5-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.5.a

La synthèse de son régioisomère nécessita quant à elle quatre étapes de synthèse. Tout d'abord une étape de formylation permettant l'obtention de **II.6** avec un rendement de 64% en présence du « Turbo Grignard » et du *N*-formylpiperidine comme source d'aldéhyde. L'aldéhyde ainsi obtenu fut protégé en dioxolane en présence d'éthylène glycol et d'une quantité catalytique d'APTS•H₂O. Le produit **II.8** a été obtenu avec un rendement quantitatif et fut directement impliqué dans une réaction de substitution nucléophile aromatique permettant l'introduction du triazole avec un rendement de 82%, composé **II.9**. La dernière étape fut l'étape de déprotection de l'aldéhyde dans une solution de HCl 2M à température ambiante. Le composé final **II.5.b** fut obtenu avec un rendement de 96% sans purification (Schéma 6).

Résumé de thèse

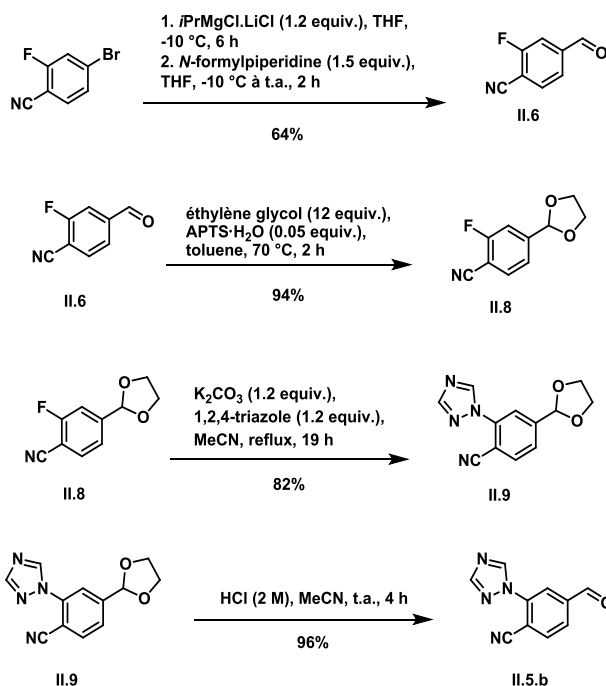


Schéma 6: Synthèse en quatre étapes du 5-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.5.b

4.2 Synthèse des 2-chloro-*N*-cyclopropyl-4- ou 5-formylbenzamides II.11

Pour la synthèse de la seconde famille d'aldéhyde, deux différentes voies peuvent être envisagées :

- La voie A : qui consiste en une réaction d'échange halogène-métal et une formylation suivie d'un couplage peptidique.
- La voie B : qui consiste d'abord en un couplage peptidique suivie de la réaction d'échange halogène-métal.

Dans les deux cas un proton acide est présent sur la molécule pouvant perturber la réaction (Figure 11).

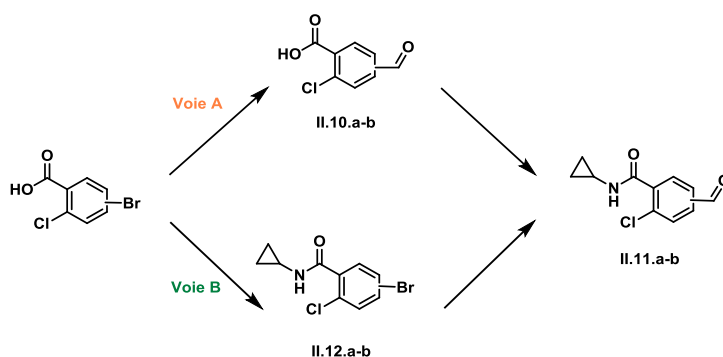


Figure 11: Stratégies de synthèse

Nous avons tout d'abord commencé par la voie A et nous avons procédé à la réaction d'échange halogène-métal et de formylation en présence de MeLi (pour déprotonner le proton acide), de *t*-

BuLi (pour réaliser l'échange avec l'halogène) et du DMF (source d'aldéhyde). Quel que soit le temps de lithiation seulement 50% de conversion fut atteint et le produit final **II.10** fut constamment obtenu en mélange avec du produit de départ et des produits de dégradation. Une seconde étape de couplage peptidique en présence de T₃P et de DIPEA a permis l'obtention des composés finaux **II.11.a** et **II.11.b** avec des rendements respectifs de 42% et 35% sur deux étapes (Schéma 7).

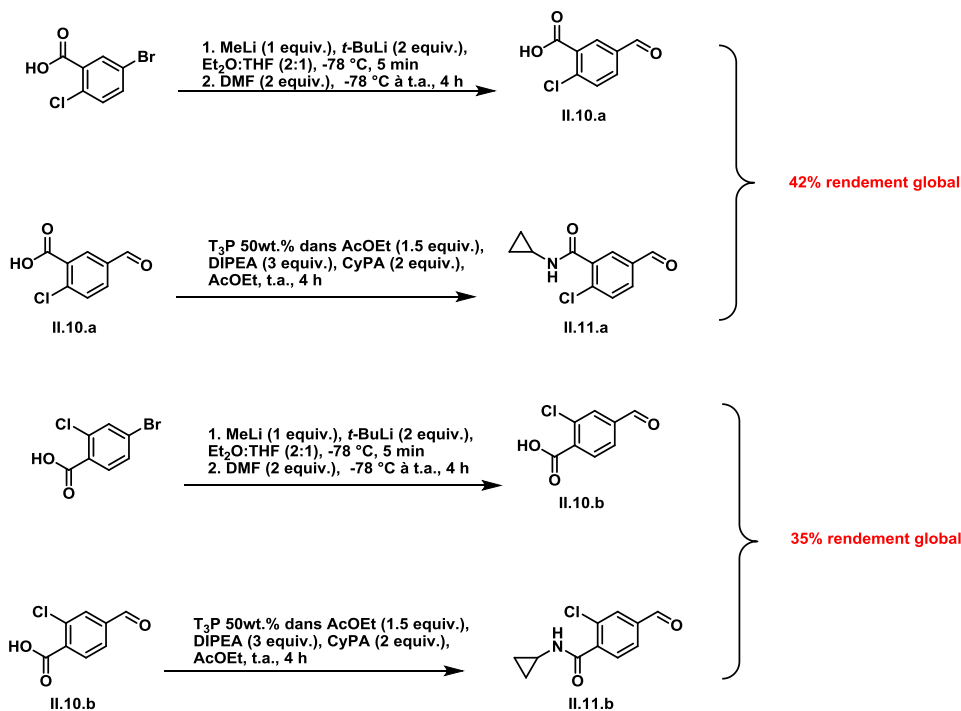


Schéma 7: Voie A: Synthèse des 2-chloro-N-cyclopropyl-4- et 5-formylbenzamides II.11.a-b

Nous avons ensuite tenté d'obtenir ces produits en passant par la voie B. La première étape correspondant au couplage peptidique entre la cyclopylamine et les acides 4- ou 5-bromo-2-chlorobenzoïque ont permis d'accéder quantitativement aux composés **II.12.a** et **II.12.b** avec des rendements respectifs de 82% et 95%. La seconde étape fut l'échange halogène-métal, étape une fois de plus difficile à réaliser, la conversion n'étant jamais complète. Par cette voie de synthèse les composés **II.11.a** et **II.11.b** ont été obtenu avec des rendements de 48% et 40% sur deux étapes (Schéma 8).

La voie B présente des résultats légèrement plus élevés, elle sera donc favorisée.

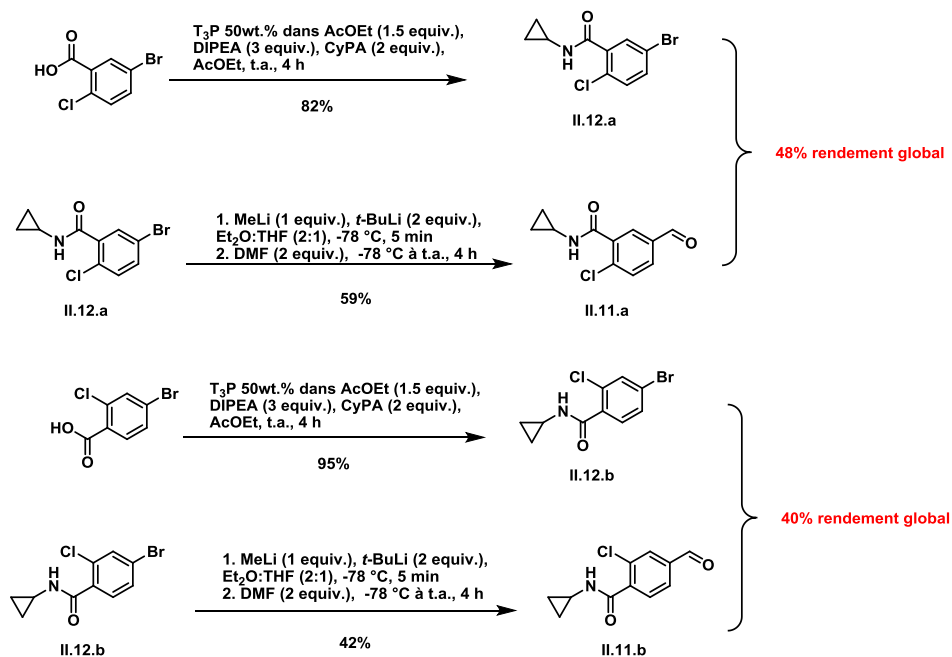


Schéma 8: Voie B : Synthèse des 2-chloro-N-cyclopropyl-4- et 5-formylbenzamides II.11

5 REACTION DE COUPLAGE ENTRE LES INTERMÉDIAIRES 1 ET 2

Nous avons enfin abordé la dernière étape de la synthèse correspondant au couplage entre les partenaires **1** et **2**. Pour cela il a fallu générer *in situ* un intermédiaire difluoroénolate, formé à partir de la libération d'une fonction trifluoroacétate en présence de LiBr et de NEt_3 . Les vingt-quatre produits furent obtenus après addition des aldéhydes. Ils ont tous été envoyés chez Bayer CropScience pour procéder à leurs purifications, analyses et tests biologiques afin de déterminer leurs potentielles activités en tant qu'agonistes des récepteurs GABA.

Un composé a fourni d'intéressants résultats avec un $\text{pI}_{50} = 6.6$ en tant qu'agoniste des récepteurs GABA des *Drosophila melanogaster*. Présentement, d'autres recherches sont en cours (Schéma 9).

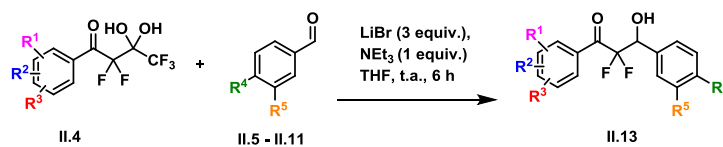


Schéma 9: Synthèse des composés II.13

CHAPITRE III : SYNTHÈSE DES QUINOLEINES 2,4-BIS FLUOROALKYLS SUBSTITUEES

1 INTRODUCTION

Les composés aromatiques hétérocycliques ont été découverts dans les années 1800. Nous les retrouvons à la base de beaucoup de structures de composé naturel. Ils sont largement utilisés dans divers domaines d'applications et nombre d'entre eux possèdent des propriétés biologiques utiles à la chimie pharmaceutique et agrochimique.

Dans ce chapitre, nous nous sommes principalement intéressés à une classe spécifique d'hétérocycles ; les quinoléines, découvert par F. Runge en 1834.

De nombreux alcaloïdes dérivés de la quinoléine se sont révélés être de puissant agent contre la malaria ou la leishmaniose par exemple.

Depuis leur découverte 200 ans plus tôt, l'étude des quinoléines n'a eu de cesse d'intéresser les chimistes et de nombreuses méthodes de synthèse ont été développées.

Présenté précédemment, l'introduction d'un atome de fluor sur une molécule peut améliorer ses propriétés physico-chimiques. De ce fait, la combinaison entre une molécule possédant un fort degré d'activité biologique et le fluor est naturellement devenu un des nouveaux challenges de la synthèse organique.

D'après la littérature, la plupart des méthodes décrivent l'introduction d'un atome de fluor ou d'un groupement fluoré en divers position sur la quinoléine. Parmi elles seulement quelques-unes décrivent la synthèse de quinoléines possédant deux groupements fluorés et moins encore décrivent leur introduction en position 2 et 4.

2 PRESENTATION DE LA STRATEGIE DE SYNTHÈSE

Le but de ce projet fut de développer une méthodologie de synthèse de dérivés quinoléiques possédant des groupements fluorés émergents en position 2 et 4. La stratégie mis en place implique l'utilisation de Réactifs Fluoroalkyl Amines (FARs) qui ont permis l'obtention d'une nouvelle série de composés avec de bons rendements, dans des conditions douces et avec une complète régiosélectivité.

Les FARs sont de puissants outils pour l'introduction de différents groupements fluorés. Il en existe trois commerciaux ; l'amine 1,1,2,2-tétrafluoro-*N,N*-diméthyléthane (**A.1**; TFEDMA), l'amine 2-chloro-*N,N*-diéthyl-1,1,2-trifluoroéthane (**B.1**; réactif de Yarovenko) et l'amine *N,N*-diéthyl-1,1,2,3,3,3-hexafluoropropane (**C.1**; réactif d'Ishikawa). Ils sont préparés à partir d'oléfine et de diméthyl- ou diéthylamine (Figure 12).

Résumé de thèse

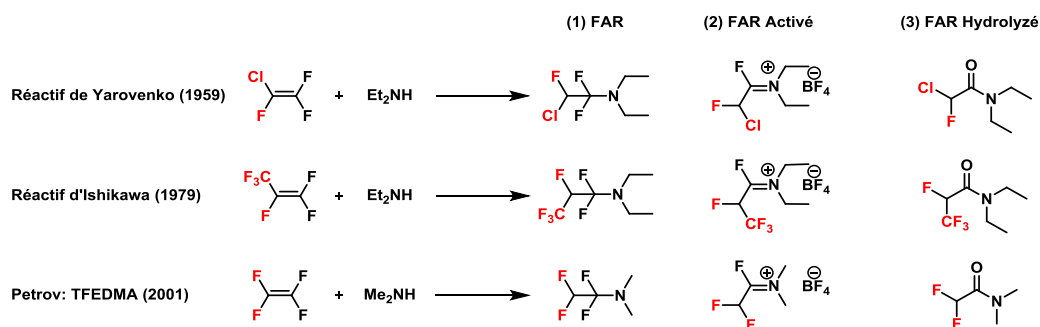


Figure 12: Réactifs Fluoroalkyl Amines (FARs) commerciaux

Activés par les acides de Lewis, ils donnent accès à un sel d'iminium très réactif possédant un fort caractère électrophile (Schéma 10).

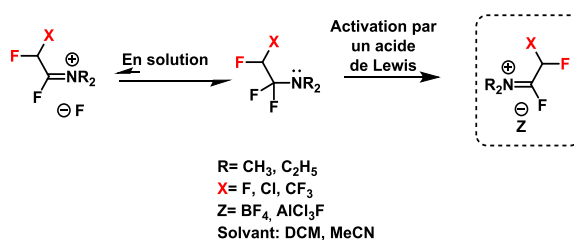


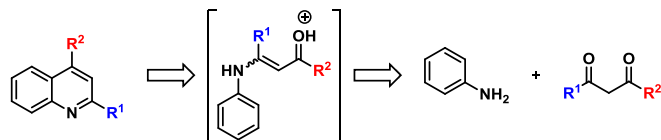
Schéma 10: Activation des FARs par les acides de Lewis et conversion en sels d'iminium

En présence d'une *N*-arylimine, la réaction de ces deux intermédiaires mène à la formation de quinoléines 2,4-bis fluorées. Cette réaction est une réaction analogue des réactions de Combes et de Meth-Cohn qui utilisent respectivement une β -dicétone et une aniline ou le réactif de Vilsmeier en présence d'une énamine aromatique (Schéma 11).

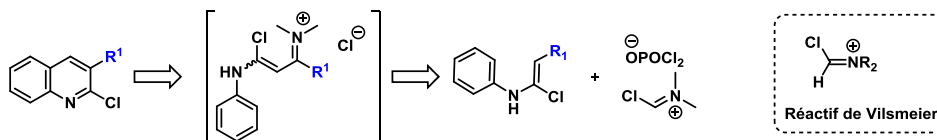
La synthèse de ces quinoléines est réalisée en deux étapes. La première est la condensation d'une cétone fluorée sur l'aniline donnant accès à une imine qui réagit en tant que nucléophile sur le FARs activé. Le vinamidinium intermédiaire obtenu cyclise ensuite suivant une réaction de substitution électrophile aromatique pour former la quinoléine de manière intramoléculaire.

Résumé de thèse

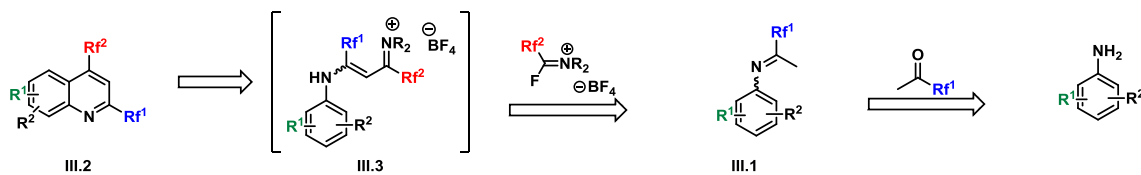
Réaction de Combes



Réaction de Meth-Cohn



Projet de synthèse



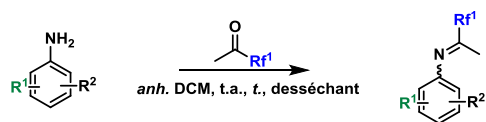
R = Me, Et
R¹ = H, F, OMe, Cl, NMe₂, OCF₃, CF₃, Ph, SPh, naphthol
R² = H, Me
R^{f1} = CHF₂, CF₃
R^{f2} = CHF₂, CHFCl, CHF₂CF₃

Schéma 11: Schéma rétrosynthétique de la synthèse des dérivés quinoléiques

3 SYNTHÈSE DES DERIVES QUINOLEIQUES : DEVELOPPEMENT D'UNE NOUVELLE METHODOLOGIE

3.1 Synthèse des imines fluorés

La première étape est une étape de condensation de la di- ou trifluoroacétone sur l'aniline dans le dichlorométhane anhydre en présence d'un agent desséchant. Les imines **III.1** ont été obtenues avec de bons rendements. Certaines réactions ne furent pas complète malgré l'addition d'acétone et certains produits furent obtenus en mélange avec des sous-produits tels que : le produit de départ, les produits de condensation de l'acétone sur elle-même et d'autres non-identifiés. Ces imines ne furent pas purifiées afin d'éviter leur dégradation, ce qui n'altéra en rien leur réactivité (Schéma 12).



III.1.a-m: $Rf^1 = CF_3$: 15-93%
 III.1.aa-vv: $Rf^1 = CHF_2$: n.d-98%

Schéma 12: Synthèse des imines fluorées **III.1**

3.2 Synthèse des quinoléines

La seconde étape est l'attaque nucléophile des imines fluorées **III.1** sur les FARs activés par le $BF_3 \cdot Et_2O$ donnant accès au vinamidinium intermédiaire **III.3**. Cet intermédiaire est ensuite impliqué dans une réaction de substitution électrophile aromatique intramoléculaire amenant à la formation des quinoléines **III.2** substituées par des groupements fluorés en position 2 et 4 sans assistance externes. Dans les rares cas où la réaction ne fut pas complète, le vinamide **III.3'** a été obtenu après hydrolyse (Schéma 13).

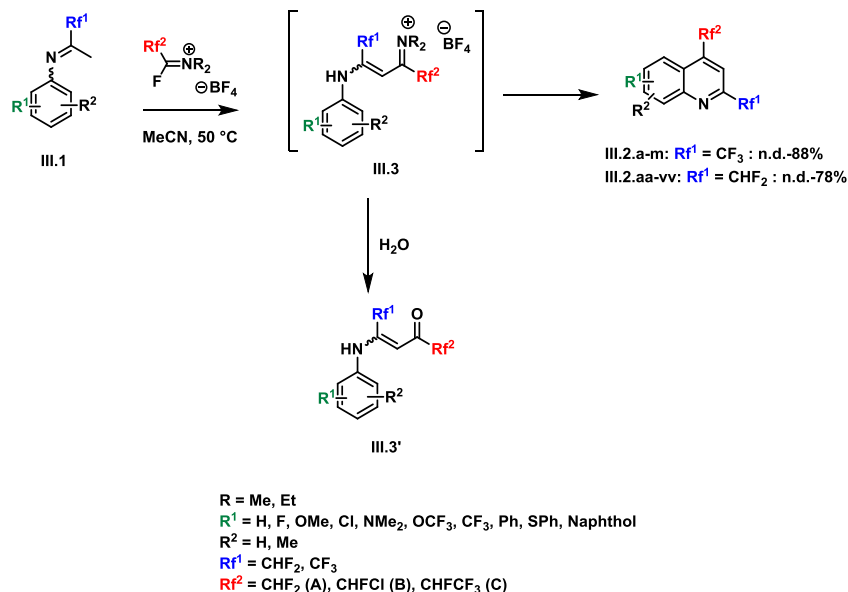


Schéma 13: Synthèse des quinoléines III.2

Les quinoléines ont été obtenues avec de bons rendements après purification sur colonne chromatographique. La régiosélectivité de la réaction a été confirmée par l'obtention d'un produit unique substitué en position 7 lorsque l'aniline de départ est substituée en position *mé*ta par rapport au groupement amino.

4 REACTION DE FONCTIONNALISATION EN POSITION 8

Une étude des quinoléines présentes sur le marché a révélé la commercialisation de deux produits possédant une fonction acide carboxylique en position 8. Afin d'étudier le potentiel de nos composés en tant que produits phytosanitaires, nous avons tenté d'introduire ce même type de fonctionnalité sur nos dérivés. Les réactions d'oxydation que nous avons tentées sur les quinoléines substituées en position 8 par un groupement méthyle, n'ont pas abouti aux résultats escomptés. Une stratégie alternative mise au point utilisant des conditions de réactions très dures a permis l'obtention d'un seul analogue substitué par un groupement acide carboxylique en position 8 à hauteur de 64% de rendement (Schéma 14).

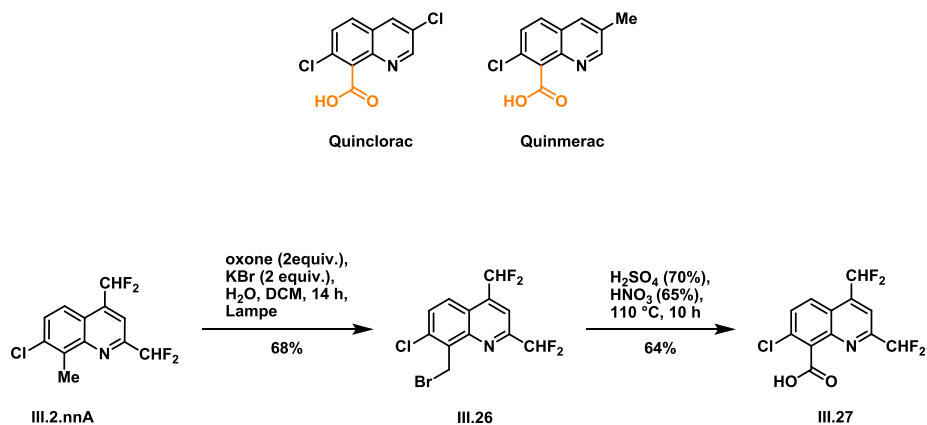


Schéma 14: Fonctionnalisation de la quinoléine III.2.nnA en position 8 par un acide carboxylique

5 ETUDES DES PROPRIETES PHYSICO-CIMIQUES

La difficulté que nous avons rencontrée lors de l'oxydation de nos produits, nous a amené à penser que la densité électronique de ces derniers était très faible, ce qui les rendaient inertes face à de telles réactions.

Pour répondre à cette hypothèse, nous avons réalisé une étude spectrophotométrique et électrochimique sur une série homogène de composés. Celle-ci nous a confirmé que sur un large domaine de voltampérométrie, ces produits étaient inertes vis-à-vis de l'oxydation comme de la réduction. Elle nous a aussi permis de déterminer quel genre de substituants rajoutés sur la quinoléine seraient susceptibles de favoriser le bon fonctionnement de ces réactions d'oxydo-réductions.

6 DEVELOPPEMENT DE QUINOLEINES SUBSTITUEES EN POSITION 3

La dernière partie de ce chapitre s'est articulée autour de la synthèse de quinoléines substituées en position 3 par divers groupements. Pour cela nous avons tout d'abord procédé à la synthèse de molécules possédant une fonction carboxylate en position 3 à partir de la méthode de synthèse précédemment développée. Celle-ci utilisant néanmoins des acétoacétates d'éthyles fluorés permettant l'obtention de phénylamino-acétates fluorés **III.28**.

Ces derniers réagissent avec les FARs activés pour donner les quinoléines **III.29** désirées (Schéma 15).

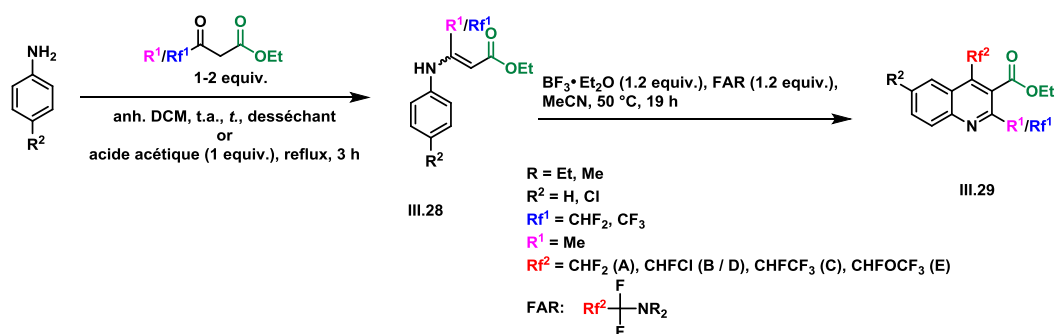


Schéma 15: Synthèse des quinoléines substituées en position 3 par une fonction carboxylate

L'introduction spécifique de cette fonction a ensuite permis la post-fonctionnalisation de ces composés par des groupements acide carboxylique, carbamate, amine, halogènes et ester boronique (Schéma 16). Ces réactions furent réalisées sur un seul exemple, ce qui ouvre la voie à une plus large exemplification.

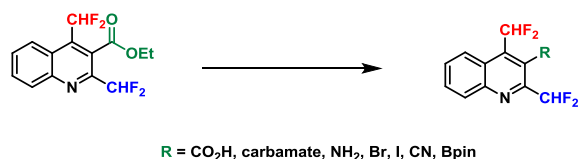


Schéma 16: Post-fonctionnalisation des quinoléines carboxylates

CONCLUSION GENERALE

Durant cette thèse, nous avons pu réaliser l'étude de deux projets distincts.

Tout d'abord, la synthèse de composés possédant un motif α,α -difluoro- β -hydroxy cétone. Lors de cette étude, vingt-quatre produits finaux ont été obtenus à l'issue d'une synthèse multi-étape convergente. L'étude de leurs activités biologiques en tant qu'agonistes des récepteurs GABA a ensuite été effectuée.

Le second projet concernait la synthèse de plusieurs quinoléines substituées en position 2 et 4 par des groupements fluoroalkyles à partir des FARs. Ces produits furent obtenus dans des conditions douces, avec de bons rendements et avec une complète régiosélectivité. La difficulté de les fonctionnaliser en position 8 a mené à une étude spectrophotométrique et électrochimique afin de mieux en comprendre les raisons. Enfin, nous avons réalisé la synthèse de composés possédant divers groupements en position 3, permettant une post-fonctionnalisation utilisant une chimie très variée.

Durant cette thèse de nombreux points n'ont pu être abordés ou approfondis et il serait intéressant d'en donner suite, tels que :

Projet 1 :

- La modulation des groupements sur les cycles aromatiques.
- La synthèse de produits mono et non-fluorés.
- L'amélioration des propriétés physico-chimiques par dérivatisation.
- Le développement et la synthèse de motifs cycliques des α,α -difluoro- β -hydroxy cétones.

Projet 2 :

- Elargir la synthèse des quinoléines à l'aide du développement de nouveaux FARs.
- L'étude de l'insertion de groupements électrophiles sur les quinoléines par déprotonation des fonctions difluorométhylées.
- L'étude de l'activation de la liaison C-F.

CHAPTER I

Introduction

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1 FLUORINE, A SUBSTITUENT OF CHOICE

1.1 Fluorine discovery

Fluorine entered in the periodic table in 1869, although it has not been isolated at that moment. Several chemists fought for its isolation but results were often severe injuries, intoxication or death. It was only in 1886 that the highly reactive, toxic and corrosive green-yellow gas of molecular fluorine (F_2) was observed for the first time. Henri MOISSAN, was the first French scientist who won the Nobel Prize, in 1906, for this discovery (Figure 13). His work dealt with the isolation of fluorine by electrolyzing potassium hydrogenfluoride (KHF_2) in a solution of hydrogen fluoride (HF) at low temperature using platinum electrolyzer. With this major advance, the electric furnace was born, which revolutionized the chemical industry. ¹

Fluorine, symbolized by F with an atomic number $Z = 9$, is the first element of the halogen group. It possesses only one stable isotope in natural abundance on Earth: ^{19}F . The most stable radioisotope is ^{18}F , with a half-life of 110 minutes, which is use PET (Positron Emission Tomography).



Figure 13: Henri Moissan, winner of the Nobel Prize (1906)

1.2 Fluorine and nature

Fluorine is the 13th most abundant element on Earth's crust. It is principally found under mineral form: fluorspar which is a calcium fluoride (CaF_2) ore, fluorapatite which refers to a phosphate mineral of the formula $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ and cryolite, a rare mineral involved in the preparation of aluminium (Na_3AlF_6) (Figure 14). However, fluorine is not found in seawater due to the low solubility of these minerals.



Fluorspar

Cryolite

Fluorapatite

Figure 14: Minerals containing fluorine

Despite its predominance on Earth, only twelve metabolites have been identified containing fluorine. It is almost insignificant compared to the other halogens which are present in greater number (I-, Br-, Cl-containing halogenated natural products: >3000). Fluoroacetate was the first (1943) and the most ubiquitous fluorinated metabolite identified in the shrub of *Dichapetalum cymosum*. It is found in many plants known to be extremely toxic. Plants accumulating fluoroacetate also accumulate fluorocitrate, another metabolite obtained by the condensation of fluoroacetyl-CoA with oxaloactate by citrate synthetase.² Sir R. Peter *et al.* discovered in 1953, from an extract of seed lipids of *Dichapetalum toxicarium*, eight fatty acid chain derivatives of ω -fluoro-oleic acid, metabolites present in the same sample. Then in 1969, the structure of a new metabolite, nucleocidin, was elucidated from the study of the bacterium *Streptomyces calvus*. It is only in 1986, that the last metabolite was reported: 4-fluorothreonine was extracted from *Streptomyces cattleya* (Figure 15).³⁻⁴

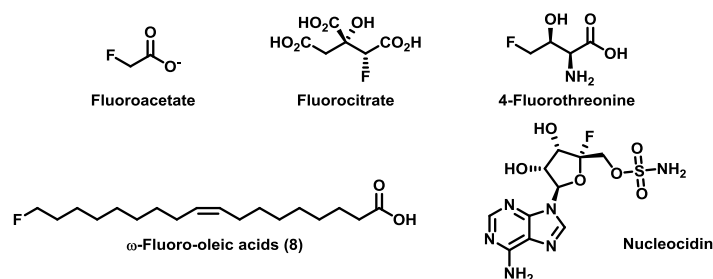
*Dichapetalum cymosum**Dichapetalum toxicarium**Streptomyces calvus*

Figure 15: Plants and bacteria containing fluorinated metabolites

Since then, no more fluorinated metabolites were discovered and natural bioactive fluorine-containing compounds are clearly not predominant. So how can we explain this emerging gold rush toward the introduction of fluorine into organic chemistry?

1.3 Fluorine properties

The suspected properties of fluorine can be found in many reviews.⁵⁻²²

One of the most important aspect in the synthesis of bioactive compounds in pharmaceutical industry is to develop molecules that can withstand physiological pH long enough to enter in bloodstream and cross cell membranes. This parameter is also considered when molecules are designing to tackle insect, but other parameters such as resistance to air and water as well as their degradability can intercede. Moreover, active molecules should be transported in enough quantity to act on the target and be metabolized into non-toxic materials. Fluorine can improve the physico-chemical properties and pharmacologic features such as metabolic stability, bioavailability (quantity of compound which reaches the target) and protein-ligand interaction of compounds, in comparison with their non-fluorinated analogues.²³ Nowadays, the introduction of fluorine into bioactive compounds in organic chemistry research has become routine. The increased efficiency of drugs and agrochemical ingredients lead to a reduction of required doses and consequently has a positive impact on the environment. The properties of fluorine are reported hereafter:

1.3.1 Atomistic properties

Fluorine is the smallest of the halogens with a van der Waals (vdW) radius of 1.47 Å, in between those of a hydrogen atom (1.20 Å) and an oxygen atom (1.52 Å). The substitution of a hydrogen or a hydroxyl group by fluorine as mimic is commonly realized to observe the resulting changes and its influence on biological properties of active compounds.

Fluorine is also the most electronegative element of the periodic table (3.98, on Pauling's electronegativity scale), with a very low polarizability forming the strongest bond with carbon (CH₃-F: 108.1 kcal/mol) among all halogens even slightly higher than the C-H bond strength. This bond strength increases with addition of fluorine atom (Table 1).¹⁹

The notion of bioisostere is an important point to consider. It defines the capacity of atoms or functional groups possessing similar shapes or sizes to be interchanged providing the smallest modification in their biological behaviour and the same mode of action.

Fluoroalkylated groups like CF₃ are bioisosteres of isobutyl, isopropyl and ethyl groups, even if the shapes of both kinds of groups are different. CHF₂ is on the other hand a bioisostere of carbonyl groups. The consequence of this exchange is therefore almost imperceptible.

Table 1: Representative physical data of selected elements

	Element (X)					
	H	C	O	F	Cl	Br
Electronegativity	2.20	2.55	3.44	3.98	3.16	2.96
van der Waals radius (Å)	1.20	1.70	1.52	1.47	1.75	1.85
Bond length CH ₃ -X (Å)	1.087	1.535	1.425	1.382	1.785	1.933
Bond dissociation energy CH ₃ -X (kcal/mol)	103.1	88	90.2	108.1	81.1	67.9
Ionization potential (kcal/mol)	313.9	259.9	314.3	402.2	299.3	272.7
Atom polarizability (Å ³)	0.67	1.76	0.82	0.56	2.18	3.05

1.3.2 Electronic effects

The high electronegativity of fluorine confers to the C-F bond a high ionic character and strongly polarizes it.

Fluorine is always electron-withdrawing by inductive effect, but can be electron-donating by resonance when it is linked to an unsaturated carbon. However, fluoroalkyl groups are only electron-withdrawing (Figure 16).

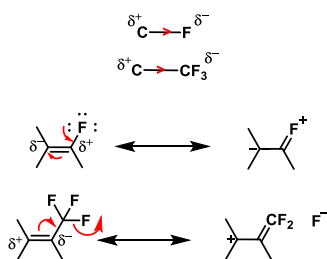


Figure 16: Electronic effects of fluorination

A fluorine atom impacts the stability of a carbocation if it is located either on the carbon in α or in β position. When fluorine is directly linked to the carbocation, the partial charge is stabilized by the lone pairs electron at fluorine. This is called the “push effect” (Figure 17).

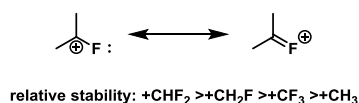


Figure 17: Back donation stabilization of a fluoroalkyl cation

When fluorine is β -linked to the carbocation, only the electron-withdrawing effect of fluorine is sensed and the carbocation is strongly destabilized, this is called the “pull effect”.

1.3.3 Bioavailability

The need of lead compounds in medicinal chemistry and in the agricultural field increases more and more each day. In both areas, scientists are facing issues related to the extension of the population, strict regulations and the most important, resistance phenomenon. In agrochemical research, as well as in pharmaceutical research, the development of new compounds leading to a better quality of life either by the health and the well-being or by the increase of crop quality and yields is the backbone of scientific research.

To help scientists, rules have been defined based on the analysis of bioavailability criteria of marketed compounds. First published was the empirical “Rule of Five” for oral absorption of drugs by Lipinski *et al.*²⁴, a guide which should roughly predict good drug candidates. Analogously, Briggs proposed the “Rule of Three” (reported by Tice²⁵) after having analysed selected commercially available agrochemicals. These rules ensure good uptake and distribution within an organism by *in vivo* high-throughput screening (HTS) tests (Table 2).²⁶

According to this table, several parameters are implied in the development of new hit, such as the lipophilicity (determined by logP) and the capacity to be a donor or an acceptor of hydrogen

bonds. Addition of fluorine into bioactive compounds may help to tune these parameters and design compounds with increased activities and to modulate their bioavailability.

Table 2: Physical chemistry-based bioavailability guidelines

	Lipinski's "Rule of Five" for oral absorption	Briggs' "Rule of Three" for agrochemical <i>in vivo</i> HTS
MW	<500	300 ± 100
log P _(octanol/water)	<5	3 ± 3
H-bond donors (sum OH+NH)	<5	≤3
H-bond acceptors (sum O+N)	<10	/
Δlog P _{(log P_(octanol/water) - log P_(hexane/water))}	/	≤3
mp (°C)	/	≤300
EH*	/	30 ± 5

*The equivalent hydrocarbon (EH) number used to estimate the volatility of a compound.

1.3.3.1 Perturbation of pKa

Insertion of fluorine into common functionalities impacts the acidity or the basicity of proximate groups which can be tuned to modulate the enzyme-substrate bonding affinities. Replacing hydrogen by one fluorine atom increases the Brønsted acidity of neighbouring groups and the capacity to give a hydrogen bond and decreases the Brønsted basicity and the capacity to accept a hydrogen bond (Table 3).

Basicity of amine groups are reduced with the introduction of fluorine, due to their strong electronegativity. Nitrogen becomes less easily protonated and consequently less basic. For instance, amines bearing fluorine atoms close to nitrogen exist mostly in neutral form at physiological pH, which increases their bioavailability.

Table 3: The effect of fluorine substitution on pKa values

Carboxylic acid	pKa	Alcohol	pKa	Ammonium	pKa
CH ₃ CO ₂ H	4.76	CH ₃ CH ₂ OH	15.9	CH ₃ CH ₂ NH ₃ ⁺	10.6
CH ₂ FCO ₂ H	2.90	CF ₃ CH ₂ OH	12.4	CF ₃ CH ₂ NH ₃ ⁺	5.7
CHF ₂ CO ₂ H	1.34	(CH ₃) ₃ COH	19.2	C ₆ H ₅ NH ₃ ⁺	4.6
CF ₃ CO ₂ H	0.52	(CF ₃) ₃ COH	5.1	C ₆ F ₅ NH ₃ ⁺	0.36

1.3.3.2 Lipophilicity

The lipophilic factor is important to design bioactive molecules as it controls substance absorption, passage through cell membranes and transport from blood to organs. Indeed, an excess of lipophilicity causes a poor solubility in water. On the contrary, a low lipophilicity causes a poor solubility in lipidic media and blocks the passage through membranes. A perfect log P solubility balance between both must be found. A logarithmic coefficient of the distribution of a molecule between water and octanol is measured to quantify this effect. One should note the difference between lipophilicity and hydrophobicity. Indeed, it was observed that in unsaturated compounds (like aryl or allyl), fluorination tends to increase lipophilicity because of the electron-withdrawing effect of fluorinated groups, which reduces hydrogen bonding (hence

hydrophilicity) (Table 4). However, fluorination of aliphatic chains decreases lipophilicity while hydrophobicity increases creating a third phase, not miscible with organic solvents nor with water.

Table 4: Hansch-Leo coefficients π ($\log P_{C_6H_5X} - \log P_{C_6H_6}$) for selected substituents

Substituent	π ($\log P_{C_6H_5X} - \log P_{C_6H_6}$)	Substituent	π ($\log P_{C_6H_5X} - \log P_{C_6H_6}$)
F	0,14	SCH ₃	0,61
Cl	0,71	SCF ₃	1,44
NO ₂	-0,27	SO ₂ CH ₃	-1,63
CH ₃	0,56	SO ₂ CF ₃	0,55
CF ₃	0,88	NHSO ₂ CH ₃	-1,18
CH ₃ CH ₂	1,02	NHSO ₂ CF ₃	0,92
CF ₃ CF ₂	1,89	CH ₃ -C=O	0,02
OH	-0,67	CF ₃ -C=O	0,55
OCH ₃	-0,02	CH ₃ -CO-NH-	-1,27
OCF ₃	1,04	CF ₃ -CO-NH-	0,08

1.3.3.3 Hydrogen bonding

Hydrogen bond displays an important role in interactions between a substrate and its biological target.

Despite its high electronegativity and the presence of its lone pairs electron, fluorine is a weak hydrogen bond acceptor (Figure 18). Indeed, it was reported that the strength of the -CF \cdots H-bond (2-3.2 kcal/mol) is two times weaker than the -O \cdots HX- bond (5-10 kcal/mol). It can be in part explained by the weak polarizability of C-F bond. However, the weakness of the -CF \cdots H-hydrogen bond does not prevent its influence on neighbouring groups. The electron-withdrawing character of fluorine or fluorinated groups modifies the pKa of proximate functions and consequently their capacity to give or receive hydrogen bonds (see 1.3.3.1).

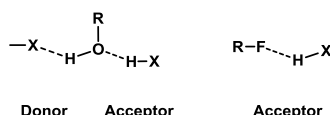


Figure 18: Comparison of potential hydrogen bonds between hydroxyl and fluorine moieties

1.3.3.4 Metabolic stability

In rare cases, compounds entering in the body are directly eliminated untouched but most of the time they are eliminated after being metabolized. Cytochrome P450 monooxygenase is an enzyme involved in the metabolism *via* oxidation. It is a powerful enzyme which metabolises almost everything and which does not allow a long stay of bioactive compounds in target systems. Substitution of metabolically labile sites by fluorine can block their inherent oxidative degradation and avoid the formation of metabolites. The C-F bond confers metabolic, oxidative and thermal stability to the molecule and prevents the deactivation of active compounds. Oxidative metabolism is not blocked by the strength of the C-F bond, but by the unfavourable formation of O-F bonds (Figure 19).

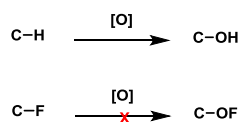


Figure 19: Oxidative metabolism process

Functional groups like CHF_2 , CF_3 , C_2F_5 are almost completely inert towards oxidation, hence the interest of their use as bioisosteres.

This is for example illustrated by the drug candidate SCH-48461 developed for its cholesterol-lowering properties. However, it demonstrates to be metabolically unstable and suffers from enzymatic hydroxylation on its aryl rings and other oxidative degradation reactions. Its fluorinated analogue Ezetimibe proved to be more efficient as confirmed by ED_{50} values as metabolic oxidation is avoided by fluorine substitution on aryl rings (Figure 20).¹²

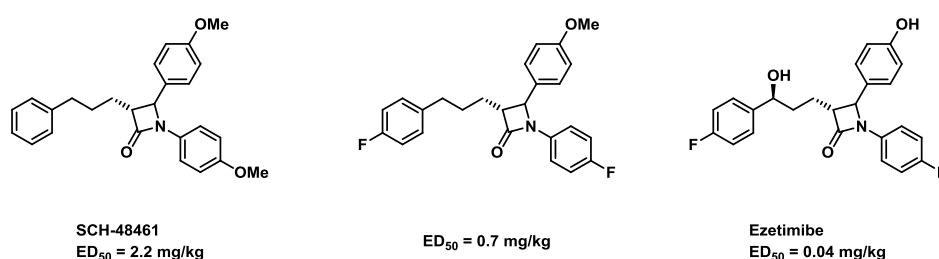


Figure 20: Structures of hypercholesterolemia drug Ezetimibe

1.4 Fluorine in human life science

The improvement of metabolic properties of drugs was rendered possible by new techniques of fluorination and the development of new fluorinated reagents, which allow the creation of new compounds at the cutting edge of chemical innovation.²⁰

Fluorine-containing molecules have become leaders on the chemical market. The number of organo-fluorine compounds is constantly increasing even though they are almost absent among natural products, which are source of many bioactive compounds. In the pharmaceutical field the occurrence of fluorine in marketed drugs has considerably increased. Indeed, only 2% of commercial compounds in 1970 were F-containing, whereas this percentage has reached 18% in 2006. According to The Pesticide Manual, 23 of the 543 commercially available compounds were F-containing in 1977 (4%),²⁷ 126 among 858 in 2003 (14%),²⁸ 140 among 908 in 2009 (15.4%)²⁹ and 155 among 920 in 2014 (17.7%).^{9, 16, 20-21, 30-31} Among the halogenated compounds, 28% are F-containing and are subdivided in 3 classes of phytosanitary products on the market: herbicides (54%), insecticides (27%) and fungicides (19%).¹⁴

Since the first synthesis of 5-fluorouracil (antitumoral activity) in 1957,³² several other compounds bearing either one fluorine atom or fluorinated groups have been developed, covering almost the entire field of pharmaceuticals and agrochemicals (Figure 21).

Industrial applications of fluorinated compounds expanded through the ages. They started in the 1930s with the use of chlorofluorocarbons (CFC) as refrigerants for air conditioning equipment (FREON®) and extinguishing chemicals (HALON®). Then fluorine was used in military applications with the development of inert materials like TEFLON® (PTFE polymer in 1940) useful in the development of new equipment in the production of enriched ^{235}U . This radioactive

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element was obtained by sublimation of extremely corrosive and volatile UF_6 for an energetic purpose.

Due to their environmental impact, CFC were removed from the market and most of the fluorochemical industries reoriented themselves in other fields like fluoropolymers and the synthesis of fluorinated synthons for agrochemicals or pharmaceuticals.

Material sciences were also impacted by fluorine with the emergence of liquid crystals for LCD-TV and semi-conductor manufacturing for microchips fabrication.

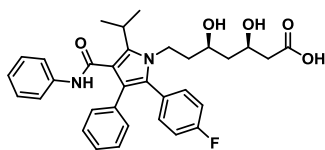
Recently, fluorine chemistry has found new applications in nuclear medicine, with the development of radionuclides used in PET. ^{18}F ($t_{1/2} = 110$ min) has the longest half-life among radionuclides with particular interest regarding to imaging of biological systems [^{11}C ($t_{1/2} = 20$ min), ^{13}N ($t_{1/2} = 10$ min), ^{15}O ($t_{1/2} = 2$ min)].³³ It is produced in a cyclotron prior incorporation into radiotracers used to scan organs giving information on their physiological role. Recently, FDA approved its use for monitoring amyloid plaques in the brain of Alzheimer and Parkinson patients and on persons who suffer from epilepsy, which opens a route for several new other applications.

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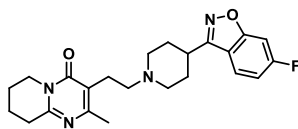


5-fluorouracil

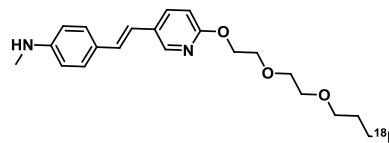
Pharmaceuticals:



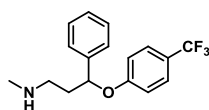
Atorvastatin
Anticholesterol agent
Pfizer (Lipitor®)



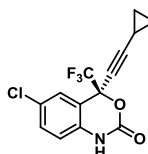
Risperidone
Schizophrenia treatment
Janssen (Risperidal®)



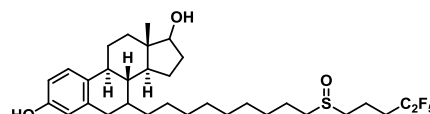
Florbetapir ¹⁸F
Radiopharmaceutical
Eli Lilly (Amyvid®)



Fluoxetine
Antidepressant
Eli Lilly (Prozac®)

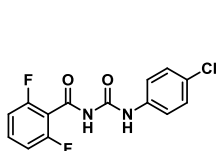


Efavirenz
Antiviral
Bristol-Meyers Squibb (Sustiva®)

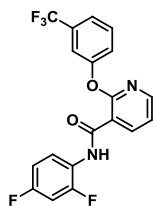


Faslodex
Anticancer
Astra Zeneca (Fulvestrant®)

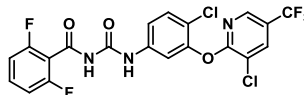
Agrochemicals:



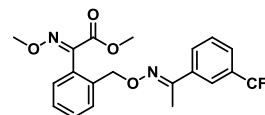
Diflubenzuron
Insect growth regulator
Philips Duphar (Dimilin®)



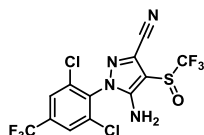
Diflufenican
Herbicide
Bayer CropScience (Quartz®)



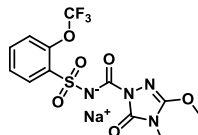
Fluazuron
Insect growth regulator
Novartis (Acatak®)



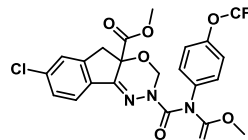
Trifluoxystrobin
Fungicide
Syngenta (Flint®)



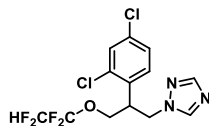
Fipronil
Insecticide
Rhône-Poulenc (Frontline®)



Fluocarbazon sodium
Herbicide
Bayer CropScience (Arvesta®)



Indoxacarb
Insecticide
Dupont (Steward®)



Tetraconazole
Fungicide
Phyteurop (Antene®)

Figure 21: Examples of fluorinated pharmaceuticals and agrochemicals

1.5 Conclusion

The expansion of the use of fluorine led to the formation of new bioactive compounds in pharmaceutical and agrochemical research. Indeed, they have proved their efficacy by improving physico-chemical properties, mode of action and interaction with the target. Nearly one third of the blockbusters are fluorinated ingredients.

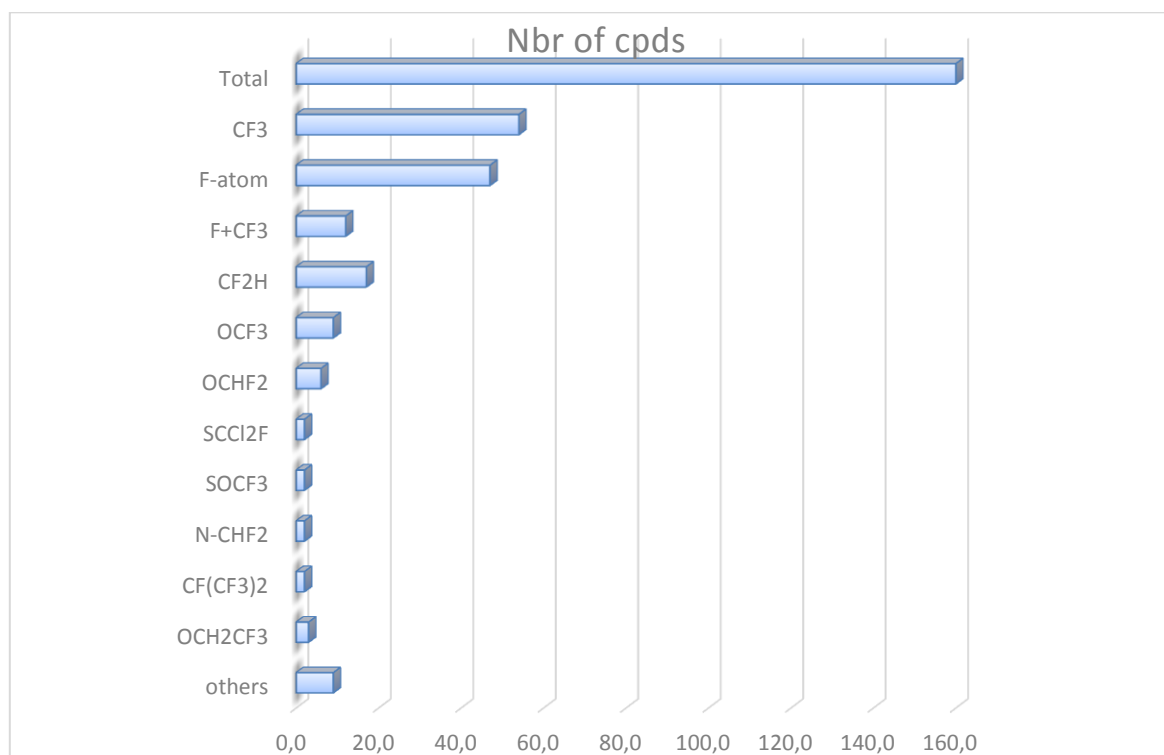
Fluorine might henceforth be the answer to the development of economic, efficient and environmentally safe compounds.

With the increasing number of methods to introduce fluorine and its unexpected properties, it seems clear that fluorine chemistry will continue to astonish us and that the number of fluorinated ingredients will keep growing at a rapid pace.

2 OBJECTIVES OF THE PROJECT

Nowadays, the access to food in quality and quantity is a real challenge to which scientist must answer with environmental regulation and an affordable price. To avoid food shortage and high prices, it is important to protect crops. In an agrochemical context, among the 150000 molecules synthesized and tested, only one will be a commercially available compound, and we have previously seen that fluorine may take a part in this run.

The graphic presented below (Graphic 1) depicts the occurrence of fluorinated groups in agrochemistry. F- or CF₃-substituted aliphatics, aromatics and heteroaromatics represent the major part of fluorinated compounds for phytosanitary use (F: 28%; CF₃: 33%; F+CF₃: 7%). With the development of new fluorination reactions became interesting the introduction of new fluorinated moieties such as CHF₂ (10%) and OCF₃ (5%).



Graphic 1: Occurrence of emergent fluorinated substituents in agrochemistry³¹

The purpose of my PhD project was divided in two parts. The first one was the design and the synthesis of α,α -difluoro- β -hydroxy ketones. These products should act as GABA agonist receptors and target the central nervous system (CNS) of insects. The synthesis of such compounds has already been reported in literature; however, none of them described the synthesis of polyfluorinated ingredients for agrochemical purpose (Figure 22).

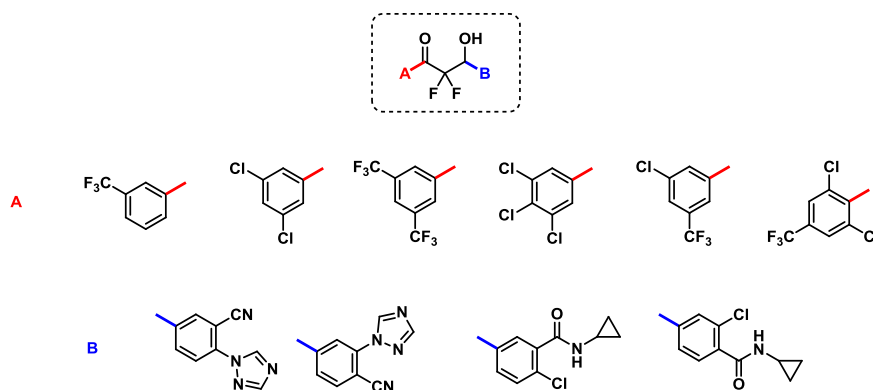
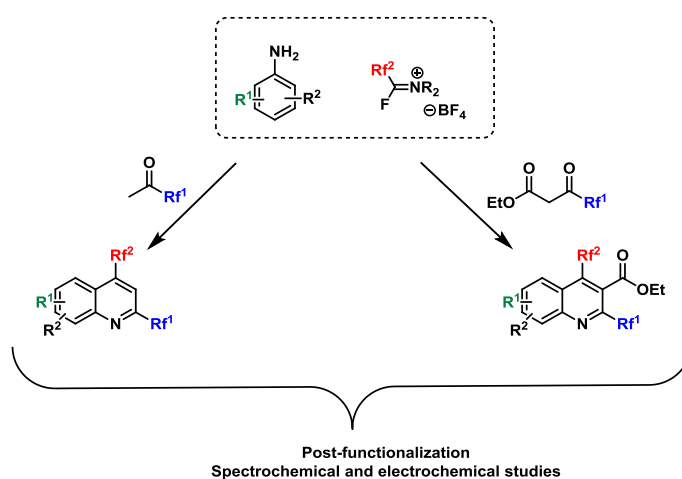


Figure 22: Synthesis of the α,α -difluoro- β -hydroxy ketone motif in the design of modern crop protection compounds

The second project was the synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines using fluorinated iminium salts. Indeed, quinoline derivatives are important and useful building blocks for pharmaceutical and agrochemical purpose due to their broad biological activities. The aim was to develop a new series of bis-functionalized heterocycles (quinolines) substituted by emergent fluorinated groups, based on an industrially applicable approach using FARs. These compounds can be accessed in good yields, under mild condition and with complete regioselectivity. In a second time, we wanted to increase the scope of their action by post-functionalization of the quinoline derivatives in various positions. In parallel electrochemical and spectrochemical studies should evaluate the properties of these new compounds (Figure 23).



R: Me, Et
 R^1 : H, F, OMe, Cl, NMe₂, OCF₃, CF₃, Ph, SPh, fused phenol
 R^2 : H, Me
 Rf^1 : CHF₂, CF₃
 Rf^2 : CHF₂, CHFCI, CHF₂CF₃

Figure 23: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

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All compounds were tested at Bayer CropScience for HTS; as new phytosanitary ingredients. Biological evaluations are not all reported in this manuscript due to confidentiality reasons.

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CHAPTER II

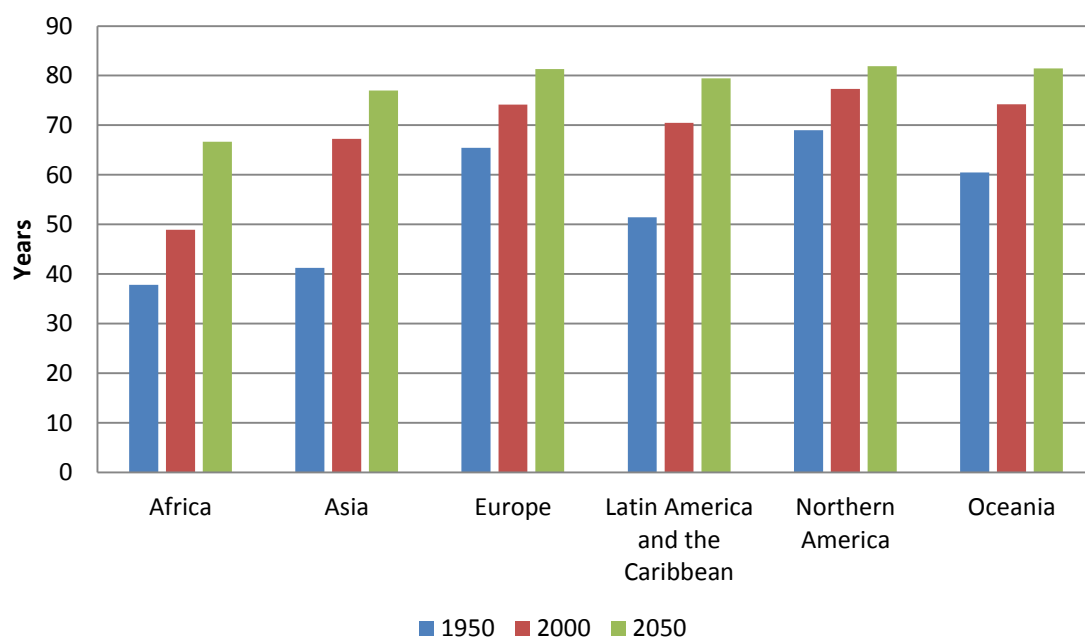
Synthesis of α,α -difluoro- β -hydroxy ketones

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1 INTRODUCTION

Human health improvement, which includes comfortable living condition, development of new drugs, new medical techniques, sanitation and the supply of food and water in quantity and quality helps to raise life expectancies on all continents.³⁴ Indeed we are, in 2017, 7.4 billion, we were 5.7 billion twenty five years ago, and the population will reach 9.9 billion in 2050 (Graphic 2).³⁵⁻³⁶



Graphic 2: Life expectancy at birth for selected periods by continent³⁷

The massive increase of the population forces scientists to find new efficient and economic methods to satisfy the food demand. The main objective is to find new phytosanitary active compounds which are non-toxic, highly active, rapidly decompose, but which are respectful towards the environment to practice a smart and safe crop. Three types of pesticides are known:

- **Herbicides:** used in the elimination of unwanted plant species or to control plants growth.
- **Fungicides:** used principally to control plant pathogens, but also to prevent or cure fungal infection of human being and animals.
- **Insecticides.**

The aim of this project is focused on the last class of pesticides. Insects are causing major damages on the human being and animals' health, but not only. They are also impacting crops, property and clothing, due to their facile adaptability, fecundity and mobility. These damages are apparent and usually caused by their feeding habits. Most insecticides (75% of the worldwide market) act on the Central Nervous System (CNS) and present some phytotoxicity issues. Up to now, four major groups dominate the worldwide market: pyrethroids, organophosphates, methylcarbamates, neonicotinoids. But it is important to note that organophosphates and methylcarbamates inhibit acetylcholinesterases (Enzymes implied in the hydrolysis of acetylcholine. Acetylcholine being an excitatory neurotransmitter whose increased

concentration leads to hyperactivity then to the death of the insect) while others act directly on neuronal receptors and/or ion channels (Figure 24).³⁸⁻⁴⁴

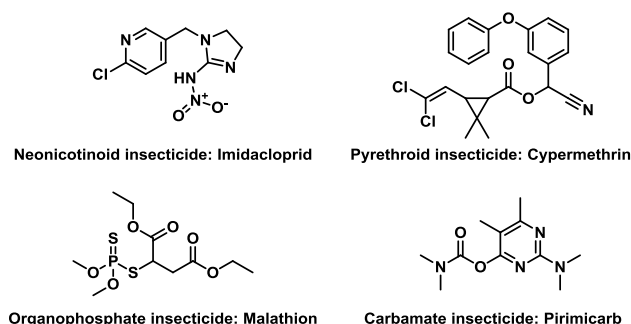


Figure 24: Examples of active substances of insecticides

In this chapter, we are interested in the synthesis of new insecticides acting on the CNS. They can interfere or inhibit the impulse transmission across the synapse between nerve cells. Indeed, the transmission is voltage dependent and influences directly the membrane potential.³⁴

In 1990 Sattelle *et al.* already predicted the importance of targeting CNS in the design of novel insecticides: “An ideal strategy for the design of insecticides would include maximizing the differences in potency of a compound between specific receptors of the target pest and related sites in non-target species. Our increasing knowledge of insect ligand-operated ion channels makes bio-rational design a tool that should enhance the return from existing insecticide discovery approaches. In the near future, the molecular pharmacology of invertebrate neurotransmitter receptors will undoubtedly play an important role in the design of safer, more effective pest control agents.”⁴⁵⁻⁴⁶

1.1 Nervous System

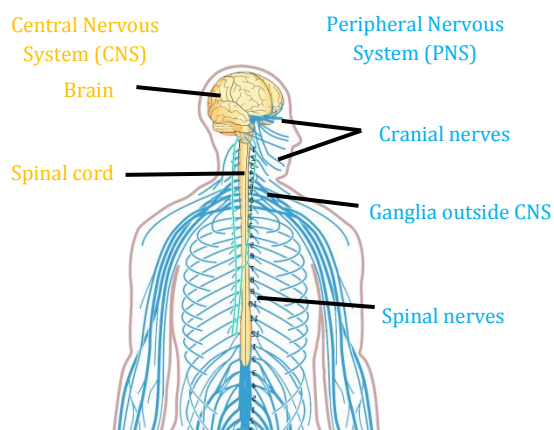
1.1.1 The Nervous System of mammalian

The nervous system is constituted of all nerves. It allows the communication with the outside world, and coordinates the action, on the one side. On the other side, it allows the fast communication between different parts of the body and control inside body mechanisms. Two parts form the nervous system (Figure 25-A):

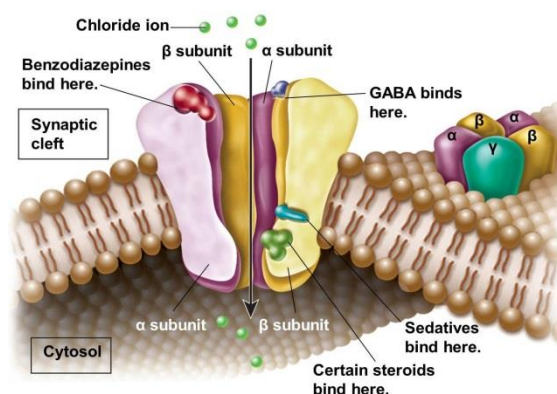
- The central nervous system (CNS) composed by nerves in the brain and the spinal cord located in the skull and the spine.
- The peripheral nervous system (PNS) composed by all other nerves of the body.

In the 1940s, Eugene Roberts *et al.*⁴⁷ demonstrated the presence of a huge concentration of gamma-aminobutyric acid (GABA) in mammalian brain tissue, spinal cord and ganglia, which was implied in a specific neurobiological role. GABA is a neurotransmitter largely distributed in the neuraxis. Although GABA may be found in peripheral tissues, its predominant effect is on the CNS. The activation of GABA receptor usually results in a hyperpolarization of synaptic cells; therefore, it is considered, according to the large number of GABAergic neurons present in the body, as the major inhibitory neurotransmitter of the CNS. At least three different classes of GABA receptor may be activated (Figure 25-B):^{46, 48-56}

- A bicuculline (antagonist) and muscimol (agonist) sensitive GABA_A receptor, which is linked to the chloride channel and is modulated by benzodiazepines, barbiturates and steroids. These modulations modify the conformation of the receptor and activate or inhibit the affinities with other sites due to allosteric alteration.
- A baclofen sensitive GABA_B receptor, which acts on the conductance of Ca²⁺ and K⁺ channels through glycoprotein G interactions (protein which is involved in transmitting signals from the outside to the inside of the cell).
- A baclofen and bicuculline insensitive GABA_C receptor also linked to a chloride channel, but not modulated by benzodiazepines or barbiturates, and which is activated by *cis*-4-aminocrotonic acid (CACA) and *trans*-4-aminocrotonic acid (TACA) GABA analogues.



A: Nervous system



B: GABA and GABA receptor

Figure 25: Nervous system of mammalian (A); GABA receptor, GABA and binding sites (B)⁵⁷

1.1.2 Analogy with the insect's CNS

The central nervous system of insects is constituted of the brain, the ventral ganglia and the ventral nerve cord (Figure 26-A).⁵⁸⁻⁵⁹

By analogy with the mammalian nervous system, the same key organs can be found. Both vertebrates and invertebrates share a brain linked to the spinal cord or to the ventral ganglia and both possess nerves which belong to the PNS. Like vertebrates, invertebrates employ GABA as inhibitory neurotransmitter in the brain and in neuromuscular junctions (Figure 26-B).^{53, 60}

Targeting GABA receptors can be carried out by using GABA receptor antagonists (which will block the opening of the chloride channel) or by using GABA receptor agonists (which will increase the frequency of the chloride channel opening). The toxicity responses of targeting GABA receptors in insects are convulsions and a spontaneous increase of neuronal activity. GABA receptors of insects in the CNS are close to GABA receptors in vertebrates, but they have different binding sites. Three different GABA receptors have been identified in insects (*Drosophila*):^{45-46, 50-51, 54, 60-65}

- The resistance to dieldrin receptor (Rdl), which is similar to GABA_A receptors in vertebrates because it is linked to a chloride channel, activated by benzodiazepines and barbiturates, but insensitive to bicuculline.
- The glycine like receptor of *Drosophila* (Grd).
- The ligand-gated chloride channel homologue 3 (Lcch3).

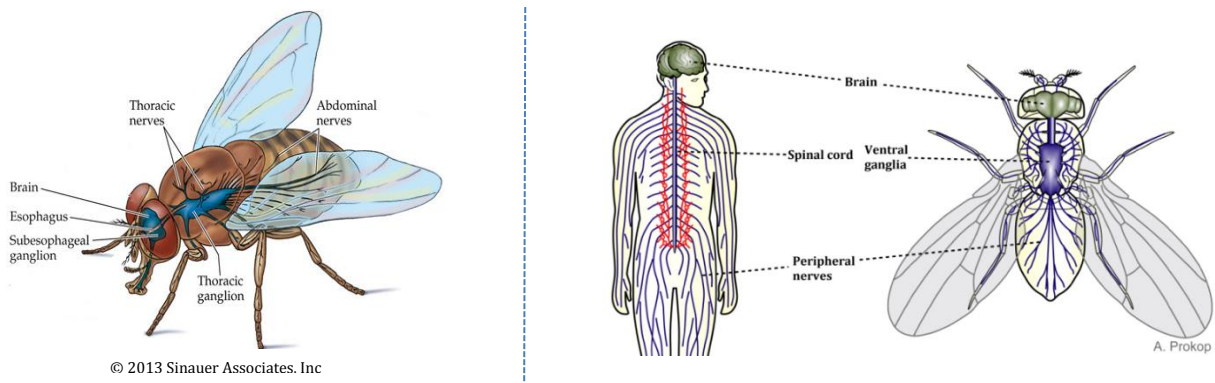


Figure 26: Nervous system of insect (left)⁶⁶; Analogy between vertebrate and invertebrate nervous system (right) modified from⁶⁷⁻⁶⁹

The activation of the GABA_A receptor by two molecules of GABA opens the chloride ion channel, implying a change in the potential of this membrane. This action increases the influx of chloride ions, which leads to a hyperpolarization of this membrane and a decrease of the neurone excitability, which slows down brain activity.^{50, 54, 63, 70}

In a normal cell (A), during the transmission of a nerve impulse, GABA are released from the pre-synaptic neuron (B) and will bind to the post-synaptic neuron GABA receptor (C). This allows the opening of the chloride channel (D) and the flow of ionic chloride into the neuron (E) to regulate the neuronal activity (Figure 27).

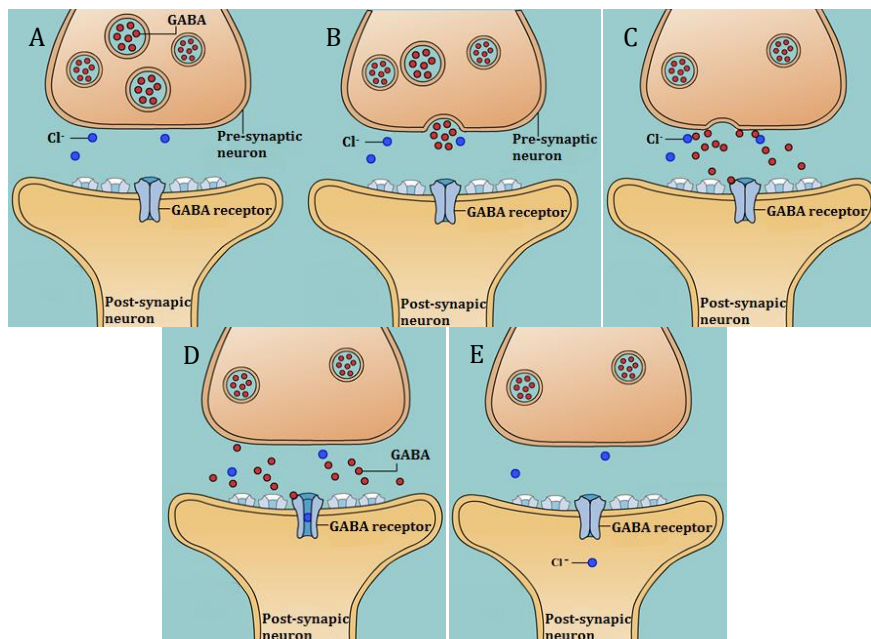


Figure 27: Activity of the cell membrane in presence of GABA⁷¹

However, when GABA receptor agonists are present in the system (A), they will also bind to the GABA receptor (B) and increase the frequency of the chloride channel opening. They allow the passage of multiple ionic chlorides into the post-synaptic neuron (C, D and E). This absence of synaptic control leads to a hyperexcitation of the central nervous system (Figure 28).

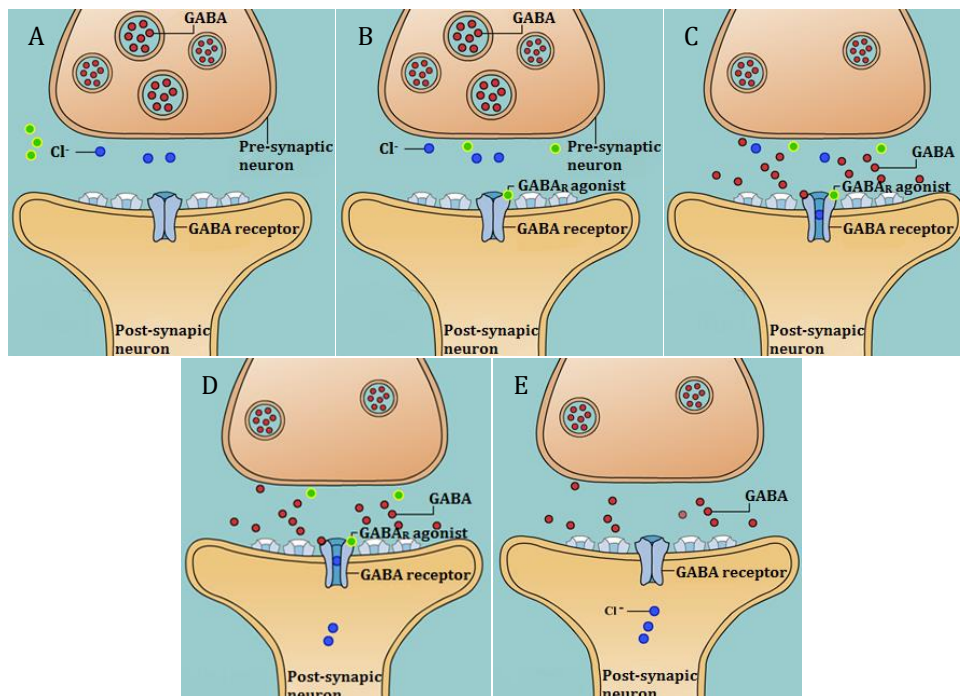


Figure 28: Activity of the cell membrane in presence of GABA receptor agonist⁷¹

For example, avermectins are GABA receptor agonists. They open the GABA receptor and allow the passage of chloride through the channel of the post-synaptic membrane. Insects poisoned by avermectins suffer from ataxia and paralysis (Figure 29).^{34, 72-76}

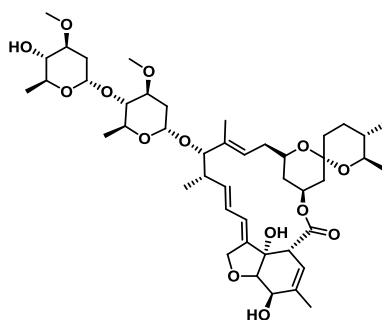


Figure 29: Avermectin B1A

2 STATE OF THE ART

Fipronil was the first phenylpyrazole derivative (Figure 30-A) to be introduced in 1993 for pest control as an anti-parasitic. It has an estimated world market of US\$150 million. Like most of insecticides targeting CNS, it acts as GABA receptor antagonist by blocking the influx of chloride into the post synaptic cell, which produces the same symptoms as avermectin (GABA receptor agonist); hyperpolarization of the cell, that conduces to a hyperactivity of the neuron and a reduction of the transmitted nervous information, which induces convulsion, paralysis and finally death (related to potential balance effects).^{72, 77} Resistance to this type of insecticides, *i.e.* those targeting CNS, often happens among insect population and provokes an important change of the structure of the GABA receptor.^{73, 78}

The purpose of this project was to develop new insecticides acting as GABA receptor agonists (Figure 30-B) based on the synthesis of a α,α -difluoro- β -hydroxy ketones. This motif has already proved its efficacy in the pharmacological field by acting as a renin inhibitor⁷⁹, GABA_B receptor agonist⁸⁰ and antibacterial inhibitor⁸¹ (Figure 31, Figure 32, Figure 33, Table 5). Moreover, the literature reported several active compounds containing the difluoromethylene ketone unit as inhibitor of enzymes like HIV-1 protease⁸²⁻⁸⁶, elastase⁸⁷⁻⁸⁸ and other examples.⁸⁹⁻⁹²

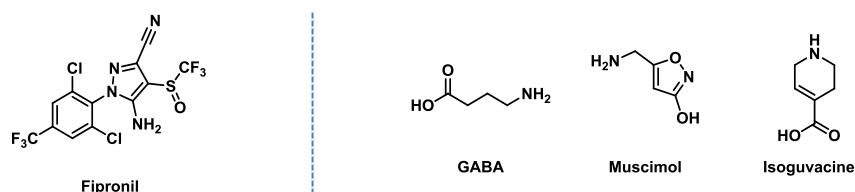


Figure 30: Fipronil structure (left); Chemical structure of GABA and GABA receptor agonists (right)

Examples of active molecules:

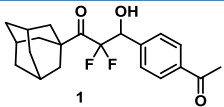
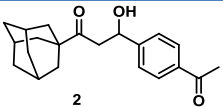
		Compound	GABA _B EC ₅₀ (μ M)
	1	1	24.9 \pm 1.30
	2	2	> 100

Figure 31: GABA_B receptor inhibitor⁴²

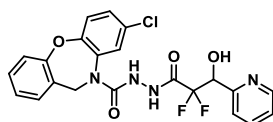


Figure 32: Antagonist PEG₂ inhibitor⁹³

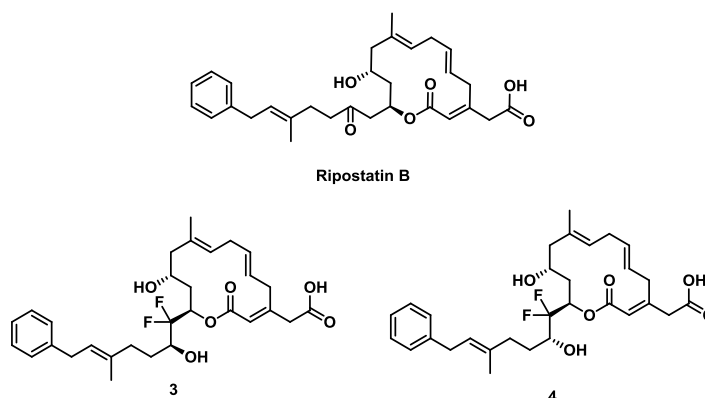
Figure 33: Antibacterial inhibitors⁸¹

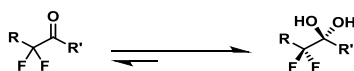
Table 5: Antibacterial inhibitors

Compound	IC ₅₀ (μM) Escherichia Coli	IC ₅₀ (μM) Staphylococcus aureus
Ripostatin B	0.018	0.081
3	3.1	45
4	0.035	0.068

Organofluorine compounds have become incredibly attractive due to properties that fluorine can confer to an active molecule, like lipophilicity, bioavailability, and resistance to metabolic degradation compared to the non-fluorinated analogues.⁹⁴

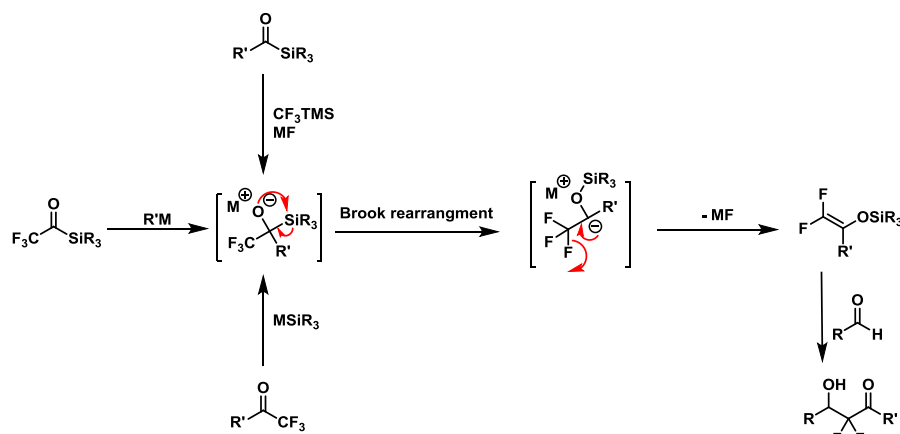
More specifically the difluoromethylene motif is widely used in drug design as a key functionality, because it can act as a bioisostere of hydroxymethylene or etheral group.⁹⁵⁻⁹⁶

Moreover, the presence of a CF₂ in α -position of a ketone activates it towards hydration. Difluoromethyl ketones easily convert into the stable tetrahedral-hydrate, in order to position itself in a tetrahedral-hydrate conformation (Scheme 1).⁹⁷ Enzymes may easily create bonds with this hydrate form, which serves as a transition state mimic toward several proteases such as HIV-1 protease.^{92, 94-95, 98-104}



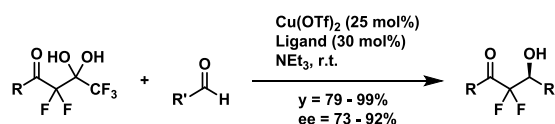
Scheme 1: Tetrahedral-hydrate conformation of difluoromethyl ketone

The development of chemical strategies to access α,α -difluoro- β -hydroxy ketones is widely studied in literature. They are usually obtained by selective mono-defluorination of the corresponding trifluoromethyl moiety or from protected enols. Most reactions use difluoroenol silyl ethers as intermediates. The effective combination of acylsilane and trifluoromethyltrimethylsilane leads to the key intermediate difluoroenoxy silane. They are formed *in situ* after a Brook rearrangement and a fluoride elimination process, leading to the formation of a reactive nucleophile. Further reaction with aldehydes as electrophiles leads to the targeted α,α -difluoro- β -hydroxy ketones. The aldol reaction can be also promoted in some cases by the addition of a catalytic amount of ammonium fluoride. Nevertheless, this reaction is usually slowed down by the poor stability of the trimethylsilyl fluoroenol ethers (Scheme 2).¹⁰⁵⁻



Scheme 2: Brook rearrangement/ Fluoride elimination sequence and addition onto an electrophile

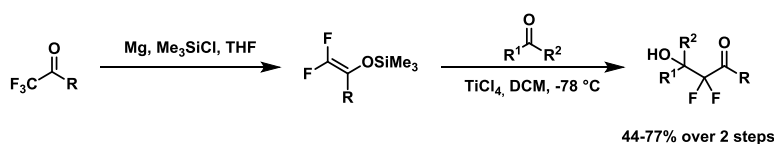
Such key intermediates may also be obtained *in situ* from trifluoromethyl- α,α -difluoro- β -keto *gem*-diols which react with aldehydes in an enantioselective way using copper catalysis and a chiral ligand to provide the targeted compounds in high yields and enantiomeric excess (ee) (Scheme 3).⁹⁴



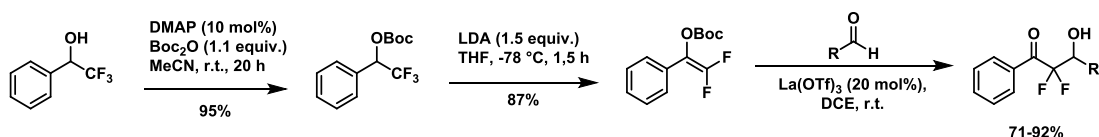
Scheme 3: Enantioselective aldol reaction copper catalysed

The same type of reaction can be carried out by two other strategies. Either using $Mg(0)$, which promotes defluorinative silylenolization of trifluoromethyl ketones (Scheme 4).¹¹⁶⁻¹¹⁷ Or from *Boc*-protected difluoroenols which are obtained in two steps from 1-phenyl-2,2,2-trifluoroethanol using a catalytic amount of 4-dimethylaminopyridine (DMAP), followed by β -elimination of fluoride when treated with lithium diisopropylamide (LDA) (Scheme 4).⁸⁹ These intermediate finally lead to the formation of the desired α,α -difluoro- β -hydroxy ketones using a catalytic amount of $La(OTf)_3$ or $TiCl_4$ as Lewis acids.

Reaction 1:

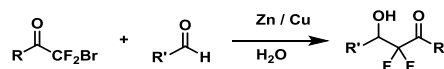


Reaction 2:



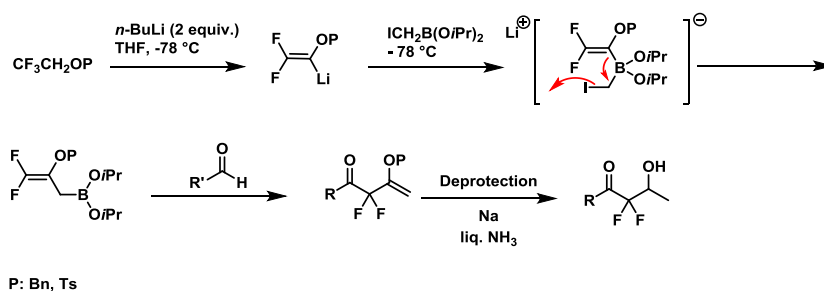
Scheme 4: Reaction 1: Magnesium-promoted selective defluorinative silylation of trifluoromethylketone. Reaction 2: Synthesis of difluoroenol *O*-*Boc* ester from trifluoromethyl alcohol

The targeted molecules may also be synthesised by a Reformatsky reaction between a bromodifluoromethyl ketone and an aldehyde under mild conditions (Scheme 5). However, the major drawbacks of the Reformatsky reaction are the use of stoichiometric amounts of organometallic reagents which create large amounts of waste.¹¹⁸⁻¹²³

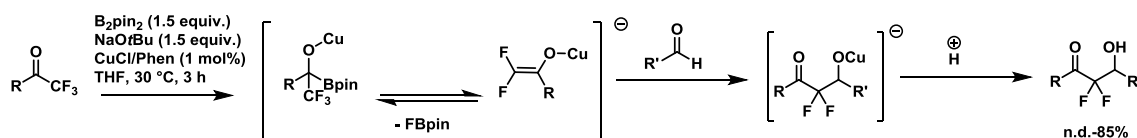


Scheme 5: Reformatsky reaction

Instead of starting from the difluoroenol silyl ether, it is possible to perform the synthesis from the *O*-protected trifluoroethyl ether. The starting material is treated with 2 equivalents of *n*-BuLi in THF to provide the difluorovinyl lithium intermediate. It is further submitted to a homologation reaction with diisopropyl iodomethylboronate. The next step implying the allylation of an aldehyde leads to the corresponding homoallylic alcohol in good yield. This product undergoes then deprotection in liquid ammonia in presence of sodium to provide the targeted molecule in 75-82% yields (Scheme 6).^{92, 124-126}

Scheme 6: Preparation and reaction of γ,γ -difluoroallyl-boronates

As an alternative to an already known methodology, the formation of the difluorohydroxy ketone motif can be realized using a copper-catalysed reaction of trifluoromethylketone with aldehyde and B_2pin_2 in presence of NaOtBu . All compounds were obtained in moderate to good yield but the methodology requires optimization (Scheme 7).¹²⁷



Scheme 7: Aldol reaction via a copper difluoroenolate

The introduction of the α,α -difluoro- β -hydroxy ketone motif becomes more and more studied and finds a certain interest. Indeed, many methodologies are published to access this type of moiety, such as defluorinative alkylation of *N,O*-acetals followed by a Reformatsky type reaction and a deprotection by catalytic hydrogenolysis using palladium among many others.^{95, 128-130}

3 OVERVIEW OF THE SYNTHETIC STRATEGY

The purpose of this project was to synthesize a series of molecules potentially active as GABA receptor agonists by combining the α,α -difluoro- β -hydroxy ketone motif and two aromatic rings bearing different substituents (Figure 34).

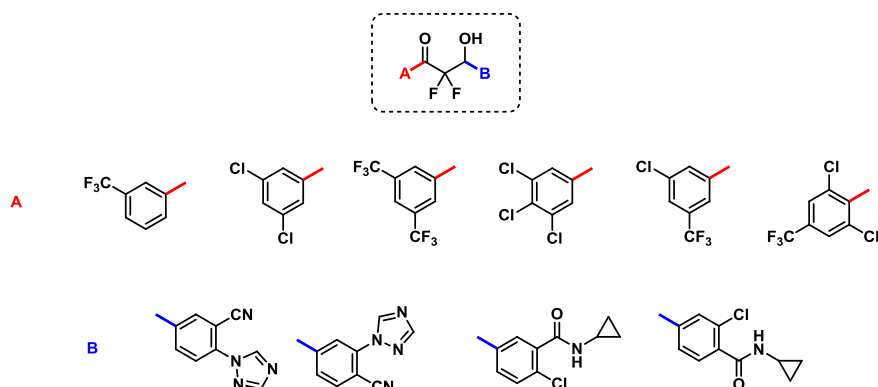


Figure 34: Defined substituents in the design of the target molecule

The targeted molecules were designed according to the potential activity of its substituents. Indeed, we have noticed that the α,α -difluoro- β -hydroxy ketone motif was largely described in the literature for its properties in the pharmacological field. The substitutions on aromatic rings were chosen according to their potential properties in the agrochemical field. Those substituents play the role of the lipophilic part and we have decided to combine both motifs (aromatic ring and α,α -difluoro- β -hydroxy ketones) in order to design new insecticides targeting the CNS.

On the first aromatic ring (**A**), two types of substituents were chosen:

- The trifluoromethyl moiety, which may enhance the physico-chemical properties of the molecule according to the previously presented benefits of fluorine.
- The chlorine substituent, which can be used as precursor for the introduction of various functional groups.¹³¹

On the second aromatic ring (**B**), other substituents were chosen, according to two families:

- The first family conjugates both chlorine and cyclopropylamide:
 - Chlorine may be used for the same reason as previously presented.
 - The cyclopropyl moiety is considered as an alkene bioisostere, which allows the retention of the *cis*-orientation and presents a high metabolic stability.¹³²⁻¹³⁵
 - Amides are widespread functionalities in both natural products and synthetic materials (Figure 35).¹³⁶

A recent survey indicates that more than 54% of biological active compounds contain an amide group.¹³⁷⁻¹³⁹ Amides are known for their high stability due to the presence of the N-C-O bond allowing resonance stabilization. They also possess a certain inertness which limits their photo-degradation and offers the possibility to perform reactions under harsh synthetic conditions.^{135, 140-141} In the agrochemical field, the development of new pesticides bearing an amide functionality becomes common due to their broad bioactive spectrum as antifungal¹⁴²⁻¹⁴³, insecticidal¹⁴⁴ and herbicidal¹⁴⁵ ingredients.

CHAPTER II: Synthesis of α,α -difluoro- β -hydroxy ketones

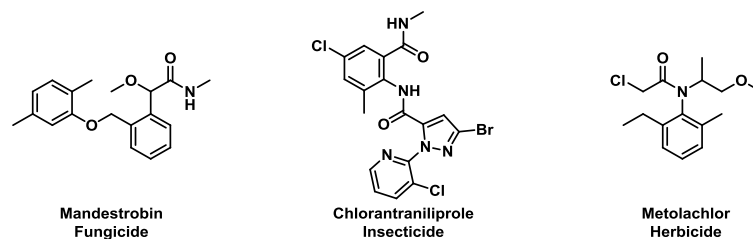


Figure 35: Amide motif present in natural and synthetic products

- The second family conjugates both triazole and nitrile moieties:
 - Triazole has been the principal topic of numerous reviews.^{141, 146} The triazole moiety presents remarkable electronic properties¹⁴⁷ and a wide range of biological activities such as fungicidal, insecticidal and bactericidal (Figure 36).¹⁴⁸⁻¹⁵⁴

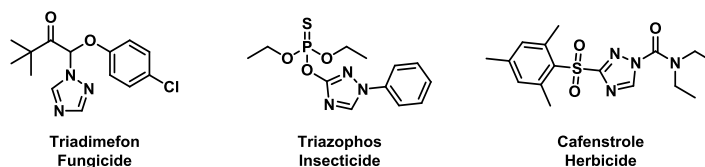


Figure 36: Examples of active compounds bearing a 1,2,4-triazole moiety

- The nitrile moiety is an important chemical group in the pharmaceutical field. Approximately 30 nitrile-containing pharmaceuticals are prescribed for a diverse variety of medical indications and 20 more lead compounds are currently in clinical development. The nitrile group is not particularly electrophilic, it is quite robust, not easily metabolized or hydrolyzed and usually passes through membranes unaltered. It plays a key role as hydrogen bond acceptor and may also serve as a bioisostere of hydroxyl or carboxyl group. It is a powerful electron-withdrawing group.¹⁵⁵⁻¹⁵⁷

No such compounds were prepared by means of the methods presented above and all compounds developed during this study are new. The employed methodology for this study also involves the formation of a difluoroenolate intermediate, generated *in situ* under mild reaction conditions by a trifluoroacetate release process.¹⁵⁸⁻¹⁶⁵

The targeted series of molecules would be synthesized thanks to a convergent pathway. We first realize the synthesis of the two key intermediates **1** and **2**, and coupled them in a last step (Figure 37).

Key intermediates **1** would be obtained in three steps. The first one is a halogen-metal exchange to provide the ketone from the brominated precursor, followed by a Claisen condensation in presence of trifluoroethyl trifluoroacetate and finally a difluorination reaction allowing the formation of the desired, 1-aryl-2,2,4,4,4-pentafluoro-3,3-dihydroxy-butanone.

Key intermediates **2** would be obtained by various methods depending on the desired substitution pattern.

A final coupling step involving key intermediates **1** and **2** affords then the target molecules that to be sent to Bayer CropScience (Monheim, Germany) to test their biological activities as GABA receptor agonists.

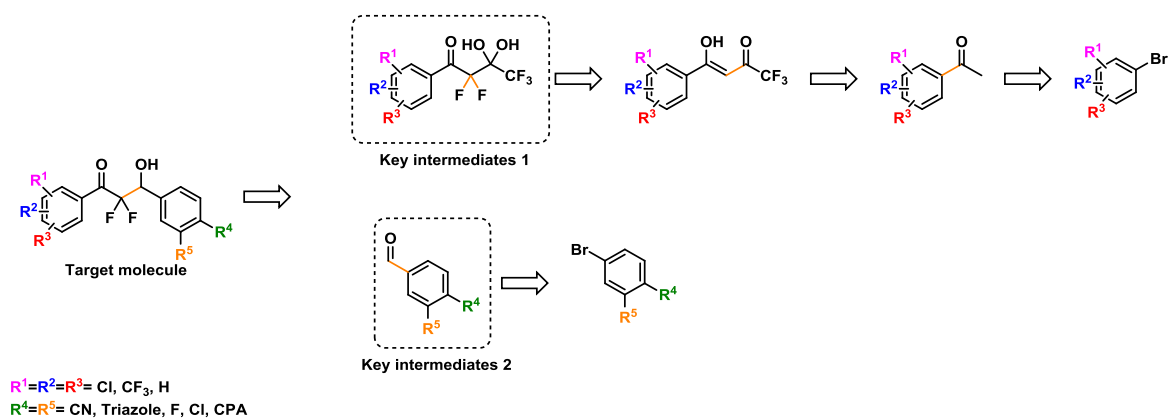


Figure 37: Retrosynthetic scheme of the synthesis of α,α -difluoro- β -hydroxy ketones

4 RESULTS AND DISCUSSIONS

4.1 Synthesis of key intermediates 1

The first part of this project was dedicated to the synthesis of key intermediates **1** (Figure 38).

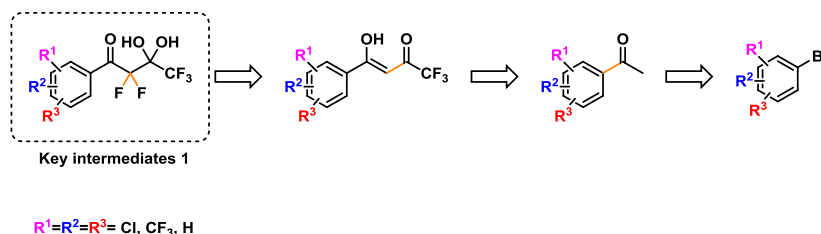
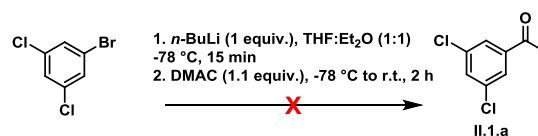


Figure 38: Retrosynthesis of key intermediates 1

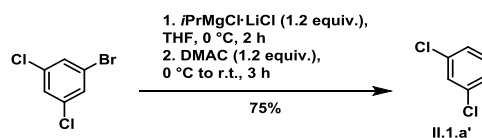
4.1.1 Synthesis of ketones II.1

Our first attempt to synthesize ketone **II.1.a** was a bromine-lithium (Br/Li) exchange, followed by trapping with an acetyl equivalent. Indeed, this reaction should be fast providing the desired ketone (Scheme 8). However, in our case only degradation was observed.



Scheme 8: Synthesis of ketone II.1.a

Instead of using an organolithium reagent, we performed then the reaction using the “Turbo Grignard reagent” ($i\text{PrMgCl}\cdot\text{LiCl}$). This reagent was preferred to control the halogen-metal (bromine-magnesium [Br/Mg]) exchange and avoid the degradation caused by the use of an organolithium reagent (Scheme 9). In this case, 75% of the reduced compound was obtained in addition to degradation products.

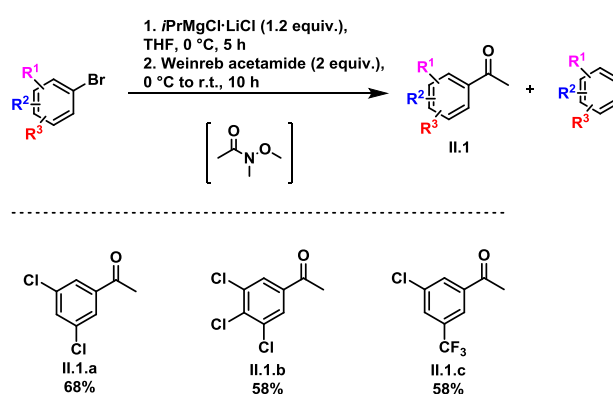


Scheme 9: Failed synthesis of ketone II.1.a using the Turbo Grignard

This probably means that dimethylacetamide (DMAC) acts as an acid rather than as an electrophile under these conditions.

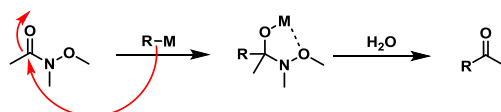
We then applied the same strategy by replacing DMAC by *N*-methoxy-*N*-methylacetamide. Nahm *et al.* reported that such reagent smoothly reacts with Grignard and organolithium reagents to afford the corresponding ketones. *N*-Methoxy-*N*-methylacetamide was routinely prepared from commercially available *N*-methoxy-*N*-methylamine hydrochloride salt and acetyl chloride.¹⁶⁶⁻¹⁶⁷

When *n*-BuLi was used to perform the Br/Li exchange, a mixture between the starting material, the reduced compound (**II.1.a'**) and the desired ketone (**II.1.a**) was obtained. Indeed the time of lithiation is important; however the same ratio of compounds was obtained as the reaction was allowed to proceed from one to thirty minutes.¹⁶⁸ Although, the Br/Li exchange occurs rapidly in THF, the use of Turbo Grignard was favored to control the reaction and avoid degradation during the Br/Mg exchange. All ketones were synthesized using the Turbo Grignard and *N*-methoxy-*N*-methylacetamide as Weinreb amide. They were obtained in *ca.* 60% yield and the remaining 40% correspond to the reduced compound (Scheme 10).



Scheme 10: Synthesis of ketones **II.1.a-c**

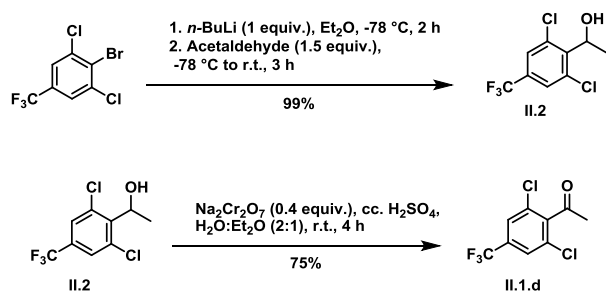
Unlike the reaction with DMAC, the reaction using the Weinreb amide involves a chelate as intermediate, in which the metal is complexed to the oxygen atoms. The complex is sufficiently stable to not be decomposed during the reaction. Then, after hydrolysis the ketone was released (Scheme 11).



Scheme 11: Chelate complex formed from the use of Weinreb amide

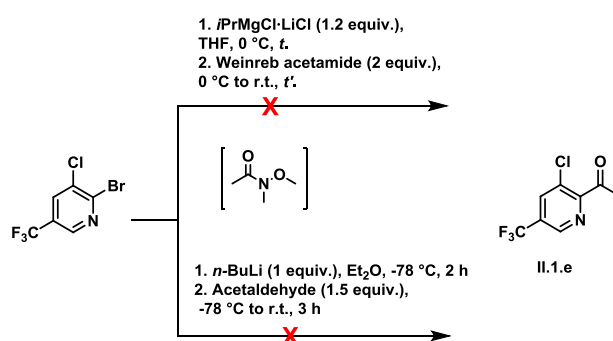
The synthesis of ketone **II.1.d** from commercially available 4-bromo-3,5-dichlorobenzotrifluoride was not efficient using the Turbo Grignard or *n*-BuLi and DMAC or the Weinreb acetamide. In both cases, only the reduced compound was observed in mixture with unknown side products. Nevertheless, the desired ketone **II.1.d** was obtained in two steps. First, a Br/Li exchange followed by trapping with acetaldehyde to provide the secondary alcohol **II.2**.¹⁶⁹ Then, a final oxidation using sodium dichromate afforded ketone **II.1.d** (Scheme 12).

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Scheme 12: Synthesis of ketone II.1.d

The attempts to synthesize ketone II.1.e from commercially available 2-bromo-3-chloro-5-(trifluoromethyl)pyridine always led to the recovery of starting material (Scheme 13).

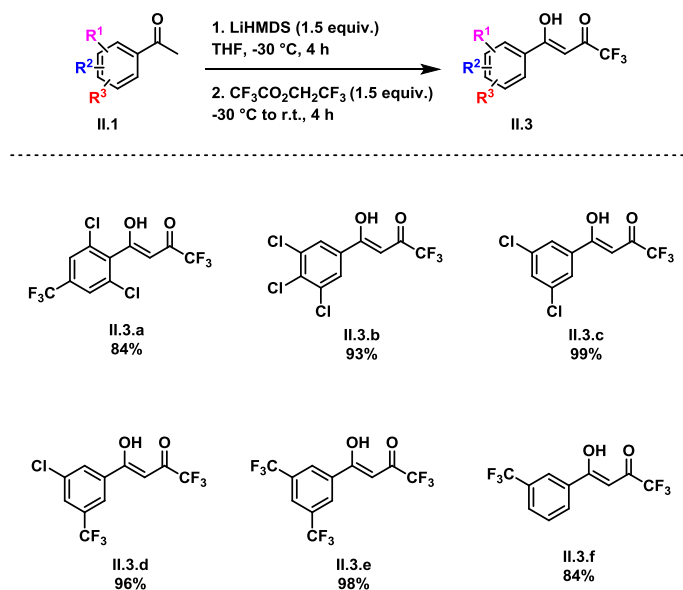


Scheme 13: Attempts in the synthesis of 1-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)ethan-1-one (II.1.e)

4.1.2 Formation of compounds II.3 by Claisen condensation

Ketones II.1.a-d were then submitted to a Claisen condensation with trifluoroethyl trifluoroacetate. Compounds II.3 were obtained with good to excellent yields without any further purification (Scheme 14).^{80, 158}

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Scheme 14: Claisen condensation affording II.3.a-f

Based on this last transformation, we can suppose the formation of eight potential structures **II.3.a-f**. Indeed as examples, structures 1 and 2 are configurational isomers (Z/E), structures 5 and 7 are conformational isomers and finally structures 2 and 3 are tautomers. All structures were not separable from each other and were not visible using usual techniques. However, we postulated that one of them should be the major one. In fact, structures 1 and 3 should be favored due to the possible formation of a hydrogen bond between the hydroxyl and the ketone moiety and minimization of the 1,3-allylic strain (Figure 39).

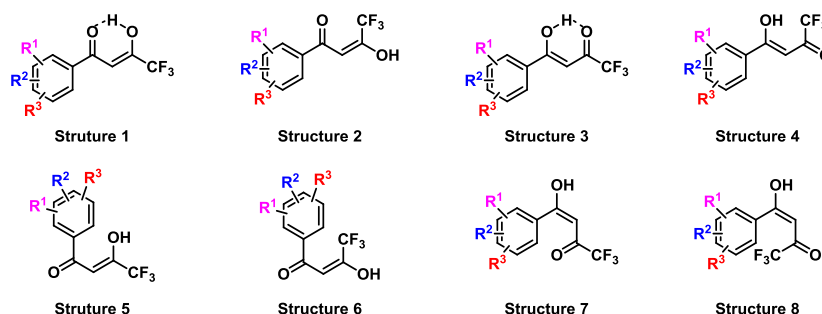
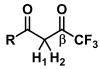




Figure 39: Postulates for the right structure of compounds II.3

Salman *et al.* in 1990 and Sloop *et al.* in 2006 put forward that the chemical shift in proton, carbon and fluorine NMR allows to determine the correct structure of these compounds (Table 6).¹⁷⁰⁻¹⁷¹ Obviously, according to their data the configuration is R-group-dependent and in our case, spectroscopic evidence seems to confirm the formation of structure 3. Our hypothesis was confirmed by single crystal X-ray diffraction studies performed for compound **II.3.f**. We can also notice the presence of the intramolecular hydrogen bond between the ketone and the hydroxyl group. From this result, we have extended this postulate to all compounds of the series (**II.3**) (Figure 40).

Table 6: NMR spectral Information for trifluoromethyl- β -diketones

Units	R	Keto 	Enol a 	Enol b 
δ (ppm) J (Hz)	Alkyl Aryl	^1H : $\text{H}_2 \sim 3.90$ ^{19}F : $\sim -80 - -84$ ^{13}C : $\text{C}_\beta > 200$	^1H : $\text{H}_3 \sim 15-18$ ^{19}F : $\sim -73 - -78$ ^{13}C : $\text{C}_\beta > 170$ $^1J_{\text{C}-\text{F}} \sim 285$ $^2J_{\text{C}-\text{F}} \sim 34-36$	^1H : $\text{H}_3 \sim 12-15$ ^{19}F : $\sim -73 - -78$ ^{13}C : $\text{C}_\beta > 160$ $^1J_{\text{C}-\text{F}} \sim 270$ $^2J_{\text{C}-\text{F}} \sim 32-36$

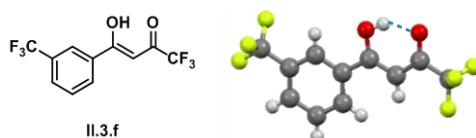
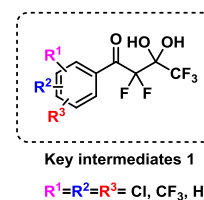


Figure 40: Crystallographic analysis of compound II.3.f

4.1.3 Formation of α,α -difluoro- β -trifluoromethyl-dihydroxy ketones II.4 by difluorination reactions

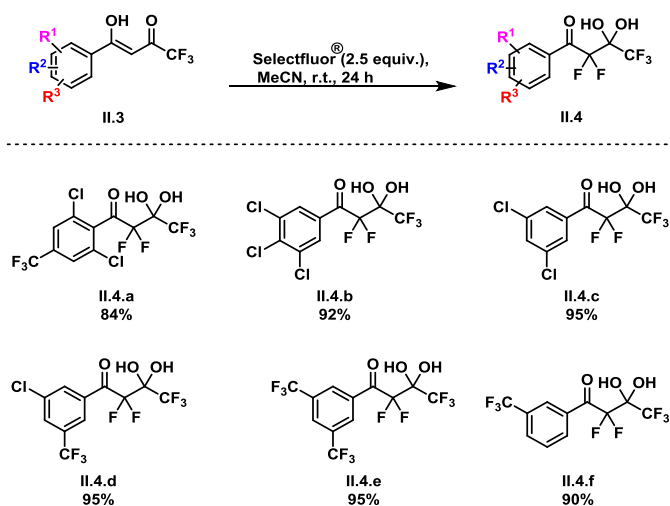
The last step towards the key intermediates **1** was the difluorination reaction in presence of Selectfluor® in MeCN. Trifluoromethyl- β -hydroxy ketones **II.3** were mixed with 2.5 equivalents of Selectfluor® to provide α,α -difluoro- β -trifluoromethyl-dihydroxy ketones **II.4**.

In order to avoid the formation of a mixture of fluorinated products, 2.5 equivalents are used to complete the reaction (Scheme 15).¹⁷²



Due to the presence of two fluorinated electron-withdrawing groups on the molecule, the carbon of the carbonyl group becomes highly electrophilic and this carbon might readily react with moisture from air or water to form hydrates.¹⁷³ The ketone moiety acts as a hydrogen bond acceptor, while the *gem*-diol can play the role of either a donor and/or an acceptor of hydrogen bond from neighboring groups. This capacity to form inter- and intra-molecular hydrogen bonds increases aqueous solubility and under this form, such compounds can possess an activity as transition state mimics.^{80, 174} As mentioned earlier, α,α -difluoromethyl ketones exist in water under hydrated form, which imparts to the molecules a tetrahedral shape. This tetrahedral intermediate is formed during the enzymatic transition state of amide bond hydrolysis of a peptide substrate. Exchange of the amide group which is enzymatically cleaved during this transition state by a fluorinated ketone can act as a transition state analogue inhibitor (Figure 41).¹⁷⁵⁻¹⁷⁶

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Scheme 15: Difluorination reaction of compounds II.3 into compounds II.4

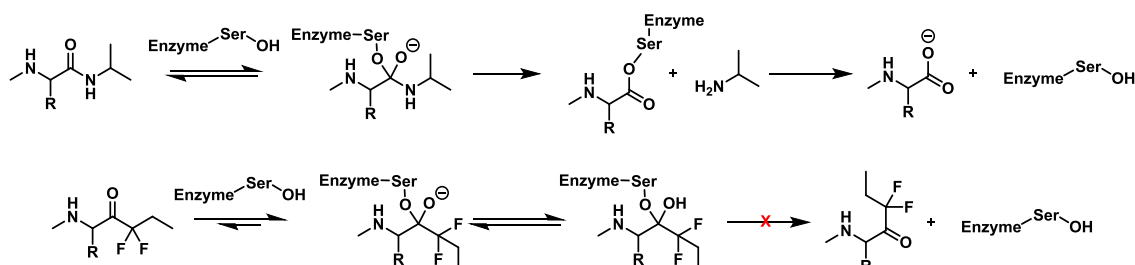


Figure 41: Serine protease inhibition by a α -amido trifluoromethylketones¹⁸

X-ray diffraction studies of compounds **II.4.b** and **II.4.c** confirmed the presence of *gem*-diols. We also can notice the presence of inter- and intra-molecular hydrogen bonds between oxygens O¹ and O³ of the same compound but also between other molecules (Figure 42).

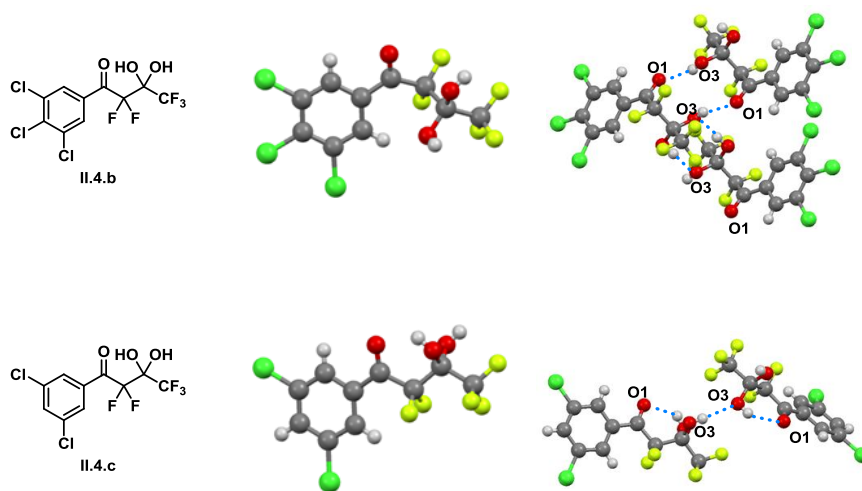


Figure 42: Crystallographic analysis of compounds II.4.b and II.4.c

4.2 Synthesis of key intermediates 2

The second part of this chapter will concern the synthesis of key intermediates 2 (Figure 43).

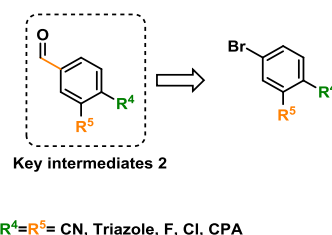
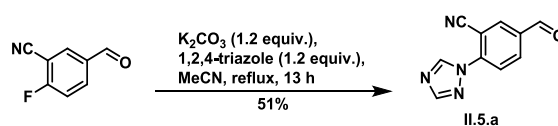


Figure 43: Retrosynthesis of key intermediates 2

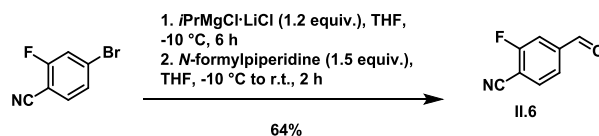
4.2.1 Synthesis of 4- or 5-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitriles II.5

Aldehyde **II.5.a** was obtained after a nucleophilic aromatic substitution of the fluorine by 1,2,4-triazole in DMF in 51% yield.¹⁷⁷⁻¹⁷⁸ MeCN, which presents the same properties of polar aprotic solvent as DMF, was used to replace it. Indeed, the reaction performed in DMF caused the formation of an emulsion during the aqueous treatment and we thought that it can explain why most of the product was lost. However, the results obtained in MeCN were the same (same yield: 51%), but the final compound (**II.5.a**) was obtained cleaner (Scheme 16).



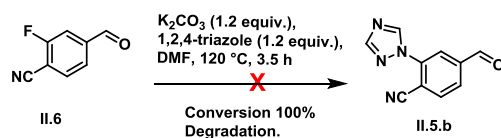
Scheme 16: Synthesis of 5-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.5.a

The synthesis of its regioisomer was not described in literature and difficult to perform. The first step was a formylation leading to **II.6**, using *i*PrMgCl in THF in presence of *N*-formylpiperidine as aldehyde source.¹⁷⁹ The aldehyde **II.6** was obtained in 44% yield albeit with the reduced compound. When performing the same reaction in presence of *i*PrMgCl•LiCl, we managed to reach 64% yield (Scheme 17).



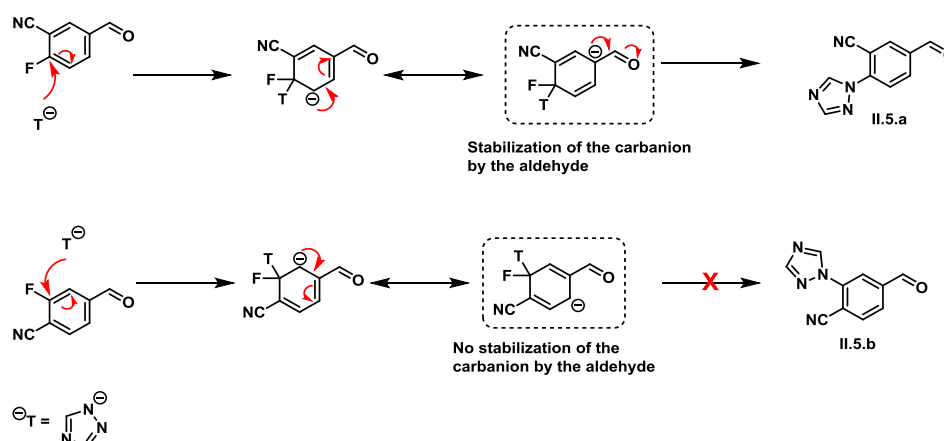
Scheme 17: Synthesis of 2-fluoro-4-formylbenzonitrile II.6

Once the aldehyde **II.6** obtained, we tried to introduce the triazole moiety using the same procedure as for **II.5.a**. The conversion was total but after work-up, NMR analysis indicated mostly degradation (Scheme 18).



Scheme 18: First attempt in the synthesis of 4-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.5.b

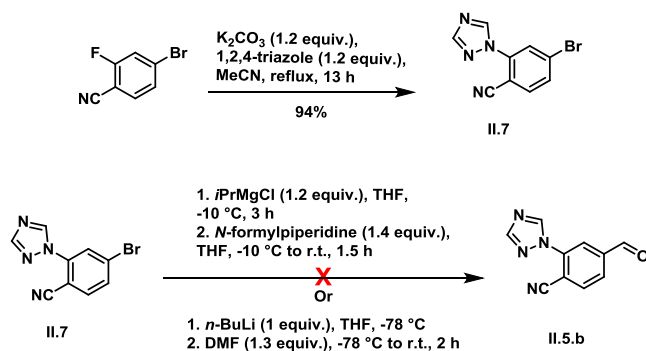
The low reactivity might be explained by the non-stabilization of the carbanion during the nucleophilic aromatic substitution process. Indeed, for the synthesis of **II.5.a**, both the formyl and the nitrile group stabilize the carbanion in the Meisenheimer intermediate. However, during the synthesis of **II.5.b**, the intermediate carbanion would be stabilized less efficiently by the formyl group (Scheme 19).



Scheme 19: Meisenheimer intermediates toward compounds II.5.a and II.5.b

Another possibility to get the desired compound **II.5.b** was to start by the addition of 1,2,4-triazole on the commercially available 4-bromo-2-fluorobenzonitrile. The reaction was performed in MeCN under reflux and compound **II.7** was obtained without any purification in quantitative yield. Then, **II.7** was submitted to a formylation reaction to provide the desired aldehyde **II.5.b**. Analogously to the first pathway, we tried to convert the bromine atom into a formyl group using *i*PrMgCl in presence of *N*-formylpiperidine as aldehyde source. Full conversion was observed. After work-up and purification by means of column chromatography, several fractions were obtained, mostly corresponding to degradation and unknown products with either loss of triazole or addition of isopropyl onto an undetermined position of the molecule.

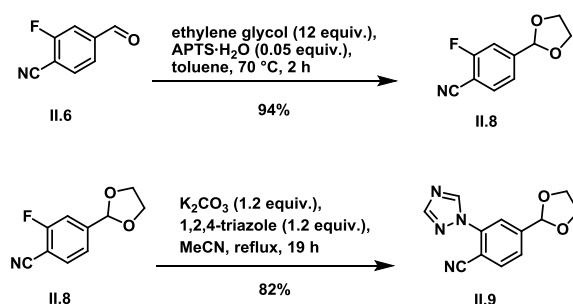
In a second attempt, we tried to introduce the aldehyde function by Br/Li exchange using *n*-BuLi. Once again, the desired compound **II.5.b** was not isolated and only degradation was observed by NMR analysis after work-up (Scheme 20).



Scheme 20: Second attempt in the synthesis of 4-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.5.b

We then decided to come back to aldehyde **II.6** and protect it as a dioxolane **II.8**.¹⁸⁰ Indeed, we suspected various side reactions on the unprotected aldehyde, due to the slower S_{NAr} when the latter group was *meta* to fluorine and thus unable to stabilize the Wheland intermediate.

To confirm our hypothesis, we firstly performed the protection of aldehyde **II.6** into the corresponding dioxolane **II.8** in toluene in presence of ethylene glycol and a catalytic amount of APTS \cdot H₂O. **II.8** was obtained in quantitative yield. The second step was the introduction of the 1,2,4-triazolyl group. The desired protected 4-(1,3-dioxolan-2-yl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.9** was obtained in 82% yield under reflux in MeCN without any purification, which confirms our hypothesis (Scheme 21).

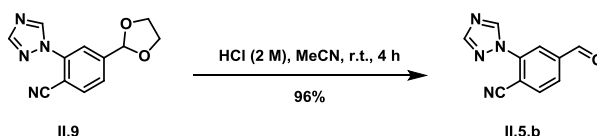


Scheme 21: Protection and nucleophilic aromatic substitution on 2-fluoro-4-formylbenzonitrile II.6

The last step was the deprotection of the aldehyde. It was important to find smooth conditions to avoid hydrolysis of the nitrile moiety into an amide or carboxylic acid.

In a first attempt, we used a catalytic amount of APTS•H₂O in acetone under reflux. After 6 h, the conversion was not complete even after the addition of APTS•H₂O in stoichiometric amount. After 24 h, degradation products appeared. Next, we tried using iron supported on silica in acetone.¹⁸¹ After 24 h, only the starting material was recovered.

Finally, we carried out the addition of HCl 2M in a solution of **II.9** in MeCN at room temperature.¹⁸⁰ After 4 h, 4-formyl-2-(1*H*-1,2,4-triazol-1-yl)benzonitrile **II.5.b** was obtained in quantitative yield (Scheme 22).



Scheme 22: Deprotection of 4-(1,3-dioxolan-2-yl)-2-(1*H*-1,2,4-triazol-1-yl)benzonitrile **II.9**

4.2.2 Synthesis of 2-chloro-*N*-cyclopropyl-4- or 5-formylbenzamides **II.11**

For this reaction, two pathways were possible, either starting with a halogen-metal exchange and formylation or by the coupling between the carboxylic acid and the primary amine.

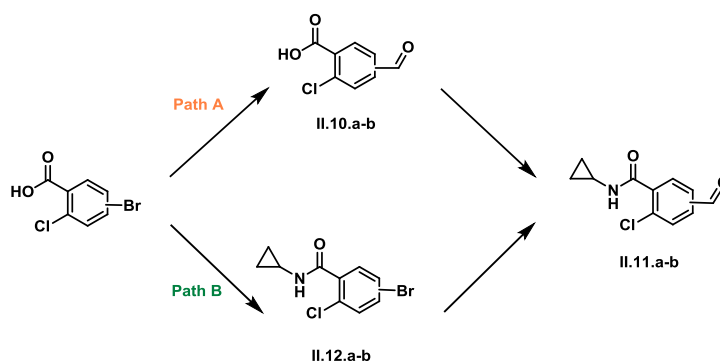
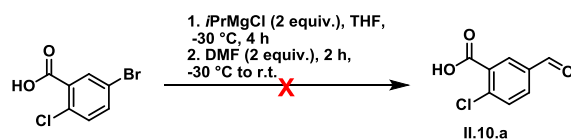


Figure 44: Synthesis strategies

In both cases an acidic proton remains on the molecule and may disturb the formation of the desired compounds (Figure 44).

4.2.2.1 Path A: halogen – metal exchange

We decided to start with a Bouveault reaction which converts an aryl halide into an aldehyde using an organometallic reagent.¹⁸² We performed this transformation *via* X/Mg exchange using *i*PrMgCl followed by DMF addition (Scheme 23).¹⁸³⁻¹⁸⁴ Under these conditions, only degradation products were observed in mixture with the reduced compound which means that the insertion of magnesium between the C-Br bond was effective, but the addition onto DMF failed.

Scheme 23: Mg/Br exchange using *iPrMgCl* to provide the 2-chloro-5-formylbenzoic acid II.10.a

Then, we tried to use *iPrMgCl*•LiCl instead of *iPrMgCl*, because addition of lithium chloride (LiCl) is assumed to break the formation of aggregates (**1**) to allow the formation of the complex (**2**). The nucleophilic property of *iPr* is enhanced due to the presence of a negative charge on the magnesium caused by the lithium counter-anion (Figure 45). Under this form, it seems that the reactivity for performing X/Mg exchange is enhanced, however the reaction between the resulting organomagnesium and electrophiles remain hard to perform.¹⁸⁵⁻¹⁸⁷

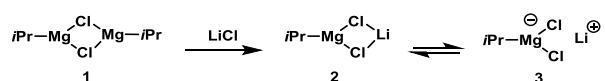
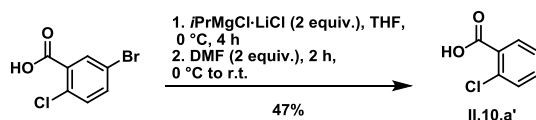
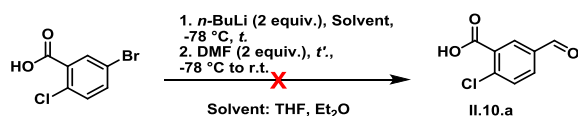


Figure 45: Isopropylmagnesium chloride lithium chloride complex formation

Once again, the formation of the magnesium intermediate was confirmed thanks to the observation of the reduced compound by GCMS analysis and after addition of the electrophile and treatment, a mixture between the starting material and the reduced compound (**II.10.a'**) in 60:40% ratio was obtained (Scheme 24).

Scheme 24: Br/Mg exchange using *iPrMgCl*.LiCl to provide 2-chloro-5-formylbenzoic acid II.10.a

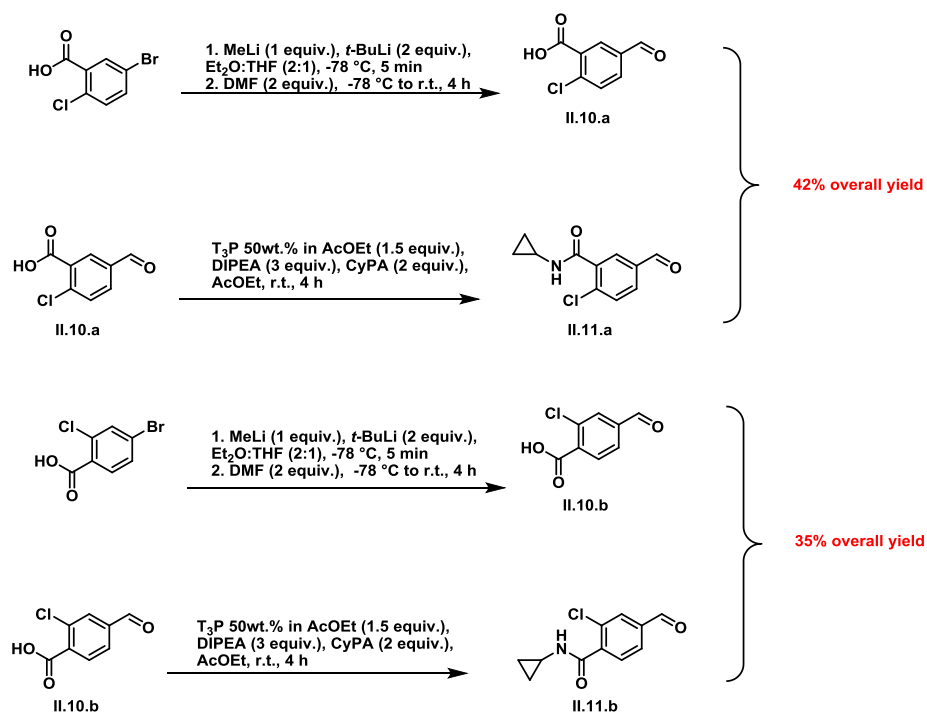
As the reaction was faster and can be performed at lower temperature, the Br/Li exchange was expected to afford the desired compound (**II.10.a**). The reaction times and various solvents were studied. Two equivalents of *n*-BuLi were used to allow the concomitant acid deprotonation and the Br/Li exchange. In one case only (not reproducible), 4% of the desired aldehyde (**II.10.a**) was observed (but not isolated) in mixture with side products (Scheme 25).

Scheme 25: Li/Br exchange using *n*-BuLi to provide 2-chloro-5-formylbenzoic acid II.10.a

Next, we employed a mixture of MeLi, which allowed the deprotonation of the acidic proton (carboxylic acid), and *t*-BuLi for the bromine-lithium exchange, being more reactive (pKa = 53; *n*-BuLi: pKa = 50) and less nucleophilic than other lithium bases. The use of *t*-BuLi was also favored, because it usually gives cleaner halogen-lithium exchanges and less side reactions. Two equivalents have to be employed for irreversible generation of lithium halide, isobutane and isobutene.¹⁸⁸

In presence of this mixture only 50% conversion was obtained and final products were always obtained in mixture with side products or starting material.

Several reactions were tried to define the right time of lithiation (5, 45, 120 min) and each time only 50% of expected compounds (**II.10**) were obtained in mixture with, most of the time, unknown side products and the starting material in the case of **II.10.a**, and only starting material for the synthesis of **II.10.b**. Attempts to purify compounds by sublimation gave no result, none of the side products were soluble in apolar solvents to perform recrystallization, and column chromatography was risky due to the presence of carboxylic acid and aldehyde functions. Both compounds were directly submitted to a peptide coupling using T₃P and *N,N*-diisopropylethylamine (DIPEA). DIPEA was used as a tertiary amine base to avoid the coupling between another secondary or primary amine rather than cyclopropylamine. The desired compounds **II.11** were obtained as solids after column chromatography with an overall yield of 42% and 35% over two steps, respectively (Scheme 26). Other peptide coupling reactions following the procedures of Cisar *et al.* and Molinaro *et al.*, using CDI, EDC, or a mixture of EDC and HOBt were tried but all gave no results and the starting material was always recovered (Figure 46).^{183, 189}



Scheme 26: Pathway A: Synthesis of 2-chloro-*N*-cyclopropyl-4- and 5-formylbenzamides **II.11.a-b**

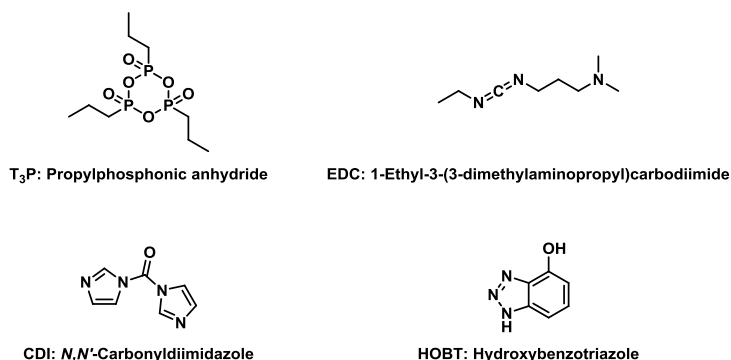


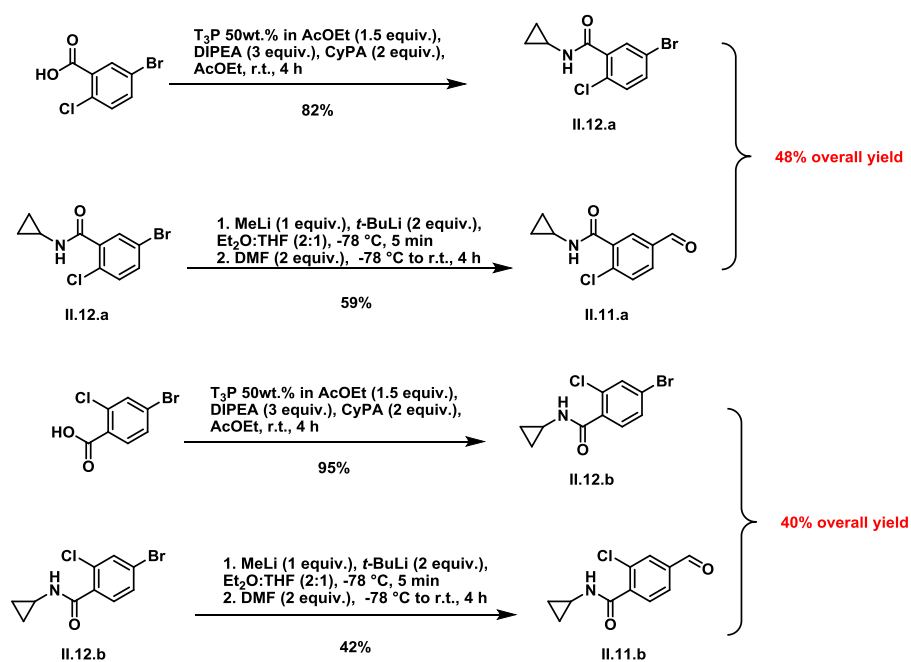
Figure 46: Peptide coupling reagents

4.2.2.2 Path B: peptide coupling

As an alternative strategy, we started by the peptide coupling and then performed the Br/Li exchange which was the tricky part of this synthesis.

The first step was easy to perform and the desired amides **II.12** were obtained in excellent yields of 82% and 95%, respectively, without any purification.¹⁹⁰⁻¹⁹¹ The second step was the Br/Li exchange using MeLi and *t*-BuLi (Scheme 27). Like previously, the second reaction was never complete and final products **II.11** were obtained in mixture with unreacted starting material **II.12** and unknown side products. Final compounds **II.11** were obtained this time with overall yields of 48% and 40%, respectively.

By comparison, path B gave slightly better results (48% and 40%, vs. 42% and 35% for path A) and was therefore favored.



Scheme 27: Pathway B: Synthesis of 2-chloro-*N*-cyclopropyl-4- and 5-formylbenzamides **II.11**

4.3 Coupling reactions between key intermediates 1 and 2

Finally, we tackled the last step of the synthesis, which consisted in the coupling between partners **1** and **2** (Figure 47).^{80, 158}

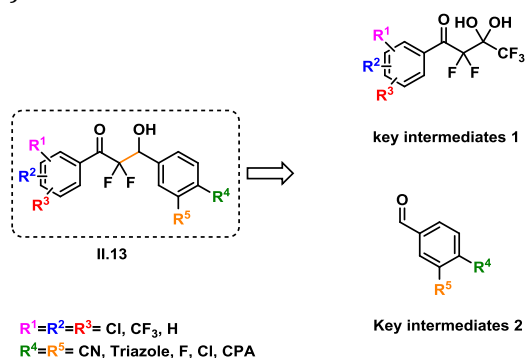
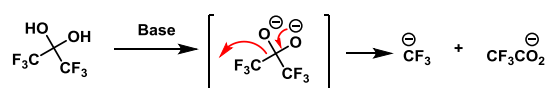


Figure 47 Retrosynthesis of the final compound

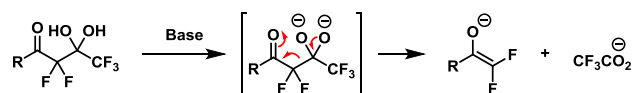
4.3.1 Synthesis of targeted molecules II.13

The synthesis of compounds **II.13** involved the generation of a difluoroenolate intermediate caused by a trifluoroacetate release reaction, followed by the addition onto aldehydes. One of the most useful and known bond cleavage is the decarboxylation; analogously the release of trifluoroacetate is based on the same principle with the only difference that the presence of a trifluoromethyl-substituted *gem*-diol is required. The first demonstration of trifluoroacetate release was published by Prager *et al.*¹⁹² from hexafluoroacetone hydrate. Colby *et al.* extended this methodology to α,α -difluoro- β -trifluoromethyldihydroxy ketones (Scheme 28). This reaction allows the formation of attractive difluoroenolates, which are useful precursors in the introduction of difluoromethylene groups. The addition of lithium bromide (LiBr) and NEt_3 increases the rate of trifluoroacetate release and a rapid C-C bond cleavage occurs.^{80, 158, 193-196}

Prager's work:



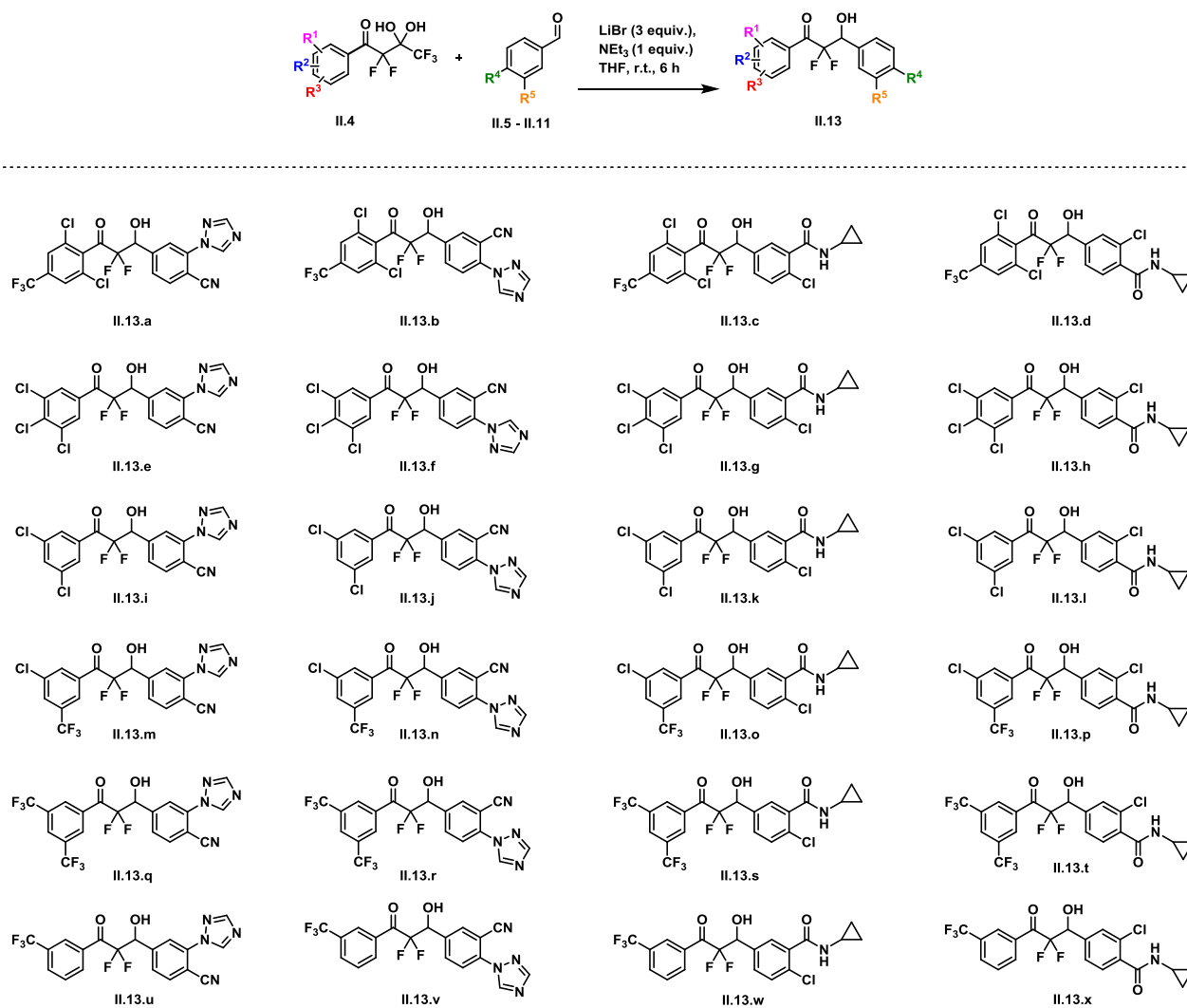
Colby's work:



Scheme 28: Trifluoroacetate release reaction

CHAPTER II: Synthesis of α,α -difluoro- β -hydroxy ketones

Following this method, twenty-four compounds were obtained rapidly and sent to Bayer CropScience for automated purification, analysis and tested for their activities as GABA receptor agonists. Indeed, the presence of several groups which can perform hydrogen bonds confer an important polar character to compounds **II.13**. The partnership between Dr. F. Leroux's laboratory and BayerCropscience permitted to use their inverse phase column chromatography equipment. Yields were not determined yet (Scheme 29).



Scheme 29: Synthesis of compounds II.13

The structural analysis confirmed the above documented final compounds (**II.13**). In one case (**II.13.g**) the formation of the difluoromethyl ketone hydrate was observed. The latter can be formed during a retro-Claisen condensation of the final compound or simple hydration of the difluoroenolate intermediate.

In the case of products **II.13.m, n, o, q** hydrate forms were observed.

The reduced forms (**II.13.g', h', k', l', o', p', s', t', w'**) of the targeted molecules (**II.13.g, h, k, l, o, p, s, t, w**) were observed in 9 cases over 12, and only for compounds which bear, on the second aromatic ring, the combination of chlorine and CPA substituents (Figure 48).

CHAPTER II: Synthesis of α,α -difluoro- β -hydroxy ketones

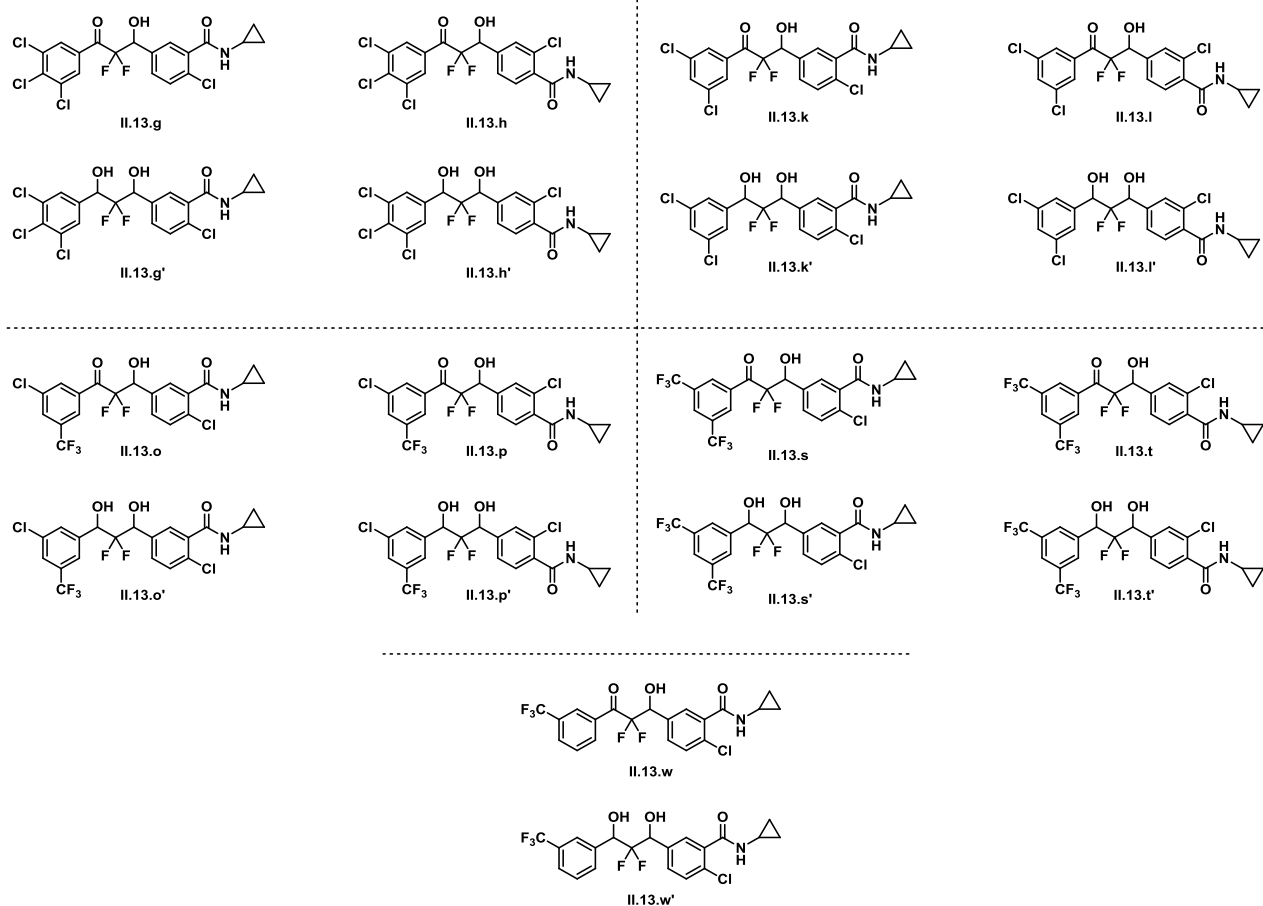
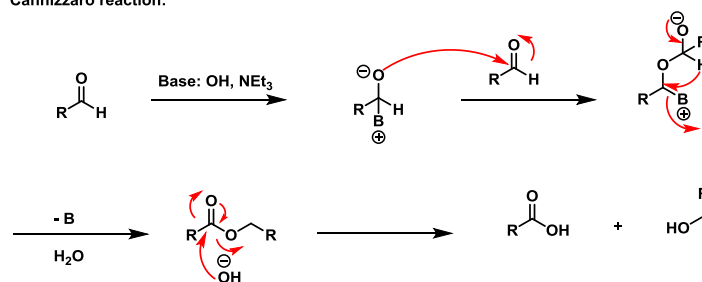


Figure 48: Reduced forms of II.13.g, h, k, l, o, p, s, t, w

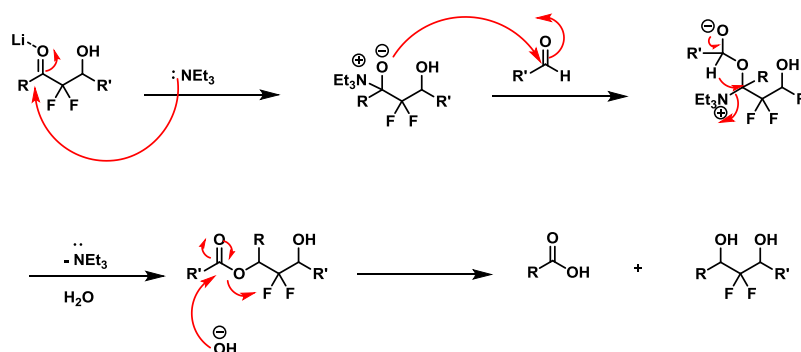
The formation of these side products may be explained by a Cannizzaro type process which occurs during the coupling reaction. Indeed, the Cannizzaro reaction results from a disproportionation of an aldehyde into an alcohol and a carboxylic acid.¹⁹⁷ In 2007, Mojtahedi *et al.* described the Cannizzaro reaction under optimized mild conditions using LiBr and NEt_3 at room temperature. Under those conditions, the reaction occurs naturally and leads to the formation of the corresponding alcohol and carboxylic acid.¹⁹⁸ By analogy, we can postulate that the formation of reduced compounds (II.13.g', h', k', l', o', p', s', t', w') came from a Cannizzaro type process on the final product (Scheme 30).

CHAPTER II: Synthesis of α,α -difluoro- β -hydroxy ketones

Cannizzaro reaction:



Mechanistic assumption for the reduction process by a Cannizzaro type reaction:



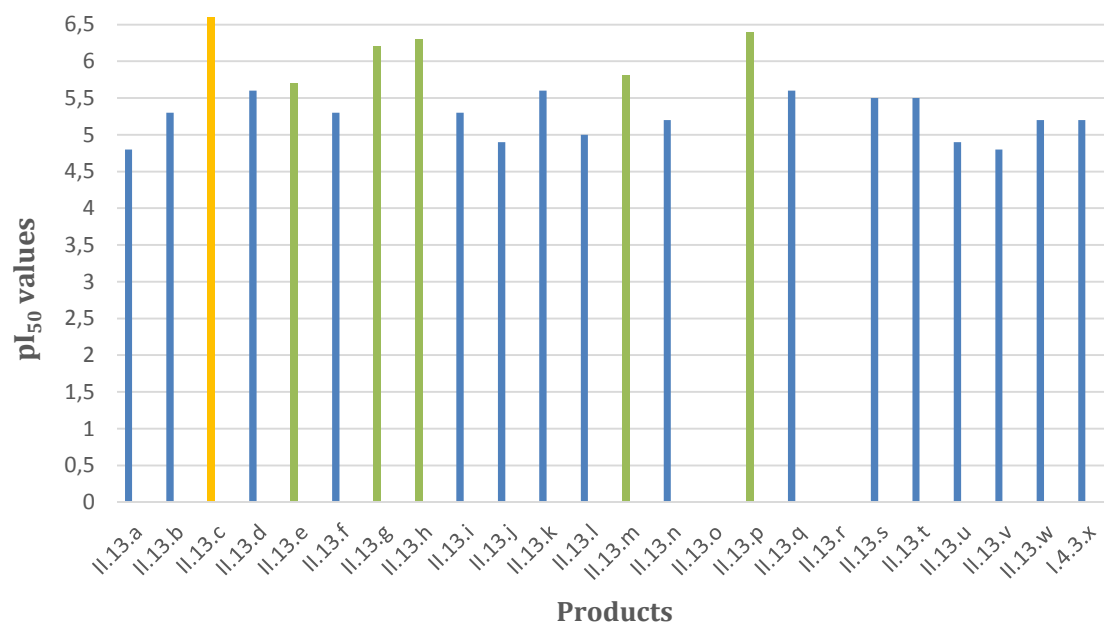
Scheme 30: Postulate for the reduction process

4.3.2 Biological analysis

Once purified, all α,α -difluoro- β -hydroxy ketones **II.13** were analyzed to see if they show any activity as GABA receptor agonists. It will be interesting to observe an activity close to a pI_{50} value around 8. The pI_{50} value corresponds to the inhibition potential of the product; it is related to the IC_{50} which represents the maximal concentration of an inhibitor that is required for the inhibition of 50% of the receptor activity ($pI_{50} = -\log IC_{50}$).

According to the results presented below (Graphic 3, Table 7), we can notice that the maximum pI_{50} obtained was $pI_{50} = 6.6$ ($IC_{50} = 10^{-6.6}$ M) as GABA receptor agonist of house fly (*Drosophila melanogaster*), and corresponds to product **II.13.c**. It is the only active compound which possesses a 2,6-Cl-4-CF₃-phenyl moiety (other active compounds possess either chlorines in positions 3, 4, 5 or chlorine and CF₃ in positions 3, 5). The positions of the chlorine and CPA moiety seem to be important because the regioisomer with the chlorine in position 3 shows a loss of one pI_{50} unit (**II.13.c**: $pI_{50} = 6.6$; **II.13.d**: $pI_{50} = 5.6$). According to the results presented below, compounds which bear the combination of Cl/CPA are more favourable to a high pI_{50} than those which bear the nitrile/triazole combination.

CHAPTER II: Synthesis of α,α -difluoro- β -hydroxy ketones



Graphic 3: The determined pI₅₀ values of the tested substances as GABA_R agonists of *Drosophila melanogaster*

Table 7: pI₅₀ values of compounds II.13

Entry	Products	pI ₅₀ (<i>Drosophila melanogaster</i>)
1	II.13.a	4.8
2	II.13.b	5.3
3	II.13.c	6.6
4	II.13.d	5.6
5	II.13.e	5.7
6	II.13.f	5.3
7	II.13.g	6.2
8	II.13.h	6.3
9	II.13.i	5.3
10	II.13.j	4.9
11	II.13.k	5.6
12	II.13.l	5.0
13	II.13.m	5.8
14	II.13.n	5.2
15	II.13.o	/
16	II.13.p	6.4
17	II.13.q	5.6
18	II.13.r	/
19	II.13.s	5.5
20	II.13.t	5.5
21	II.13.u	4.9
22	II.13.v	4.8
23	II.13.w	5.2
24	II.13.x	5.2

Up to now, no other compound has shown a selectivity as GABA receptor agonist *in vitro* or *in vivo*, except for compound **II.13.p, x** which showed an *in vivo* activity against Green peach aphid (*Myzus persicae*) at very low level ($IC_{50} = 30 \mu\text{M}$, 100% efficacy for **II.13.p** - Entry 1 and $IC_{50} = 6 \mu\text{M}$, 100% efficacy for **II.13.x** - Entry 5). However, further investigation led to no *in vivo* activity (Table 8, Entries 2-3, 6).

Table 8: *In vivo* analysis of the II.13.p, x as GABA receptor agonists of *Myzus persicae*

Entry	Compound	$IC_{50} (* 10^{-6} \text{ M})$	Efficacy (%)
1		30	100
2	II.13.p	6	50
3		1.2	0
4		30	100
5	II.13.x	6	100
6		1.2	0

Although only **II.13.p, x** show low *in vivo* insecticidal activity, several hypotheses can be raised to explain this dramatic *in vivo* inactivity at lower concentrations. It may be due to a poor bioavailability (quantity of compounds which reach the receptor unchanged), the racemic mixture (it would be interesting to separate both enantiomers) and even due to the substituent themselves. More investigations have to be done and the research is ongoing.

5 CONCLUSION

In conclusion, during this project we have performed the synthesis of molecules with a potential activity as GABA receptor agonists. The synthesis of key intermediates **1** in three steps was relatively easy once the procedure to provide ketones was optimized. All compounds were obtained in moderate to excellent yields (Figure 49).

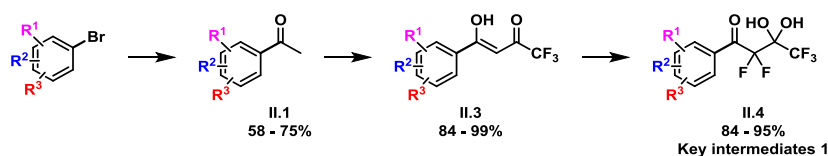


Figure 49: Summary of the synthesis of key intermediates **1**

Two different families of key intermediates **2** were synthesized. The first family (compounds **II.5**) was obtained in one step after a nucleophilic aromatic substitution of fluorine by triazole in 51% yield, while its regioisomer was obtained in four steps with an overall yield of 48%.

The second family (compounds (**II.11**)) was obtained according to two pathways; either by a halogen-metal exchange followed by a peptide coupling or by a peptide coupling followed by a halogen-metal exchange. The second pathway was favored given that compounds were obtained with a slightly higher overall yield (Figure 50).

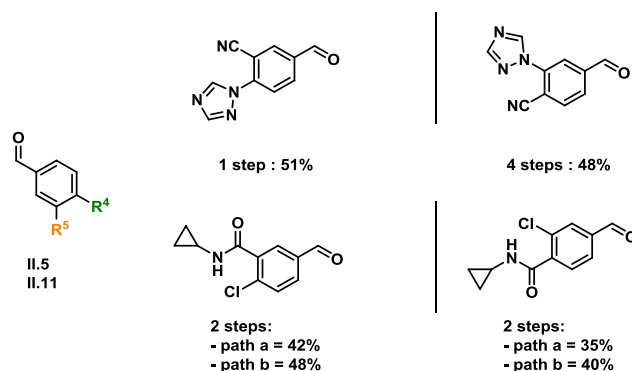


Figure 50: Summary of the synthesis of key intermediates **2**

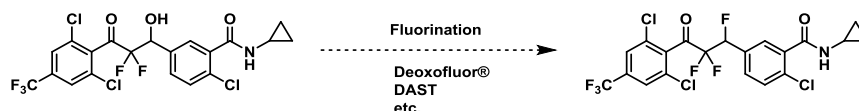
The twenty-four molecules bearing a α,α -difluoro- β -hydroxy ketone motif were synthesized under smooth reaction conditions thanks to the departure of trifluoroacetate in presence of LiBr and NEt_3 . Several side products were observed such as the hydrate form or the reduced compound which can be explained by a Cannizzaro type process due to the presence of a base.

Among the twenty-four synthesized compounds, six showed a very encouraging $\text{pI}_{50} \geq 5.7$. Two compounds (**II.13.p, x**) showed a weak insecticidal activity *in vivo*. The combination of Cl/CPA seems to be the best for the moment, *in vitro* and *in vivo*. However, the general trend of the poor *in vivo* activity of compounds may be explained by their low bioavailability or physico-chemistry or even by a low stability.

6 PERSPECTIVES

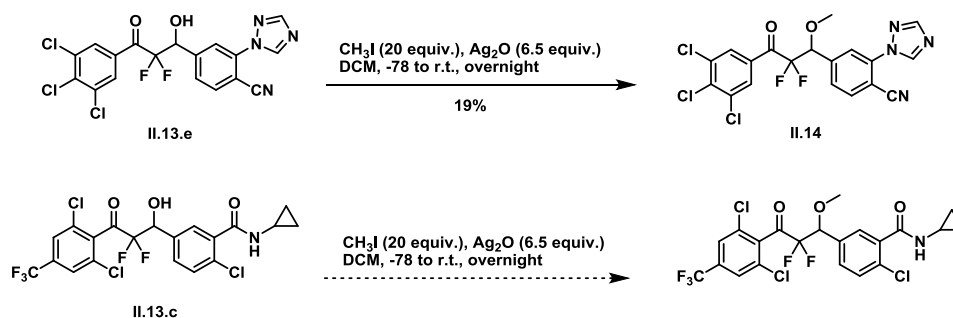
To improve the *in vitro* and *in vivo* activities of our compounds, various modifications may be applied according to various approaches.

First, we can try to exchange the hydroxyl group by fluorine using several fluorinating agents to study the importance of this moiety in the active pocket (Scheme 31).



Scheme 31: Fluorination reaction

Some tests were performed to increase the lipophilicity of compounds by *O*-alkylation. Our first attempt on **II.13.e** provided compound **II.14** in 19% yield. This reaction needs to be optimized, before being carried out on the most active compound so far (**II.13.c**) (Scheme 32).⁸⁰



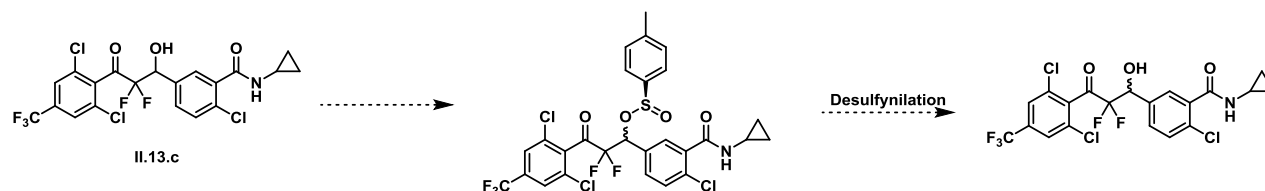
Scheme 32: *O*-Alkylation of **II.13.e**

The *O*-acylation might also be a solution to the lipophilicity issue and may allow the penetration inside membranes (Scheme 33).



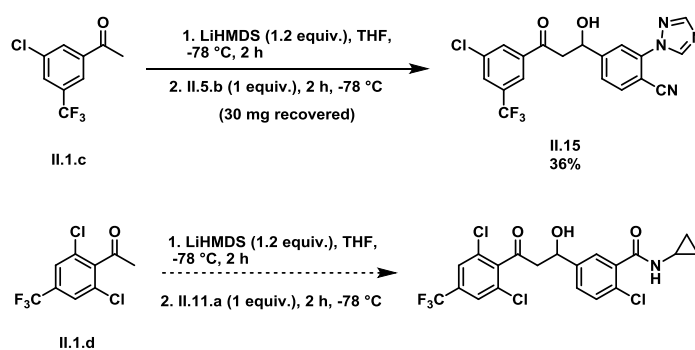
Scheme 33: *O*-Acylation of **II.13.c**

The derivatization and separation of both diastereoisomers can be an alternative to increase the activity and evaluate the importance of chirality toward the GABA receptor. The easily accessible (-)-menthyl-(Ss)-*p*-toluenesulfinate can be a reagent of choice for this strategy (Scheme 34).¹⁹⁹⁻²⁰⁰ Then after desulfinylation in acidic conditions final enantiopure alcohols can be obtained.²⁰¹⁻²⁰² An alternative is the direct synthesis of each enantiomer using copper catalysts and chiral ligands like Zhang *et al.* (Scheme 3).⁹⁴



Scheme 34: Synthesis and separation of both diastereomers

Colby *et al.* presented in 2013 that non-fluorinated analogue of their molecule which acted as a GABA_B receptor inhibitor was inactive. In the same context, it will be interesting to study the effect of the non-fluorinated β -hydroxy ketone motif on the activity of our molecules. We already have performed the first coupling between II.1.c and II.5.b using 1.2 equivalents of LiHMDS in THF at -78 °C according to the procedure by Colby *et al.*⁸⁰ Final compound II.15 was obtained in 36% yield and 54% of the starting aldehyde was recovered (Scheme 35). The reaction needs to be optimized and performed using II.1.d and II.11.a in order to obtain an analogue of the most active compound (II.13.c).

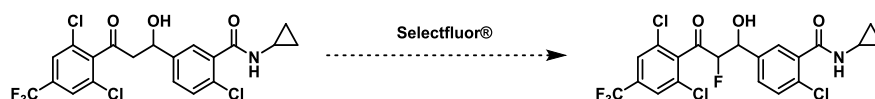


Scheme 35: Claisen condensation towards non-fluorinated analogues of II.13

We made the choice to introduce the CF₂ moiety during the synthesis of key intermediates 1. According to the publication of Baumann *et al.*¹⁷² the presence of the trifluoroacetate functionality facilitates the introduction of two fluorine atoms. It was reported that methyl ketones are not sufficiently activated to undergo difluorination even in presence of an excess of fluorinating agent. In fact, the introduction of one fluorine may decrease the acidity and the nucleophilicity of the carbon in α -position of the carbonyl. Some publications described the introduction of two fluorine atoms between two carbonyl groups. This included the paper of Leng *et al.*, which performed the introduction of two fluorine atoms between two ketones using Selectfluor® under reflux conditions. However, they faced some selectivity issues not easy to control.²⁰³ On the other hand, Nash *et al.* showed that using an excess of 3 equivalents of PhI(OAc)₂ and 15 equivalents of Et₃N·3HF at 40 °C in MeCN promoted the difluorination reaction between two carbonyls. They could perform the reaction at higher temperature using only 1.2

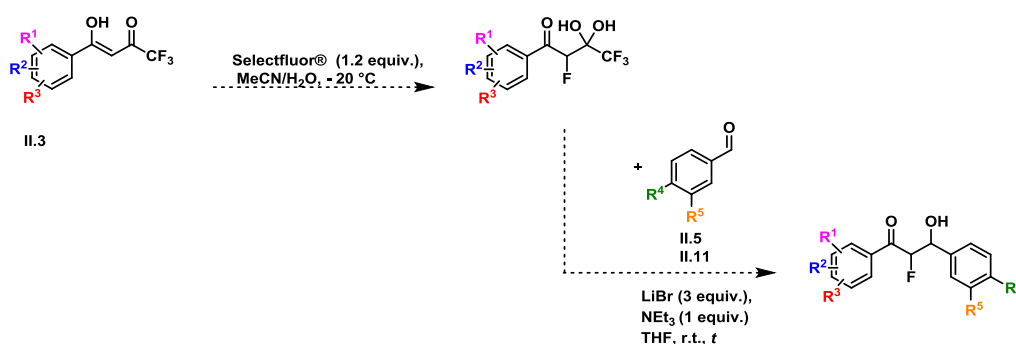
equivalents of $\text{PhI}(\text{OAc})_2$ and 10 equivalents of $\text{Et}_3\text{N}\cdot 3\text{HF}$, which led to the formation of a mixture containing the mono- and the difluorinated products but also the monoacetoxyated one.²⁰⁴

In our case, we would like to introduce only one fluorine atom, so to corroborate the Baumann *et al.* speculations, fluorination may be carried out at the last stage using Selectfluor®. Consequently, we will be in presence of the complete series of compounds and be able to evaluate their activities depending on the presence of two, one or zero fluorine atoms (Scheme 36).



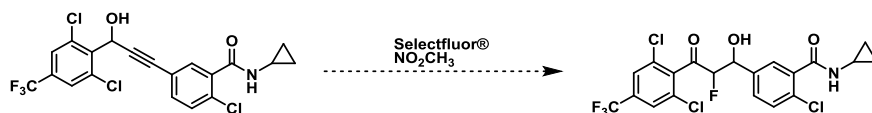
Scheme 36: Last stage fluorination reaction

According to the publication of Li *et al.*, it is also possible to perform the synthesis of α -fluoro- β -trifluoromethyldihydroxy ketones using only a small excess of Selectfluor® at $-20\text{ }^\circ\text{C}$. Then, after addition of aldehydes, we should get the desired mono-fluorinated final compounds (Scheme 37). Mei *et al.* made the same reaction using an additional $\text{Cu}(\text{II})$ catalyst.^{160, 162}



Scheme 37: Coupling reaction between α -fluoro- β -trifluoromethyldihydroxy ketones and aldehydes

In case that these reactions are unsuccessful, a recently accepted manuscript presented the possibility to get, under catalyst free conditions, the α -fluoro- β -hydroxy ketone motif from a tertiary propargylic alcohol using Selectfluor® in nitromethane.²⁰⁵ We could envisage to apply this methodology to our compounds in case where the late-stage fluorination leads to the difluorinated product (Scheme 38).



Scheme 38: Mono-fluorination from propargylic alcohol

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CHAPTER III

Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

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1 INTRODUCTION

1.1 Heterocycles

Heterocyclic compounds were discovered in the 1800s and are very useful in our daily life. They are widely distributed in nature and essential to life. For example, they are key constituents of DNA (Nucleobases: guanine, cytosine, thymine and adenine) (Figure 51).

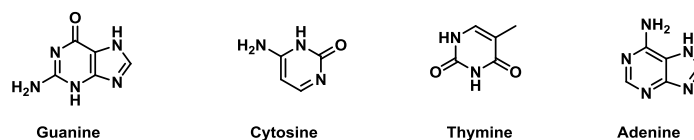


Figure 51: DNA nucleobases

In 1818 was discovered alloxan, a powerful oxidant isolated from uric acid by G. Brugnatelli.²⁰⁶ Furfural was isolated for the first time in 1832 in a small quantity as a side product of the formic acid synthesis.²⁰⁷ Two years after, F. Runge extracted quinoline from coal tar.²⁰⁸ Then in 1882 and 1884, two searchers, V. Meyer and H. E. Fischer respectively isolated thiophene as contaminant in benzene and discovered a new class of compounds named purines.²⁰⁹⁻²¹⁰ In 1912, the first vitamin, thiamine (vitamin B1) was isolated by C. Funk (Figure 52). These compounds are samples among the vast number of discovered heterocycles.²⁰⁹

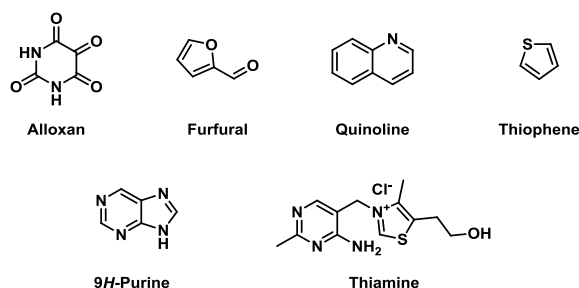


Figure 52: Heterocycles discovery

Many synthetic and natural heterocycles are active and are in clinical use. They are characterized by the presence of one or more heteroatoms in their structure. They usually have a wide range of applications and they are predominantly used in the pharmaceutical and the agrochemical field. They are used, most of the time, as platform in organic synthesis for the elaboration of new structures. The most common heterocycles are those having five- or six-membered rings and containing heteroatoms such as nitrogen (pyridine, pyrrole, pyrrolidine), oxygen (furan, tetrahydropyran), or sulphur (thiophene).²¹¹⁻²¹²

In this chapter, we will focus on *N*-based heterocycles. Indeed, the presence of nitrogen in an aromatic ring confers some specific properties.²¹³ In comparison with their carbocyclic homologues, 6-membered aromatic heterocycles bearing nitrogen are not perfectly hexagonal due to the presence of the C-N bond which is shorter. Moreover, nitrogen possesses lone pair electrons which is responsible for the unique physical and chemical properties of such compounds (like their basicity) (Figure 53-A). We were more specifically focused on quinoline

derivatives. Quinoline is a heterocyclic aromatic nitrogen compound characterized by a double-ring structure that contains a benzene ring fused to pyridine at two adjacent carbon atoms. The analogy between pyridine and benzene is like that between quinoline and naphthalene. The introduction of electronegative atoms disturbs the electron density distribution and confers a partial positive charge to adjacent carbons (Figure 53-B).²¹⁴⁻²¹⁵

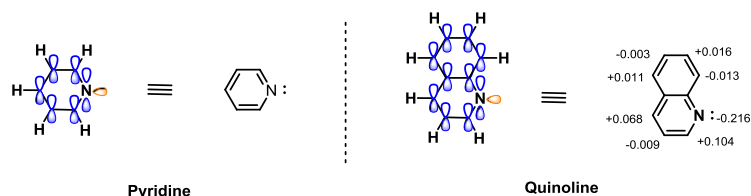


Figure 53: A) Pyridine core orbitals repartitioning; B) Quinoline core orbitals and charge repartitioning

1.2 Discovery of quinoline

As previously presented, quinoline was discovered in 1834 by F. Runge as an extracted component of coal tar, which remains the principal source of commercial quinoline. Quinoline is a weak tertiary base ($pK_a = 4.94$ of the conjugated acid), particularly toxic when it is unsubstituted. So how can we explain its fabulous versatility in many fields of organic chemistry?

The answer can be found in nature; quinoline derivatives are found as alkaloids in many different plants. In 1820, quinine was isolated as the active ingredient from the bark of *Cinchona* trees by two French chemists, J. Pelletier and J. Caventou, who used it to treat malaria. Other alkaloids such as cryptolepine, an indoloquinoline extracted from the climbing shrub *Cryptolepis sanguinolenta* from West Africa, have shown some anti-malaria activities. Chimanine alkaloids, isolated from the bark of *Galipea longiflora* trees are effective against the parasites *Leishmania sp.*, which are the agents of leishmaniasis (Figure 54).²¹⁶⁻²²⁰

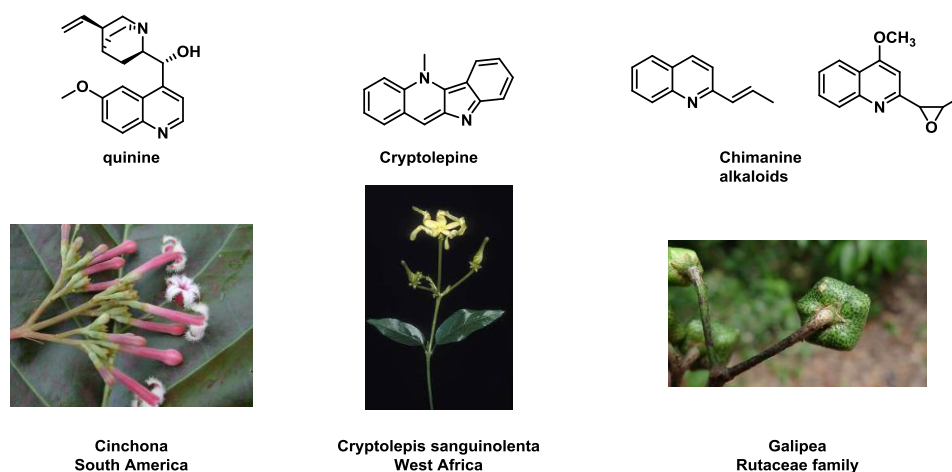


Figure 54: Natural alkaloids

Nitrogen heterocycles like quinolines are easily modified and functionalized with simple to complex functionalities, to design a multitude of compounds which possess a very essential character in organic synthesis. Quinoline scaffolds are important not only because they are key

CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

structural units in many natural products,²²¹⁻²²⁴ but because they are also building blocks which possess a wide range of applications in medicinal chemistry,^{216, 225-237} agricultural chemistry²³⁸⁻²⁴⁵ and material science²⁴⁶⁻²⁵⁶ (Figure 55).

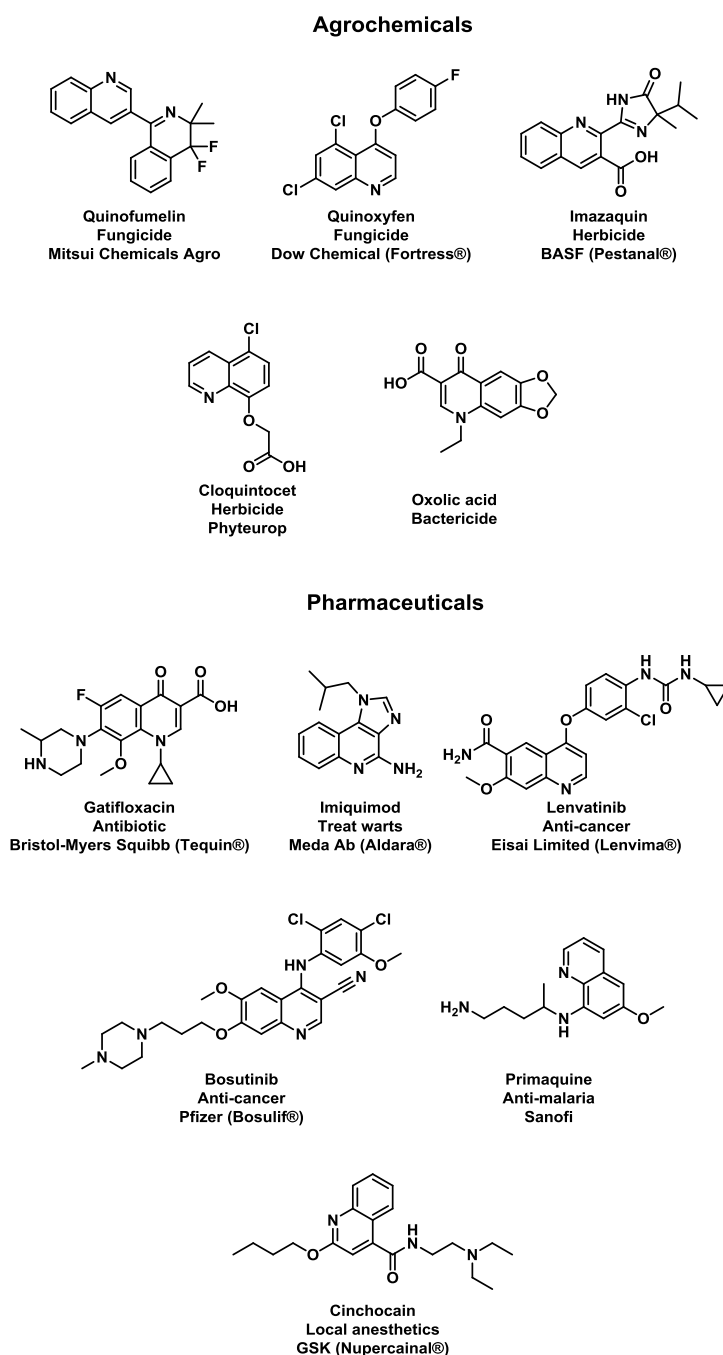


Figure 55: Commercially available quinolines as agrochemicals and pharmaceuticals

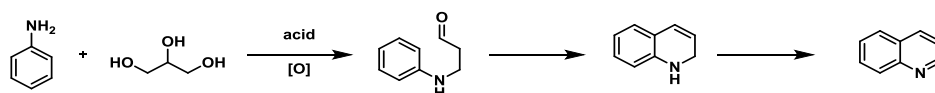
2 STATE OF THE ART

2.1 Synthesis of quinoline derivatives

Since their discovery 200 years ago, quinolines have been extensively studied and many methods were reported to synthesize them. Because of their importance as useful bioactive compounds, the discovery of always new, simple, efficient and environmentally benign protocols for their preparation remain a challenge.

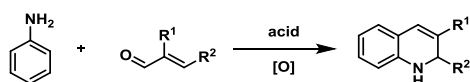
Among the existing methods, most quinoline derivatives are obtained from the reaction of aniline with various annulation partners.²⁵⁷⁻²⁶⁰

The oldest reaction to access quinolines is the Skraup reaction developed in 1880. It is the reaction between an aniline and glycerol in presence of an oxidant and concentrated sulfuric acid at high temperature (Scheme 39).²⁶¹



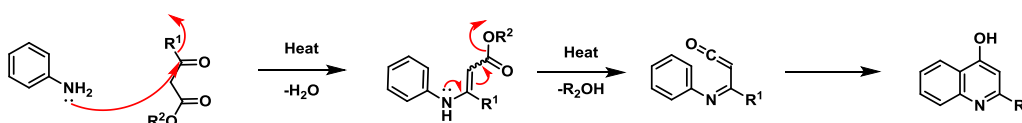
Scheme 39: The Skraup synthesis

An alternative method to the Skraup synthesis was developed by chemists O. Doebner and W. Von Miller in 1881. The Döbner–Von Miller reaction uses α,β -unsaturated aldehydes or ketones allowing a wider variety of substitution patterns under acidic conditions (Scheme 40).²⁶²⁻²⁶⁶



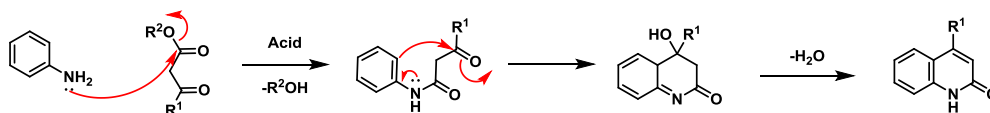
Scheme 40: The Doebner-Von Miller reaction

In 1887, the Conrad–Limpach reaction was reported as an annulation reaction giving 2-substituted quinolin-4-ols from arylamines and β -ketoesters in refluxing acid (Scheme 41).²⁶⁷



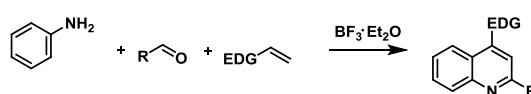
Scheme 41: The Conrad-Limpach synthesis

The Knorr reaction is complementary to the previous one. While the Conrad-Limpach reaction is performed under thermal conditions to provide the 2-substituted quinolone, the Knorr reaction is performed at room temperature in presence of an acid to provide the 4-substituted quinolone (Scheme 42).²⁶⁸



Scheme 42: The Knorr synthesis

Povarov *et al.* published in 1963 the synthesis of quinoline from anilines, aryl aldehydes and activated alkenes to form 2-arylquinolines according to an aza-diels Alder reaction (Scheme 43).²⁶⁹⁻²⁷⁰

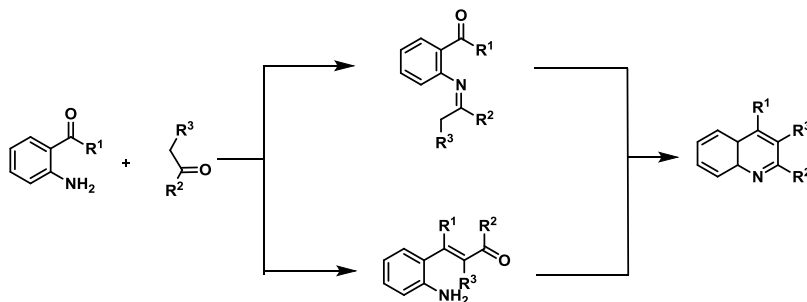


EDG: Electron-donating group
Acid: Lewis acid or Brønsted acid

Scheme 43: The Povarov reaction

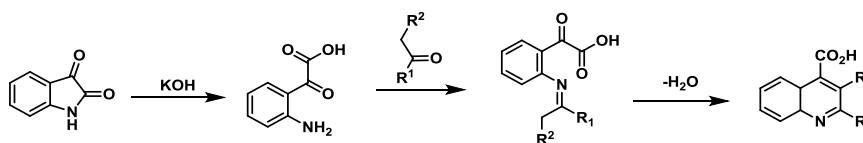
Alternatively, several other established methods for quinoline synthesis use other substrates than anilines in the cyclization process. Indeed, the described above reactions usually suffer from producing mixtures of regioisomers, especially when *meta*-substituted anilines are used.

The Friedländer reaction, developed in 1882, uses *ortho*-aminoaryl aldehydes or ketones with a α -methylene ketone in the presence of a base to form 2- and 3-substituted quinolines. In some cases, addition of a Lewis acid as catalyst can increase the rate of the reaction. The mechanism is not well understood yet and two postulates can be formulated. The first one is involving a Schiff base, while the second intermediate is obtained after a Claisen condensation (Scheme 44).²⁷¹



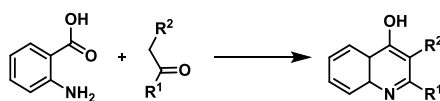
Scheme 44: The Friedländer reaction

Two other reactions can be considered as a variation of the Friedländer reaction. The first one is the Pfitzinger reaction, which combines an isatin with a α -methylene ketone under basic conditions to give 2- and 3-substituted quinoline-4-carboxylic acids (Scheme 45).²⁷²⁻²⁷³



Scheme 45: The Pfitzinger reaction

The second one is the Niementowski reaction, which involves an anthranilic acid and a α -methylene ketone for the synthesis of 4-hydroxy quinolines (Scheme 46).²⁷⁴

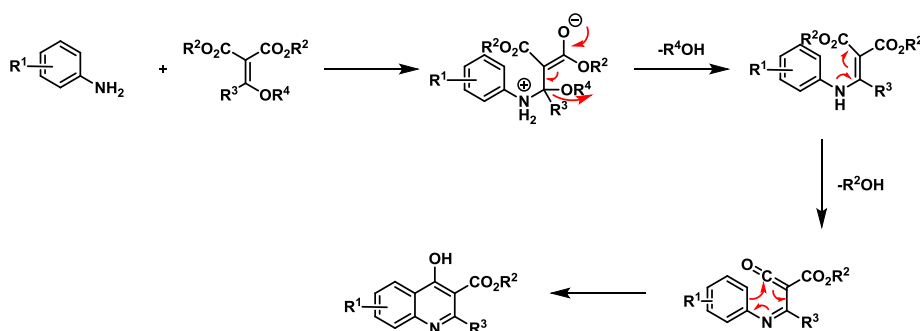


Scheme 46: The Niementowski reaction

The Friedländer reaction became the most popular and the most efficient reaction to provide quinoline derivatives. However, the difficulty of preparing the required anilines is the limitation of this approach.²⁷⁵⁻²⁷⁶ Many studies have been published, on the improvement of the Friedländer reaction, with the unique purpose to increase the scope, the yield and the regioselectivity.

New Lewis acids such as neodymium (III) nitrate hexahydrate can be used to avoid harsh conditions.²⁷⁷ The use of metal oxides without solvent can also be an alternative. Most of the time, all compounds are obtained in very good yield and with a good regioselectivity.²⁷⁸⁻²⁸⁰ These examples of improvement of the Friedländer reaction are not exhaustive.²⁸¹⁻²⁸⁷

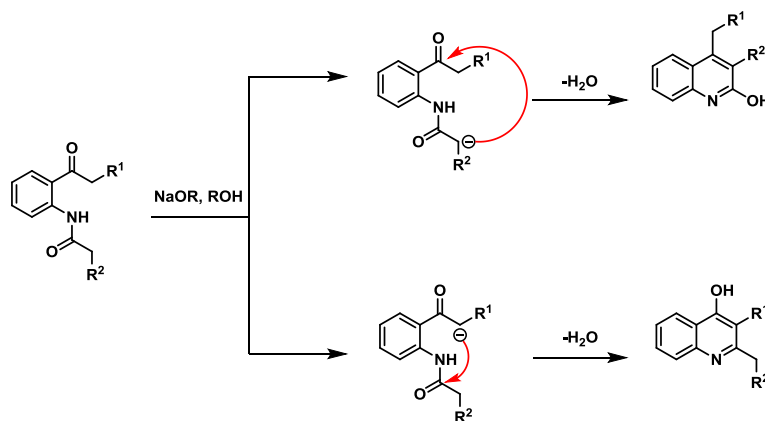
The Gould–Jacobs reaction refers to the condensation of an aniline with alkoxy-methylenemalononic esters, which, after heating affords 4-hydroxy-3-carboxylate quinolines upon benzannulation (Scheme 47).²⁸⁸



Scheme 47: The Gould-Jacobs synthesis

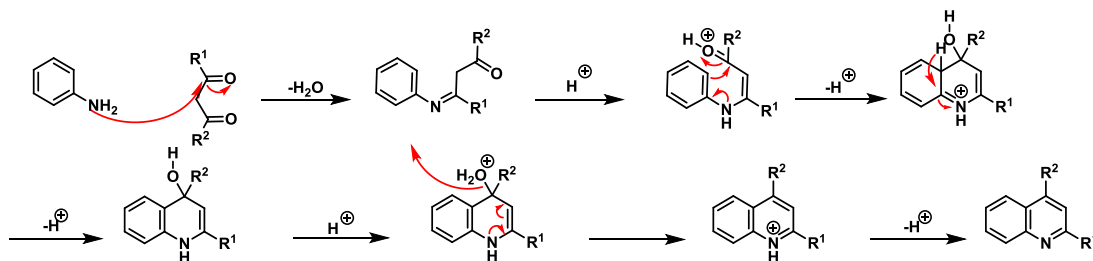
CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

The Camps synthesis is a base-catalysed intramolecular condensation, articulated on the C-H deprotonation of an anilide and its condensation on a carbonyl group in *ortho* position to afford 2-hydroxy-substituted quinolines. Depending on the structure of the starting material, 4-hydroxy-substituted quinolines can also be obtained by alternate deprotonation of the ketone, followed by its reaction on the amide (Scheme 48).²⁸⁹



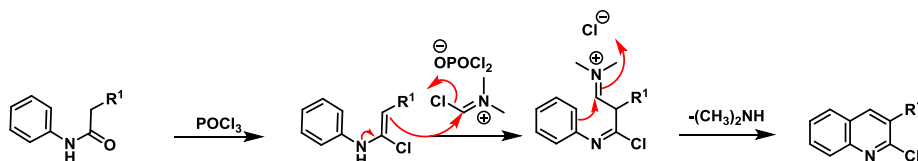
Scheme 48: The Camps synthesis

The Combes reaction consists in the condensation of aniline with acetoacetone or other β -diketones followed by a Friedel-Crafts type cyclization and dehydration in the presence of sulfuric acid or polyphosphoric acid (PPA). The first step is usually easy to perform, however the ring closure is sometimes affected by the present substituents. This reaction providing rapidly 2,4-substituted quinoline skeletons (Scheme 49).²⁹⁰



Scheme 49: The Combes reaction

The Meth-Cohn reaction involves the use of Vilsmeier reagents²⁹¹⁻²⁹² (presented later in this chapter) on *N*-aryl chloroaniline to produce 2-chloro-3-substituted quinolines. The iminium salt intermediate formed *in situ* readily cyclizes with heating assistance to form the quinoline after dimethylamine departure. Electron-donating groups can increase the rate of the reaction and it was observed that *meta*-substituted anilines provide selectively 7-substituted quinoline derivatives (Scheme 50).²⁹³⁻²⁹⁴



Scheme 50: The Meth-Cohn synthesis

Significant drawbacks mark these methodologies which revealed a lack of environmental safety measures. The reactions described above usually suffer from one or more of the following limitations: low yields of products, small scope of reaction, complex starting material, long reaction time, harsh reaction conditions, tricky work-up and sometimes expensive reagents.

Moreover, the use of concentrated acid considerably reduces the range of starting materials and possible functionalities which can be introduced on quinoline derivatives.

More efficient examples of other metal-free reactions have been recently appeared as a good alternative in the synthesis of quinoline derivatives. Indeed, these reactions often combine high yield, short reaction times and environmentally safe reactions, since they do not need metals.²⁹⁵⁻³⁰⁰

Alternatively, metal complex catalysis has opened a new page in the synthesis of quinolines. The notable advantages are a higher tolerance to most functional groups and the use of minimum amounts of reagents. Metals like rhodium, platinum, palladium, copper, iron and others have accomplished the catalytic formation of quinolines.³⁰¹⁻³¹⁴

The synthesis of quinoline derivatives is constantly evolving and many new reactions are developed on a regular basis to find an effective method which will provide new substituted quinolines.³¹⁵⁻³²⁴ However, rare are those reporting on the introduction of several fluorinated moieties onto the quinoline ring system.

2.2 Synthesis of fluorinated quinoline derivatives

As we explained previously, quinolines are very important scaffolds in many fields of organic chemistry. Fluorine is reported as the second most interesting heteroatom in life science after nitrogen (*vide supra*-Chapter I).³²⁵ It is in the logic continuity that the desires to introduce fluorine on heterocyclic skeletons such as quinolines become more and more attractive in a wide variety of organic syntheses. Indeed, combining both the highly bioactive potential of quinoline derivatives and the possibility to improve physico-chemical properties of bioactive compounds by introduction of fluorine could afford highly efficient active ingredients, but also constitutes a real challenge (Figure 56).

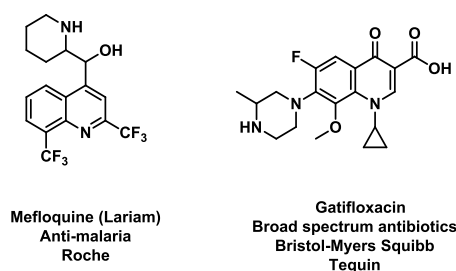


Figure 56: Examples of bioactive fluorinated quinolines

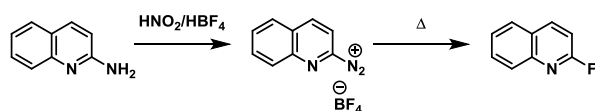
2.2.1 Monofluoroalkylation reactions

Few methods exist for the introduction of fluorine onto heteroarenes. It is usually introduced thanks to a two-step reaction, the Balz-Schiemann reaction, which allows the addition of fluorine via diazotisation and subsequent thermal decomposition of the tetrafluoroborate intermediates.³²⁶⁻³²⁷ Alternately, fluorination of arenes can be carried out using the Halex process, an industrial method which consists in a halogen exchange reaction by using a fluoride ion source (HF, KF, etc.) on a chlorinated species at high temperature.^{5, 328} More recently, fluorination reactions can be performed using nucleophilic fluorinating agents such as DAST or

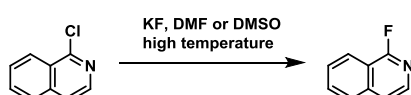
Deoxofluor®, and more occasionally by means of electrophilic fluorinating agents such as NFSI or Selectfluor®, among others (Figure 57).³²⁹⁻³³⁰

Fluorination reactions

Balz - Schiemann Reaction

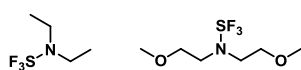


Halex process



Fluorination reagents

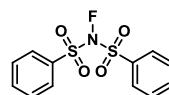
Nucleophilic fluorination



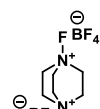
DAST

Deoxofluor®

Electrophilic fluorination



NFSI



Selectfluor®

Figure 57: Fluorination reaction methods and reagents

On the other hand, Chambers *et al.* developed the direct fluorination of quinoline derivatives using elemental fluorine F_2 in presence of concentrated H_2SO_4 under nitrogen. However, the need of special equipment and the formation of mixtures of products do not make it a reaction of choice.³³¹⁻³³²

When fluorine is not a direct substituent of the aromatic ring, it can be present as a fluoroalkyl group attached to the (hetero)aromatic backbone.

The trifluoromethyl group is frequently introduced by classical nucleophilic fluorination which involves the treatment of benzotrichlorides with HF or SbF_5 (Swarts type reaction). These reactions, although efficient and popular in industrial process, are often hard to perform in a laboratory. The CF_3 group can also be introduced by using trifluoromethylation agents according to nucleophilic techniques (Ruppert-Prakash: $TMSCF_3$) or electrophilic techniques (Umemoto, Togni) and radical pathways (Figure 58).³³³⁻³³⁷

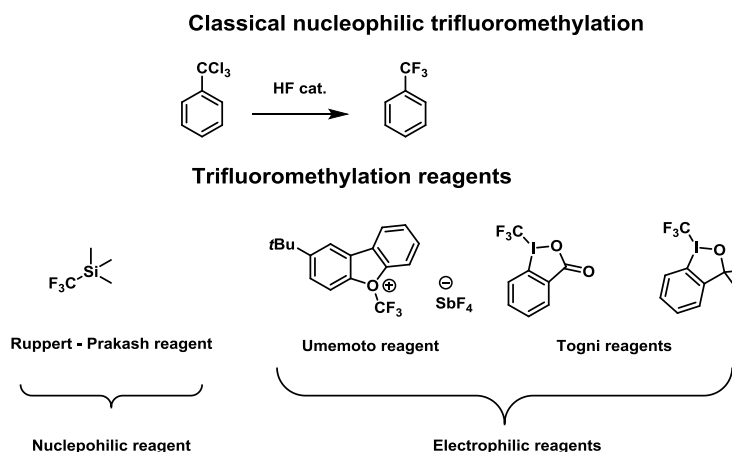
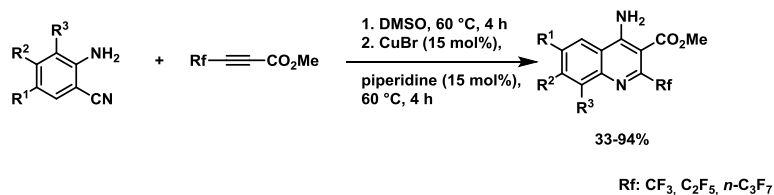


Figure 58: Useful reagents in trifluoromethylation reactions

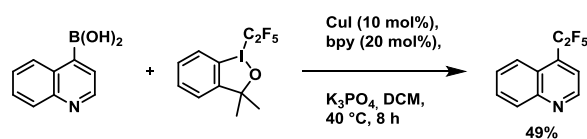
Nowadays, perfluoroalkyl groups can be introduced by metal-catalysed reactions.

Han *et al.* have presented a mild and efficient method to synthesize fluoroalkyl quinoline derivatives in high yield from 2-aminobenzonitriles or 2-aminophenyl ketones and methyl perfluoroalk-2-ynoates using copper. However, this reaction gives access exclusively to 2-fluoroalkylated quinolines (Scheme 51).³³⁸⁻³⁴⁰



Scheme 51: Copper-catalysed synthesis of 2-fluoroalkylated quinolines

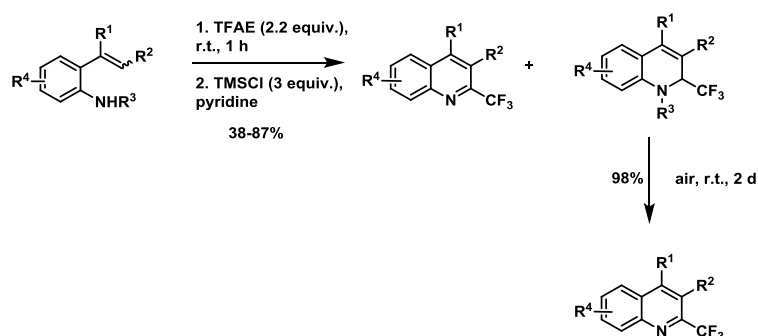
An analogue of Togni's reagent allows the transfer of the pentafluoroethyl moiety to β -ketoesters or aryl boronic acids in presence of copper iodide and 2,2'-bipyridine (bpy). The final compounds were obtained in moderate to good yields (Scheme 52).³⁴¹



Scheme 52: Copper-catalyzed pentafluoroethylation of quinolin-4-ylboronic acid with Togni's reagent analogue (BIX-C₂F₅)

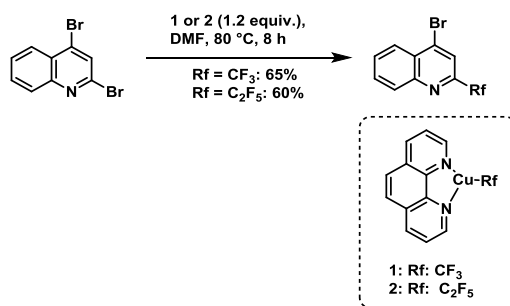
CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

The use of fluorinated starting materials can be an alternative. Perfluoroalkylated imines are prepared *in situ* from vinylanilines and perfluorinated hemiacetals or aldehyde hydrates such as trifluoroacetaldehyde ethyl hemiacetal (TFAE), then they are cyclized by action of TMSCl and pyridine. This reaction is driven by the substituents present on the starting vinylaniline. Starting materials bearing an electron-donating group (EDG) preferably provided the desired quinoline, while those bearing an electron-withdrawing group (EWG) preferably provided the substituted dihydroquinoline. Most of the time, the dihydroquinoline is obtained in moderate to good yields, and can be converted into the corresponding quinoline by oxidation under air for 2 days (Scheme 53).³⁴²



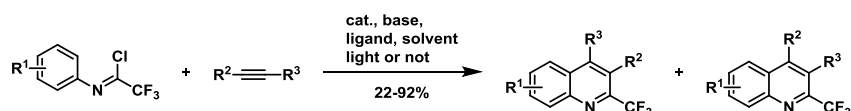
Scheme 53: Vinylaniline reaction with TFAE and further oxidation

Hartwig *et al.* developed an efficient fluoroalkylation of heteroaryl bromides (which are much less expensive than heteroaryl iodides) bearing a variety of functional groups using a phenanthroline-CuCF₃ complex under mild reaction conditions and with a very good yield. This reaction does also allow the formation of bis-fluoroalkylated compounds in small yields (18% and 30% for 1 and 2 respectively) (Scheme 54).³⁴³⁻³⁴⁴



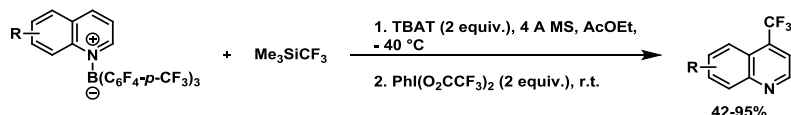
Scheme 54: Fluoroalkylation of bromoquinolines

Dong *et al.* described a Ru-catalysed reaction which provides 2-trifluoromethyl quinolines, thanks to the generation of a radical trifluoroacetimidoyl from trifluoroacetimidoyl chlorides starting materials, which further cyclized with alkynes under visible light. This reaction was also reported by Li *et al.* using the same starting material under Cu-catalysis methodology and Amii *et al.* under Rh-catalysis methodology without the need of light. The presented reactions provided compounds in moderate to excellent yields. However, only the formation of mono-fluoroalkylated compounds is depicted. Finally, the major drawbacks of these reactions are the use of expensive catalysts or the poor regioselectivity (Scheme 55).³⁴⁵⁻³⁴⁷



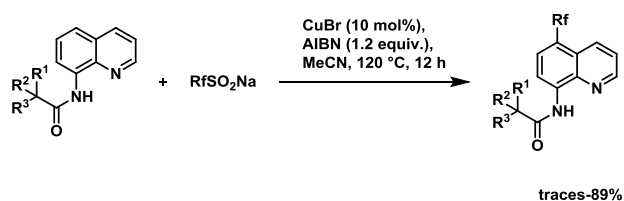
Scheme 55: Coupling cyclization of *N*-aryl fluorinated imidoyl chlorides with alkynes

Nagase *et al.* published in 2016 a last stage selective method to introduce a perfluoroalkyl moiety in position 4 of quinoline derivatives. To manage the reaction, the position 2 required to be protected by coordination to a bulky borane group which concomitantly activates the pyridine ring (Scheme 56).³⁴⁸



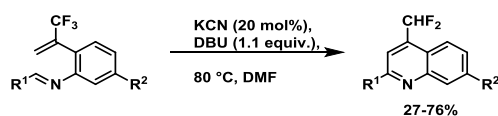
Scheme 56 Last stage selective fluoroalkylation in position 4 published by Nagase *et al.*

Jin *et al.* performed the selective C₅ trifluoromethylation of quinolines using a Cu-catalyst, which chelates the amide in position 8 and allows the insertion of $\cdot\text{CF}_3$ radical formed by the presence of azobisisobutyronitrile (AIBN) as initiator. This reaction allows the insertion of several fluorinated moieties in low to excellent yields (Scheme 57).³⁴⁹



Scheme 57: Copper-catalyzed 8-amido chelation-induced regioselective C-H fluoroalkylation of quinolines

Mori *et al.* demonstrated the formation of 4-fluoromethylquinolines *via* an intramolecular S_N2' reaction of *o*-methyleneamino-substituted α -trifluoromethylstyrenes in presence of KCN as catalyst (Scheme 58).³⁵⁰



Scheme 58: Synthesis of 4-difluoromethyl quinoline derivatives

2.2.2 Bisfluoroalkylation reactions

Simple fluorinated reagents, such as fluoroalkylacetate derivatives³⁵¹, perfluoromethylated-1,3-diketones and fluoroalkylacetate derivatives, also allow the synthesis of fluorinated quinolines.³⁵²⁻³⁵⁴

New methodologies to synthesize such powerful ingredients remain in the heart of research and more inventive methods are developed regularly.³⁵⁵⁻³⁶¹

However, one can witness that rare are the reactions which allow the introduction of two fluorinated substituents on the quinoline skeleton.

A paper published in 2001 by Kgekong *et al.*, described the synthesis of 2-, 8- and 2,8-bis(trifluoromethyl)quinoline scaffolds as potent anti-malarial compounds (Figure 59). The latter compounds showed a lower *in vitro* anti-malarial activity than chloroquine.³⁶²⁻³⁶³

It was interesting to notice that compounds bearing either the 2- or the 8- trifluoromethyl moiety were twice less active than the quinoline which bears fluorinated substituents in both 2 and 8 positions.³⁶⁴

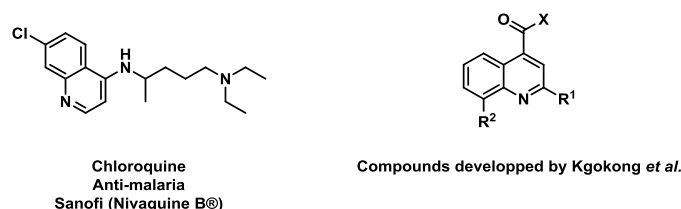
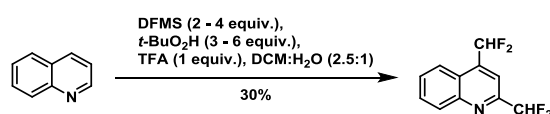


Figure 59: Structure of chloroquine and 2,8-bis(CF₃)-substituted quinolines

This study showed the impact of fluorinated substituents on bioactive molecules. In this case positions 2 and 8 were not an efficient combination, but what about positions 2 and 4?

In 2002, Sloop *et al.* developed the synthesis of 2,4-bis(trifluoromethyl)quinoline from anilines, fluorinated β -diketones which are not easy to access and PPA. Products were obtained in low yields after a cyclization step performed under harsh conditions, which produced a large amount of phosphorous-containing waste.³⁶⁵⁻³⁶⁶ Moreover, the use of unsymmetrical β -diketones often leads to mixtures of regioisomers, as already demonstrated in the publication of Hosseini *et al.* When ethyltrifluoroacetate was used as starting material, a mixture of regioisomers was obtained in 70 : 30 ratio.²⁷⁸⁻²⁸⁰

Baran *et al.* performed in 2012 the 2,4-bis(difluoromethylation) of quinoline using a new reagent, zinc difluoromethanesulfinate (DFMS) in presence of *t*-BuO₂H and TFA in a DCM/H₂O solvent system. This reaction is based on Langlois' discovery. Indeed Baran's reagent is an analogue of Langlois' reagent (sodium trifluoromethanesulfinate, NaSO₂CF₃) which promotes electrophilic trifluoromethylation reaction. The reaction is completely regioselective and occurs only at electron-deficient positions. This reaction performed under mild reaction conditions allows the access only to 2,4-bis(difluoromethyl)quinoline in only 30% yield (Scheme 59).³⁶⁷



Scheme 59: Selective bis-difluoromethylation of quinoline

Among the existing methods to synthesize quinolines bearing fluoroalkyl groups, none are suitable for an industrial process, by combining a short synthetic pathway and mild reaction conditions. Indeed, these reactions, set oneself apart sometimes by very low yields, a limited availability of the starting materials, require high temperature, long reaction times and expensive catalysts. Usual methods such as the Skraup, Doebner-Von Miller and Combes reactions are not appropriate for the synthesis of fluoroalkylated quinolines. Indeed, the unavailability of starting materials or the poor regioselectivity due to the use of unsymmetrical reactants are a serious hurdle.

Despite previously presented advances, a clean, efficient, and economic pathway is still needed to obtain useful polyfunctionalized fluoralkylated quinolines from readily available starting materials.

Consequently, we decided to focus our interest on the synthesis of compounds which bear fluorinated moieties in both 2 and 4 positions. They are scarcely described in literature and the synthetic challenge to perform a reaction with high yields, under mild conditions and with a complete regioselectivity, gives them a special appeal. The strategy developed in this chapter is based on the use of FARs described in the following subsection.

3 OVERVIEW OF THE SYNTHETIC STRATEGY

3.1 Fluoroalkyl Amino Reagents (FARs)

Fluoroalkyl Amino Reagents (FARs) are powerful tools for the introduction of various fluorinated substituents. Three different FARs were described in literature several decades ago: 1,1,2,2-tetrafluoro-*N,N*-dimethylethan-1-amine (**A.1**; TFEDMA),³⁶⁸⁻³⁷⁰ 2-chloro-*N,N*-diethyl-1,1,2-trifluoroethan-1-amine (**B.1**; Yarovenko reagent),³⁷¹⁻³⁷² and *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine (**C.1**; Ishikawa reagent).³⁷³ They are prepared from low-cost commercially available fluoroolefins and dimethyl- or diethylamine, which makes them reagents of choice for an industrial purpose (Figure 60).

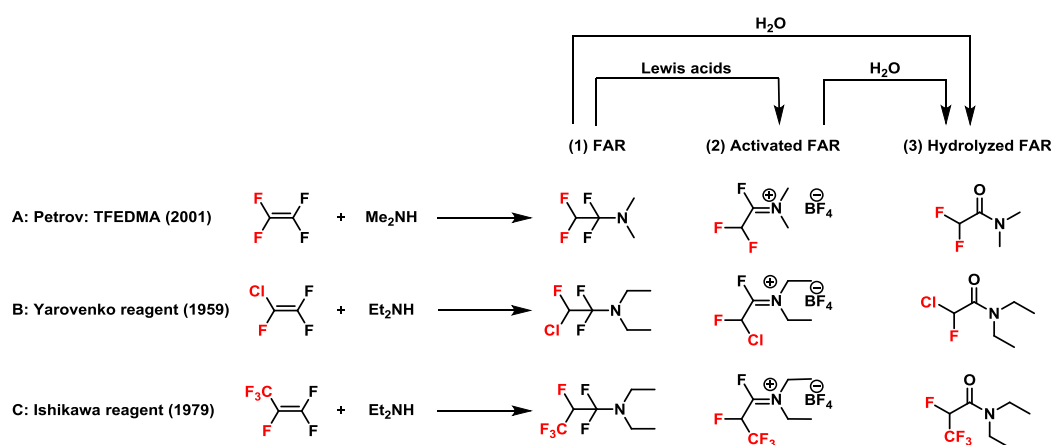
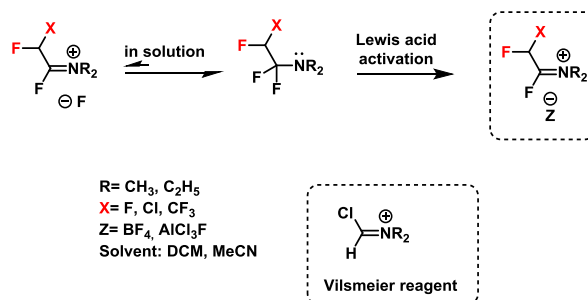


Figure 60: Commercially available Fluoroalkyl Amino Reagents (FARs)

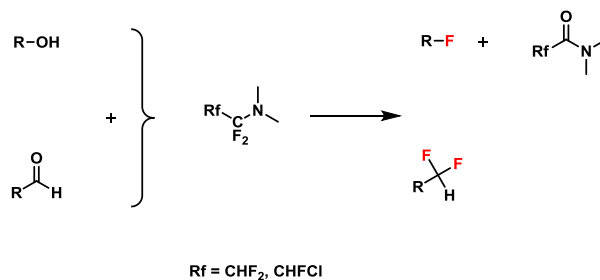
Concerning their reactivity in solution, a natural equilibrium between the amine and the iminium forms occurs due to a hyperconjugation of the nitrogen lone-pairs with the σ^* orbital of C-F bond. But this equilibrium tends in favour to the amine form. Moreover, the highly reactive fluoro iminium fluoride salts can easily be hydrolysed by air moisture to provide the corresponding acetamides. In presence of a Lewis acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$, AlCl_3) this equilibrium can be largely shifted to the formation of the iminium salt which increases its electrophilic character (Scheme 60).

FARs were reported as analogues of the Vilsmeier reagent due to the *in situ* formation of a halogenated iminium salt.³⁷⁴⁻³⁷⁵



Scheme 60: Activation of FARs by Lewis acids converting them into their corresponding iminium salts

FARs were originally used as fluorinating agents to convert a hydroxyl group into a fluorine or carbonyl groups into fluoroalkyl substituents under mild conditions (Scheme 61).^{368, 373}



Scheme 61: FARs used as fluorinating agent

In 1975, Wakselman *et al.* reported the first acylation of electron-rich heterocycles from the action of iminium salts derived from FARs upon action of a Lewis acid. The reaction between activated FARs and electron-rich aromatic substrates led to the formation of final compounds in low yields (Figure 61).³⁷⁶

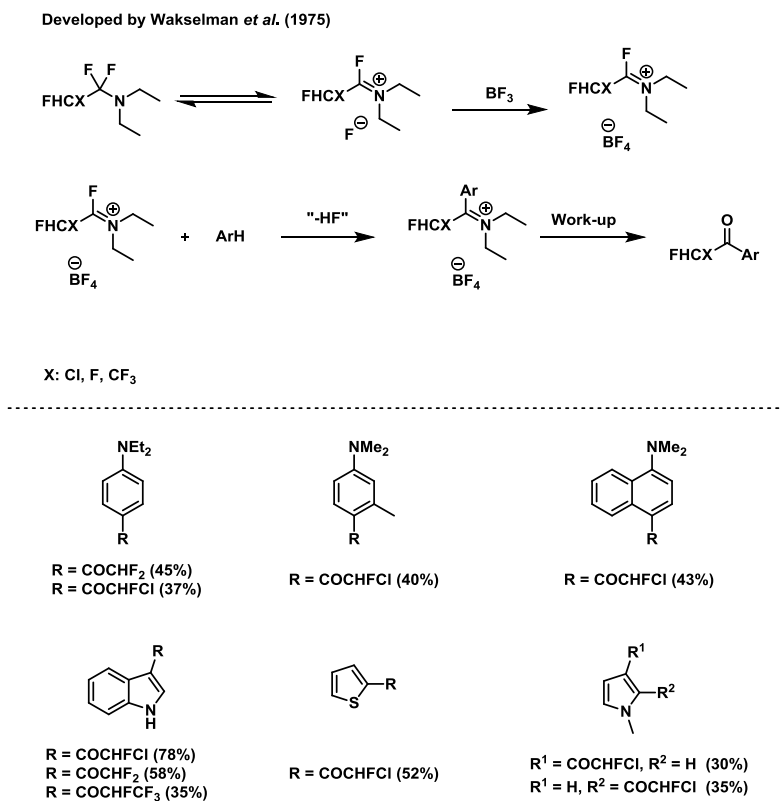


Figure 61: Reactions developed by Wakselman using FARs

Four years later, Ishikawa *et al.* employed the non-activated Yarovenko reagent (**B.1**) to perform cyclization reactions with 2-amino anilines, -phenols and thiophenols to provide various benzazoles (Figure 62).³⁷⁷ Since then no more studies on the synthesis of heterocycles using FARs have been carried out.

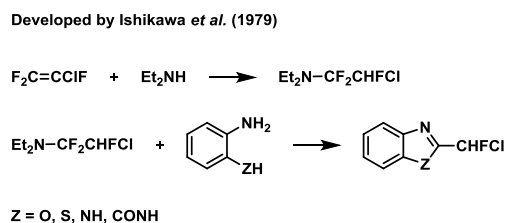


Figure 62: Reactions of FARs developed by Ishikawa

Among FARs, TFEDMA (**A.1**) is the most stable at ambient temperature, the purer after activation by a Lewis acid and it is also the most reactive one. Indeed, the presence of the small methyl groups on nitrogen makes TFEDMA less hindered, less deactivated (inductive effect +I less strong than ethyl) and thus more prone to nucleophilic attack than **B.1** or **C.1**.

A new FAR was developed in our laboratory bearing a OCF₃-group (**E.1**) which has shown a reactivity similar to that of TFEDMA (**A.1**). It was clear at this point that the development of FARs bearing a dimethylamino moiety instead of diethylamino will increase the possibility of reactions and facilitate the transfer of perfluoroalkyl groups onto molecules.³⁷⁸ Consequently, we performed the synthesis of the *N,N*-dimethyl analogue of the Yarovenko reagent **D.1** in a quantitative yield upon activation. We also attempted the synthesis of the *N,N*-dimethyl analogue of the Ishikawa reagent **F.1**, but preliminary tests did not provide a clear conclusion. We suspect the elimination of HF resulting in the formation of the corresponding α -fluoroenamine, a problem overcome by the presence of ethyl groups. Up to now, final compounds **F.2** or **F.3** have not been observed. It would be interesting to try the reaction at lower temperature to slow down the elimination of HF and use reagent **F.2** immediately after preparation (Figure 63).

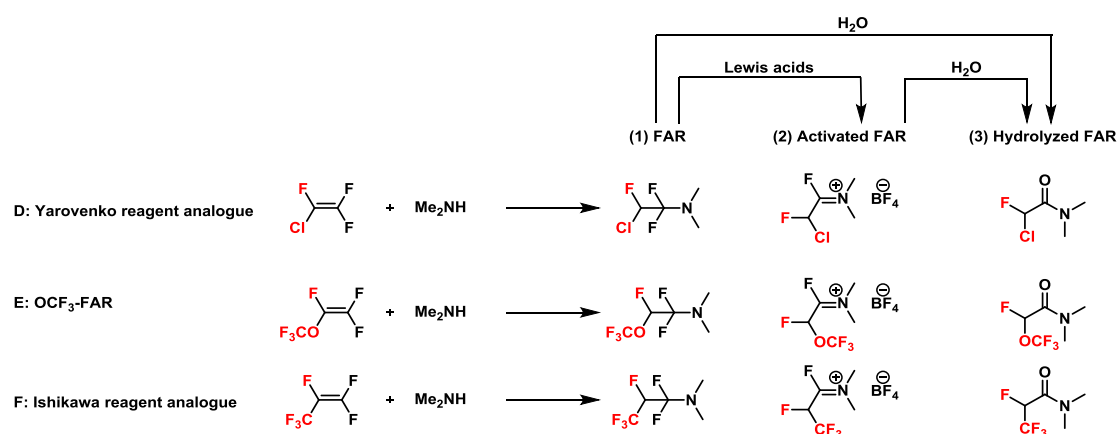


Figure 63: Preparation of new FARs-OCF₃-FAR and *N,N*-dimethyl analogues of Yarovenko and Ishikawa reagents

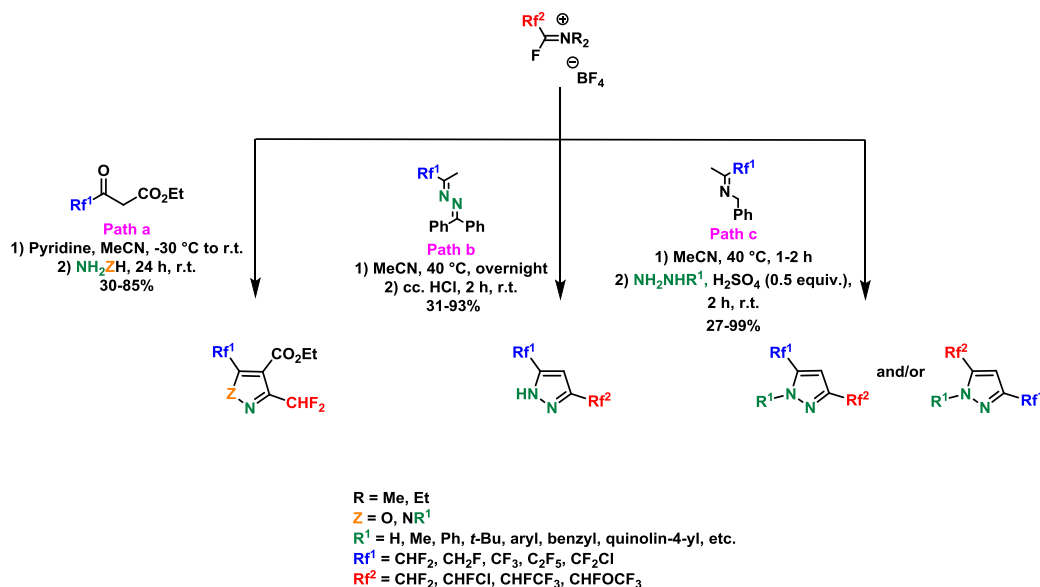
3.2 Recent discoveries using FAR chemistry

In 2008, Pazenok *et al.* employed TFEDMA in the synthesis of a key intermediate of a modern SDHI fungicide (Bixafen).³⁷⁵ In collaboration with Bayer CropScience, the laboratory of Dr. F. Leroux studied then more in detail the use of FARs in the synthesis of novel fluorinated heterocycles and more specifically the synthesis of bis(fluoroalkyl)pyrazoles and -isoxazoles (Scheme 62).

In a first synthetic pathway, activated TFEDMA **A.2** was reacted with fluorinated acetoacetates and then with hydrazines. Under these conditions, pyrazole carboxylates were formed in good yields (Scheme 62-**path a**).³⁷⁹⁻³⁸¹ The major problem of this reaction was that decarboxylation of pyrazoles was hard to perform. Considering this limitation, alternative strategies were employed.

Fluorinated azines were then treated with activated FARs. After cyclization under acidic conditions, *NH*-pyrazoles were obtained in excellent yields (Scheme 62-**path b**) but some drawbacks marked this reaction.³⁸²⁻³⁸³ Indeed, in the light of the low atom efficiency and the difficulty to remove the residual benzophenone even after several purifications, a more adapted method emerged.

In a third strategy, fluorinated azines were replaced by a combination of fluorinated benzylimines and hydrazines, which considerably increased the yields of reactions and reduced the reaction time and waste (Scheme 62-**path c**).³⁸⁴⁻³⁸⁵



Scheme 62: Synthesis of (Fluoroalkyl)pyrazoles using activated FARs: (a) from fluorinated acetoacetates, (b) from fluorinated azines, (c) from fluorinated imines

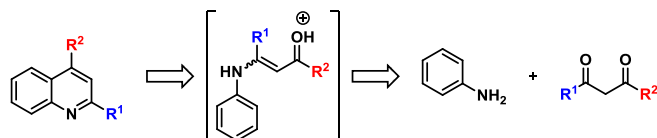
In view of the high reactivity of FARs toward *N*-benzylimines, we decided to extend the reaction scope to other imines and our study on *N*-arylimines started. Unlike before, in this case the reaction led to the formation of 2,4-bis(fluorinated)quinoline derivatives and not to the formation of bis(fluorinated)pyrazoles.

CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

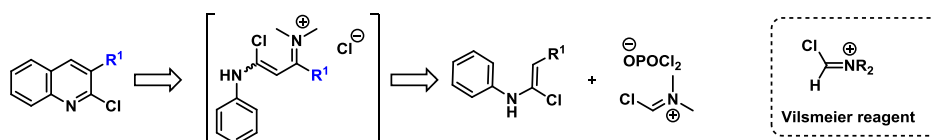
Katritzky *et al.*³⁸⁶ in 1998 and Wang *et al.*³⁸⁷ in 2009 reported the synthesis of non-fluorinated quinoline derivatives using the Vilsmeier reagent (the Meth-Cohn reaction). According to this reaction, activated Vilsmeier salt acted as electrophile on the corresponding enamine. Analogously, activated FARs acted as electrophile onto fluorinated *N*-aryl acetimines, which further cyclized into quinoline in a Combes-like cyclization process (Scheme 63).

The objectives of this project were to expand the chemistry of FARs by synthesising a series of new six-membered heterocycles and more specifically quinoline derivatives which bear in both 2 and 4 positions various fluorinated substituents, in only two steps, under mild conditions and with a complete regioselectivity. These bis(fluoroalkyl)quinoline derivatives are scarcely described in literature and can open new opportunities in the development of biological active ingredients.³⁸⁸

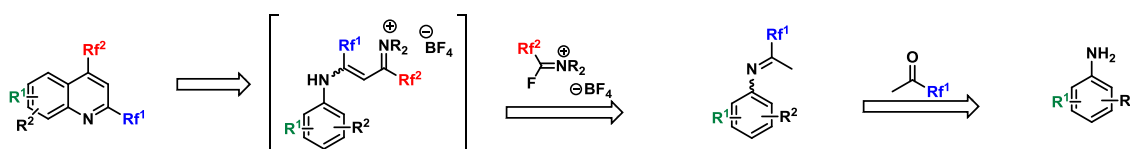
Combes reaction



Meth-Cohn reaction



PhD project synthesis



R: Me, Et
 R¹: H, F, OMe, Cl, NMe₂, OCF₃, CF₃, Ph, SPh, naphthol
 R²: H, Me
 R^{f1}: CHF₂, CF₃
 R^{f2}: CHF₂, CHFCl, CHF₂CF₃

Scheme 63: Retrosynthetic scheme of the synthesis of 2,4-bis(fluoroalkyl) quinoline derivatives by means of FARs

4 RESULTS AND DISCUSSIONS

4.1 Synthesis of quinoline derivatives: development of a new methodology³⁸⁸

4.1.1 Synthesis of ketimines

The first step of the synthetic pathway was the preparation of the key fluorinated *N*-aryl acetimines. We synthesized them by condensation of di- or trifluoroacetone onto substituted anilines at room temperature in anhydrous DCM in the presence of a desiccant (*e.g.* 4 Å MS, MgSO₄) following the publication of Perrone *et al.* (Scheme 64).³⁸⁹ The desired fluorinated ketimines **III.1** were obtained in moderate to excellent yields.

We can notice that ketimines obtained from 1,1-difluoroacetone gave overall better yields than the ones obtained from 1,1,1-trifluoroacetone. These results might be explained by the destabilization of the carbocation caused by the fluorinated moiety during the hemi-aminal dehydration step (Figure 64). The electron-withdrawing effect of CF₃ is higher compared to CHF₂. Therefore, in presence of a CHF₂ moiety, the water unit will be prompt to be removed more easily.

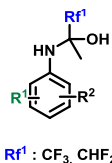
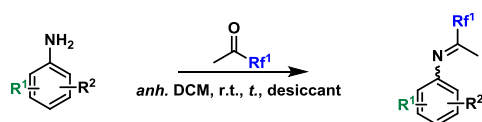


Figure 64: Hemi-aminal intermediate

In some cases, the purity of ketimines **III.1** was low; they were obtained in mixture with starting material or unknown impurities, due to either an incomplete conversion – even after introduction of additional ketone or prolonged reaction time – or side reactions, *e.g.* self-condensation of the ketone. These problems can be avoided by performing the reaction at 0 °C as reported by Perrone *et al.* However, under these conditions, condensation between anilines and ketones was either very slow or totally ineffective.

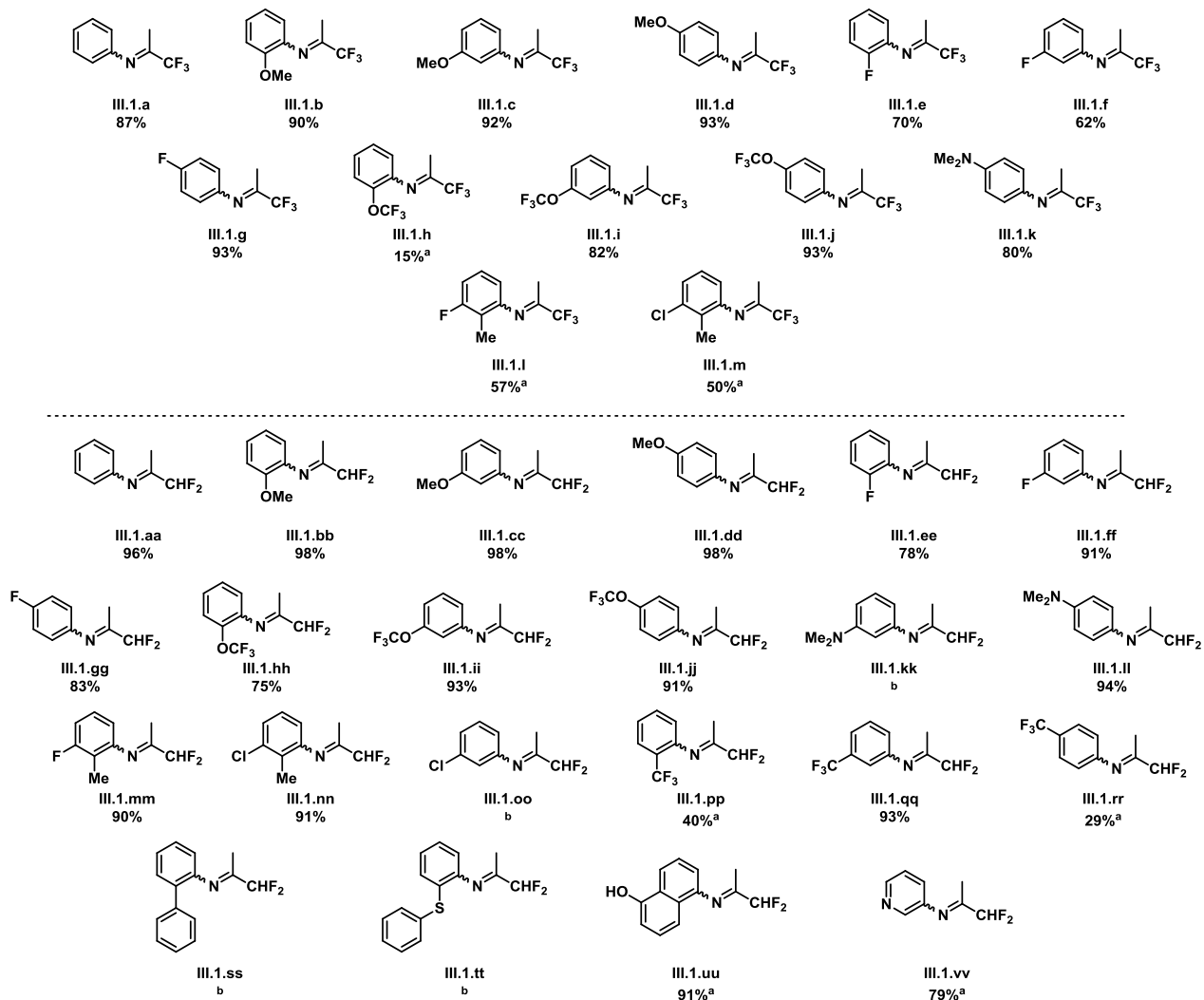
Ketimines **III.1** were not purified, due to their sensitivity toward moisture or silica. Despite the presence of side products, the reactivity of ketimines **III.1** seemed not to be affected. Their stability is acceptable and they can be stored under argon for a few weeks without hydrolysis or degradation.

CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines



^a: estimated yields by ¹H NMR
^b: yield not determined
 desiccant: MgSO₄, 4A MS

III.1.a-m: R^{f1} = CF₃ : 15-93%
 III.1.aa-vv: R^{f1} = CHF₂ : n.d-98%

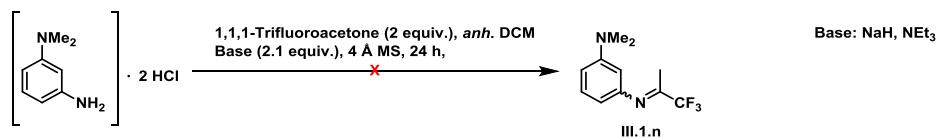


Scheme 64: Synthesis of fluorinated ketimines III.1

The determination of the Z/E conformation was not possible by common analysis techniques, except in the case of **III.1.j** whose isomers were distinguishable only on the ¹H NMR spectrum.

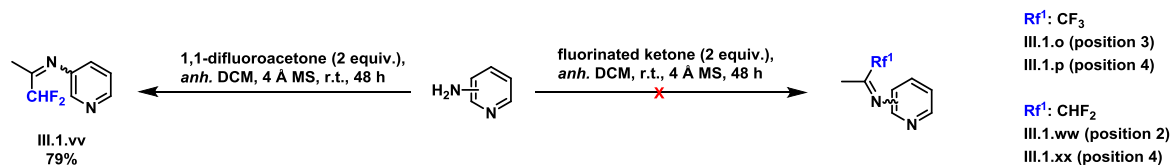
CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

The synthesis of *N,N*-dimethyl-3-((1,1,1-trifluoropropan-2-ylidene)amino)aniline **III.1.n** using either NEt_3 or sodium hydride (NaH) as base to neutralize acid counterparts never provided the final compound, while its CHF_2 analogue was obtained in mixture with side products (Scheme 65).



Scheme 65: Synthesis of *N,N*-dimethyl-3-((1,1,1-trifluoropropan-2-ylidene)amino)aniline **III.1.n**

With the idea of accessing other quinoline-like heterocycles and extending the scope of the synthesis, we decided to prepare fluorinated *N*-pyridyl acetimines. The synthesis of **III.1.vv** succeeded in 79% yield. It was obtained in mixture with impurities from 3-amino pyridine. 2- or 4-amino pyridines gave no results (**III.1.ww**, **xx**) even after heating and the starting material was always recovered in mixture with the product of ketone self-condensation and degradation. Likewise, their trifluoromethyl homologues never gave final compounds **III.1.o**, **p** (Scheme 66).

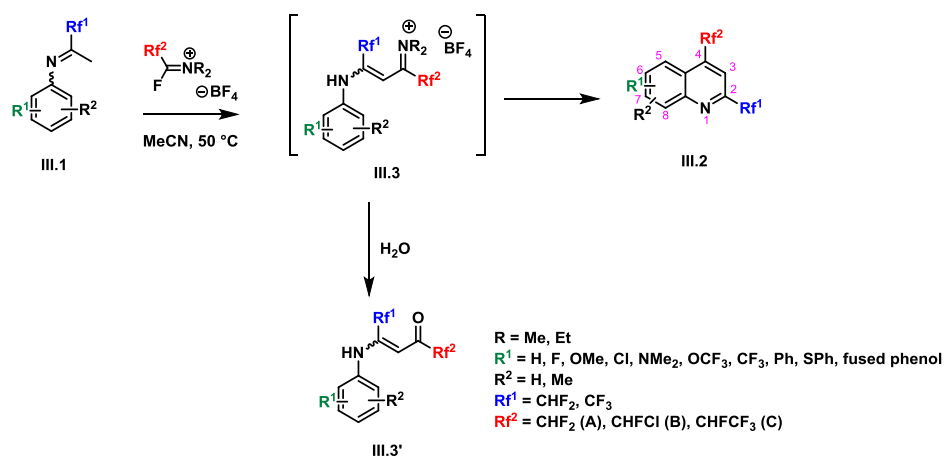


Scheme 66: Synthesis of compounds **III.1.o, **p** and **III.1.ww**, **xx****

4.1.2 Synthesis of quinoline derivatives

Ketimines **III.1** were then submitted to the second step of the synthetic pathway, namely the cyclization with activated FARs (**A.2**, **B.2**, **C.2**). In practice, FARs must be activated beforehand with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in MeCN for 15 min and directly mixed with fluorinated acetimines under argon. Fluorinated imines **III.1** reacted as nucleophiles onto iminium salts **A-C.2**, affording vinamidinium intermediates **III.3** which underwent electrophilic aromatic substitution yielding quinolines **III.2**, following a Combes-like cyclization process.

When the transformation was not complete, vinamides **III.3'** could be obtained after hydrolysis of the reaction mixture. These intermediates were not isolated, but observed in few cases only, since the cyclization occurs rapidly without external assistance (Scheme 67).



Scheme 67: Formation of fluorinated quinoline derivatives III.2 involving activated FARs

The desired quinolines were obtained in moderate to good yields (Scheme 68). One quinoline has been crystallized and X-ray diffraction analyses were performed to confirm the structure (Figure 65).

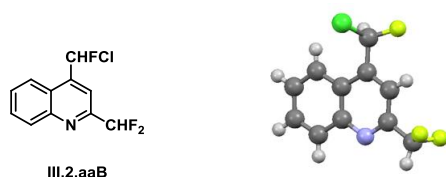
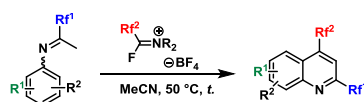


Figure 65: Crystal structure of III.2.aaB

CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines



^a: estimated yield ¹H NMR

^b: ¹⁹F NMR yield by using fluorobenzene as internal standard

^c: yield not determined (mixture or traces)

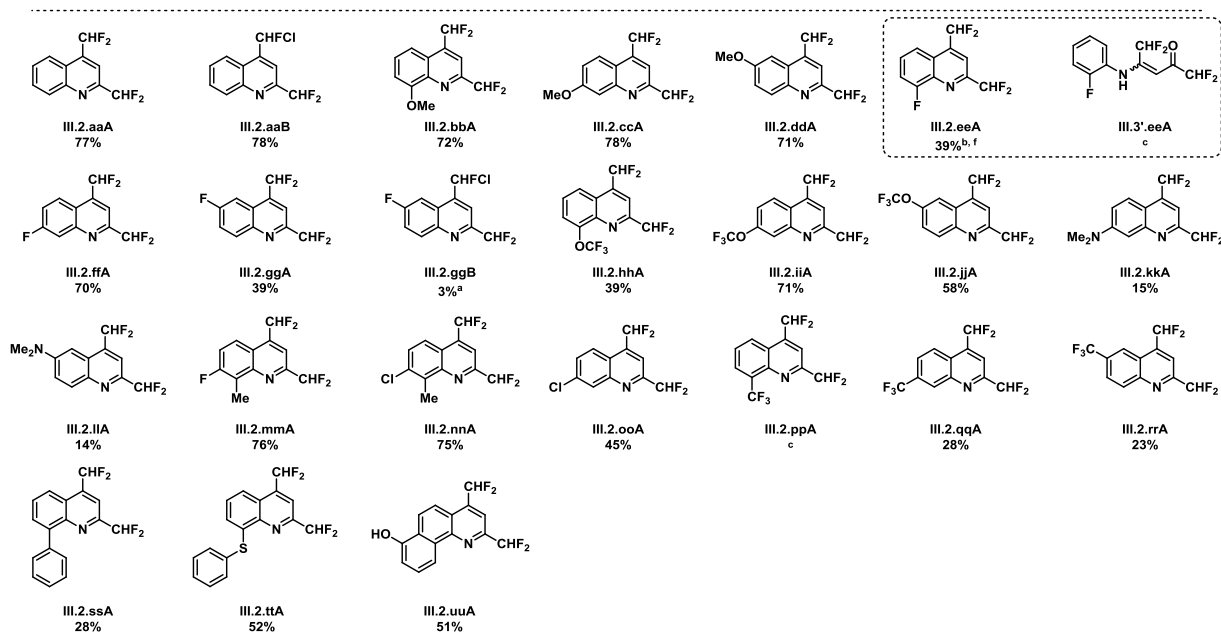
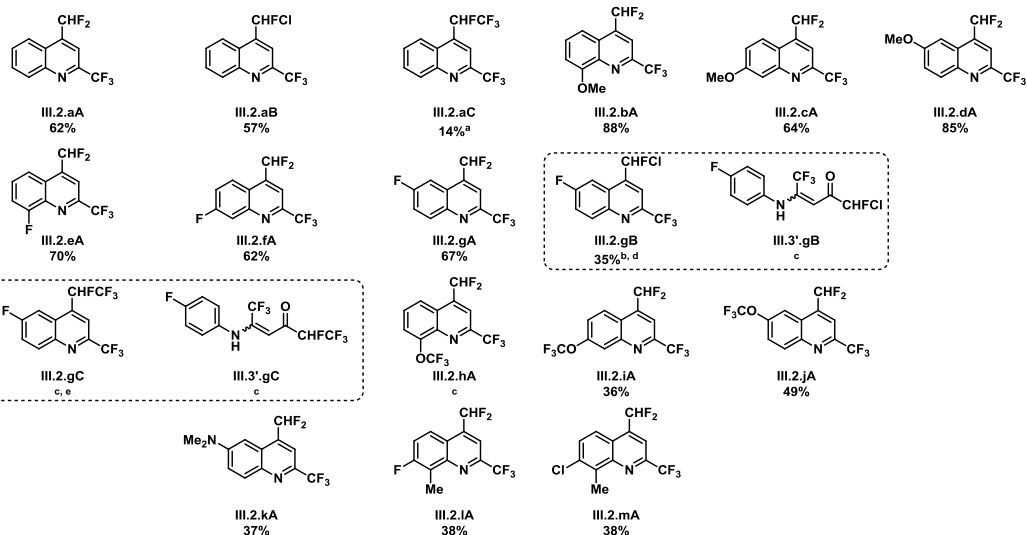
^d: ¹H NMR ratio 7:1 (III.2:III.3')

^e: ¹H NMR ratio 1:3 (III.2:III.3')

^f: ¹H NMR ratio 3:1 (III.2:III.3')

III.2.a-m: Rf¹ = CF₃ : n.d.-88%

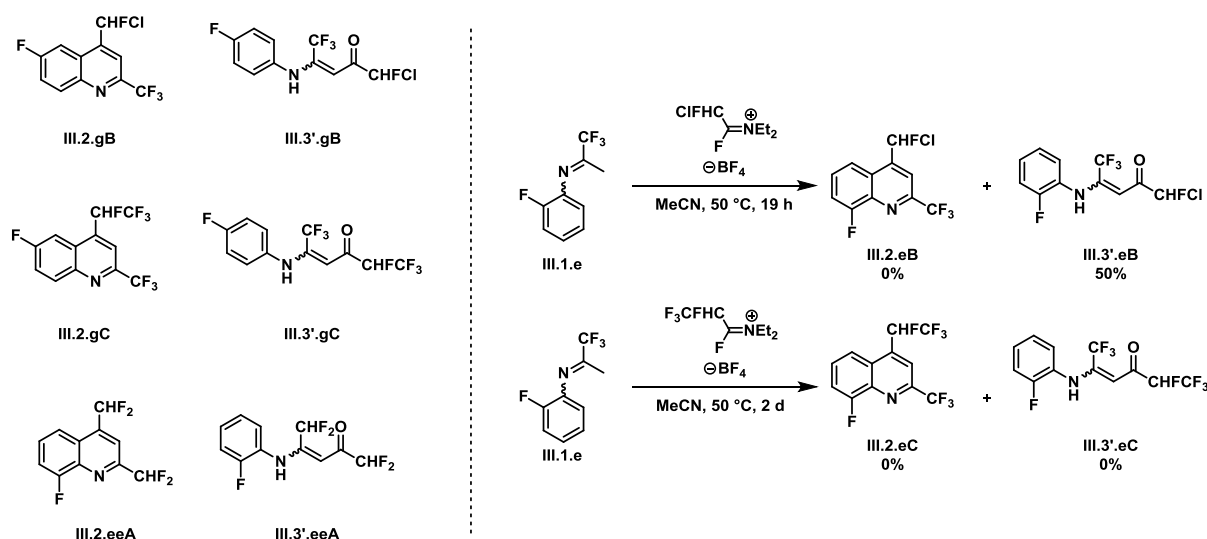
III.2.aa-vv: Rf¹ = CHF₂ : n.d.-78%



Scheme 68: Synthesis of fluorinated quinoline derivatives III.2

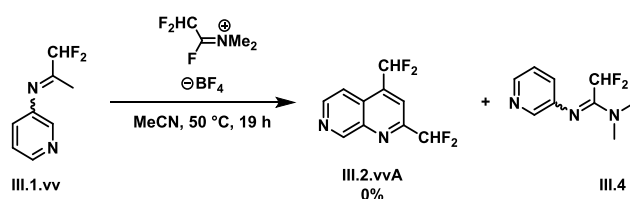
The isolation of quinolines synthesized from **III.1.pp**, **qq**, **rr** was relatively complex due to the high volatility of the final compounds.

In three reactions, the desired quinolines were obtained in mixture with the corresponding vinamide **III.3'** and were not isolated. One can notice that this occurs only from ketimines **III.1** possessing a fluoro substituent in position 2 or 4. The reaction of **III.1.e** with the activated Yarovenko reagent **B.2** led to the formation of **III.3'.eB** in 50% yield and traces of **III.2.eB** in one trial. With the Ishikawa reagent **C.2** the reaction failed and only the hydrolysed FAR **C.3** was recovered. The electron-withdrawing effect of fluorine atoms in position 2 or 4 seems to be not favourable to the cyclization and using bulky FARs could be an additional impediment for the ring closure (Scheme 69).



Scheme 69: Formation vinamides **III.3'** as interrupted cyclization products

We attempted to synthesize 2,4-bis(difluoromethyl)-1,7-naphthyridine **III.2.vvA** from **III.1.vv**. After several trials, the same mixture corresponding to starting material **III.1.vv**, 2,2-difluoro-*N,N*-dimethyl-*N'*-phenylacetimidamide **III.4** and unknown impurities was recovered. It will be interesting to optimize this reaction since naphthyridines possess a broad spectrum of biological activities (Scheme 70).³⁹⁰⁻³⁹¹



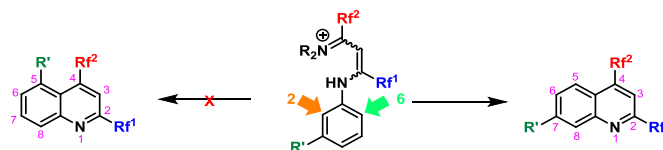
Scheme 70: Attempts to synthesize naphthyridine **III.2.vvA**

In general, quinoline derivatives prepared by using either the Yarovenko (**B.1**) or Ishikawa (**C.1**) reagents were formed in a lower yield than those synthesized with TFEDMA (**A.1**). These results confirmed the higher reactivity of the latter reagent.

Starting from imines bearing a *meta*-substituent on the arene can provide two regioisomers. Indeed, if the vinamidinium intermediate **III.3** cyclizes through the position **2**, 5-substituted quinolines would be obtained. On the other hand, 7-substituted quinolines would be obtained if the vinamidinium intermediate **III.3** cyclizes through the position **6** (Scheme 71).

During our study, only one regioisomer was obtained after purification, namely the 7-substituted quinoline. The complete regioselectivity of the reaction was naturally driven by the

bulkiness of the *meta*-substituent. Indeed, the reaction occurred on the less hindered position 6 of **III.3** (Scheme 71).



Scheme 71: Regioselectivity of the cyclization for *meta*-substituted aniline derived vinamidinium

We will focus now on the impact of substituents on the yields of quinolines. To simplify the problem, we will consider the reactions between ketimines **III.1** and TFEDMA **A.1** only.

The results can be rationalized in part by an interplay of destabilizing and stabilizing effects operating by Rf^1 on the vinamidinium intermediate **III.3** on the one hand, and on the Wheland intermediate obtained during the cyclization process on the other hand (Figure 66).

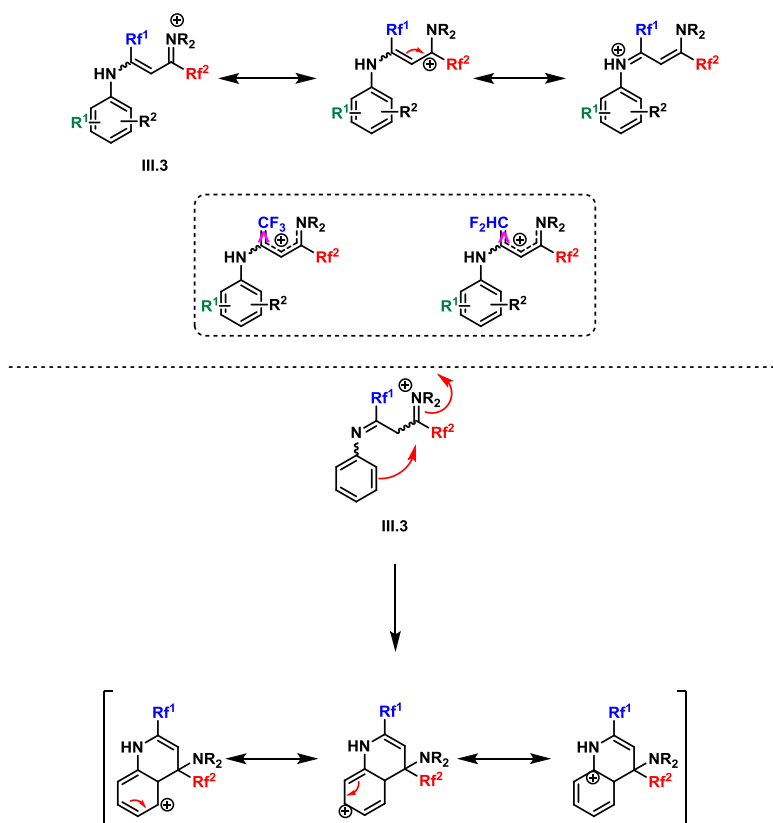


Figure 66: Stabilization / destabilization of intermediate **III.3 and the resulting Wheland intermediate during the cyclization process**

When Rf^1 is a CF_3 group, the electron-withdrawing effect of CF_3 destabilizes the vinamidinium intermediate. The addition of mesomeric donor substituents on the aromatic ring should stabilize it. We indeed noticed, that quinolines which possess methoxy or fluorine groups **III.2.b-gA**, were obtained in similar or better yields than the unsubstituted quinoline **III.2.aA** (Scheme 68). However, compound **III.2.kA** was a notable exception. The best result in terms of yields were obtained when mesomeric donor substituents are in position 2 or 4, which seems to indicate that stabilization of the vinamidinium intermediate is more crucial than stabilization of the Wheland intermediate. This could imply that the formation of the vinamidinium form is the

rate-determining step. The introduction of electron-withdrawing substituents on the aryl ring destabilized the vinamidinium and the Wheland intermediate even further and the cyclization was less efficient as one can see for compounds **III.2.h-jA** (Scheme 68).

On the other hand, when Rf¹ is a CHF₂ group, vinamidinium **III.3** is less destabilized and substituents on the aryl ring seem to affect rather the Wheland intermediate. Thus, better results were obtained for quinoline derivatives which possess a mesomeric donor substituent in position 7, due to the stabilization of the carbocation by resonance effect after cyclization. Dimethylamino quinolines **III.2.kk-IIA** were once again an exception to the rules.

In conclusion, many effects were implied, and subtler ones, like for examples conformational preferences, than those which are exposed must be invoked to really understand the observed reactivity towards the desired quinolines. The general trend is that higher yields were obtained for 7-substituted quinolines with Rf¹ = CHF₂, while when Rf¹ = CF₃, better results were obtained for 6- or 8-substituted quinolines.

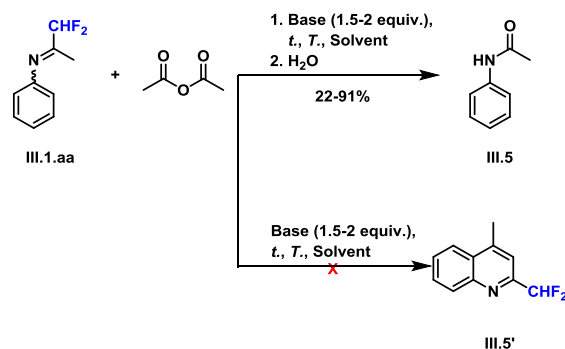
4.1.3 Comparison between the use of FARs and carboxylic anhydrides or oxalate derivatives in the synthesis of quinolines

The purpose of this part was to study the possibility to access similar quinoline derivatives using a commercially available and abundant fluorinated starting material. The use of such a reagent could considerably increase the scope of this approach and in the same time test the limitations of FARs chemistry.

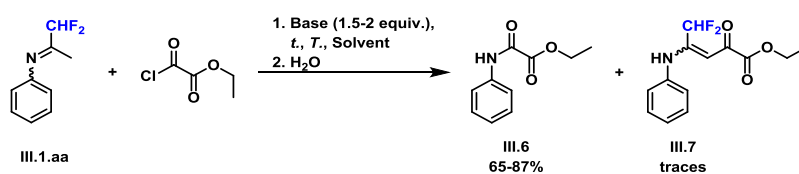
The first attempt was the reaction between imine **III.1.aa** and acetic anhydride in order to obtain 2-difluoromethyl-4-methylquinoline **III.5'**. It was performed in DCM or MeCN, from -5 to 50 °C. Bases like pyridine or DIPEA were added sometimes to neutralize the acetic acid which can be present in the starting reactant. At the end of each trial, *N*-phenylacetamide **III.5** was always obtained, in 22 to 91% yields. The compound resulted from the *N*-acylation and hydrolysis of the starting ketimine **III.1.aa** (Scheme 72, Table 9).

Table 9: Small screening of conditions for the reaction between ketimine III.1.aa and acetic anhydrides

Entry	Solvent	<i>t</i>	<i>T</i>	Base
1	DCM	19 h	-5 to 50 °C	Pyridine (1.5 equiv.)
2		1.5 h	r.t.	Pyridine (1.5 equiv.)
3	MeCN	1.5 h	r.t.	DIPEA (2 equiv.)
4		1.5 h	r.t.	/
5		19 h	50 °C	/

Scheme 72: Reaction between ketimine **III.1aa** and acetic anhydride

Next, we tried to perform the reaction between ethyl oxalyl monochloride and ketimine **III.1.aa** under the same conditions (Table 9). The corresponding ethyl-2-oxo-2-(phenylamino)acetate **III.6** was obtained as major fraction after purification in 65 to 87% yields. Only in presence of pyridine at room temperature in MeCN, traces of ethyl-5,5-difluoro-2-oxo-4-(phenylamino)pent-3-enoate **III.7** were isolated in mixture with unidentified impurities (Table 9, Entry 2) (Scheme 73).

Scheme 73: Reaction between ketimine **III.1aa** and ethyl oxalyl monochloride

So far, the use of acetic anhydride or oxalate derivatives did not lead to the formation of either the final quinoline or the vinamide intermediate.

The second part of this study was to evaluate the reactivity of ketimines in presence of fluorinated anhydrides. When trifluoroacetic anhydride was used in presence of ketimine **III.1.aa**, a mixture of **III.8** and of 2,2,2-trifluoro-*N*-phenylacetamide **III.9** was always obtained after purification. The best condition was obtained in MeCN at 50 °C without base, when the final 1,1,1,5,5-pentafluoro-4-(phenylamino)pent-3-en-2-one **III.8** was obtained in 49% yield (Table 10, Entry 5). We noticed that the addition of base favours only the acetamide formation and that at room temperature, the reaction leading to the desired enamine was too slow to reach completion (Scheme 74).

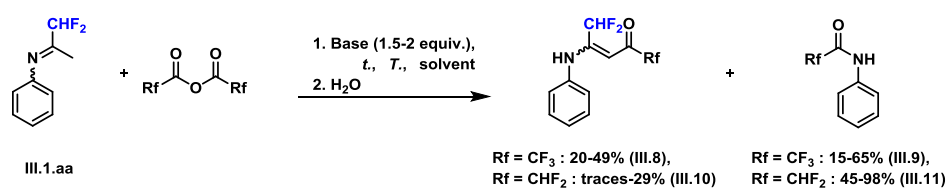
Table 10: Small screening of conditions for the reaction between ketimine III.1.aa and trifluoroacetic anhydrides

Entry	Solvent	<i>t</i>	<i>T</i>	Base	Yields (%) (III.8:III.9)
1	DCM	19 h	-5 to 50 °C	Pyridine (1.5 equiv.)	0:65
2		1.5 h	r.t.	Pyridine (1.5 equiv.)	20:54
3	MeCN	1.5 h	r.t.	DIPEA (2 equiv.)	0:35
4		1.5 h	r.t.	/	24:47
5		19 h	50 °C	/	49:15

Likewise, the addition of base in the reaction between ketimine **III.1.aa** and difluoroacetic anhydride favours acetamide formation. The generation of the vinamide was neither controlled nor reproducible. Indeed, several trials in MeCN at room temperature led to the formation of 2,2-difluoro-*N*-phenylacetamide **III.11** as major compound. But once (Table 11, Entry 2), 29% yield of the desired 1,1,5,5-tetrafluoro-4-(phenylamino)pent-3-en-2-one **III.10** were isolated (Scheme 74).

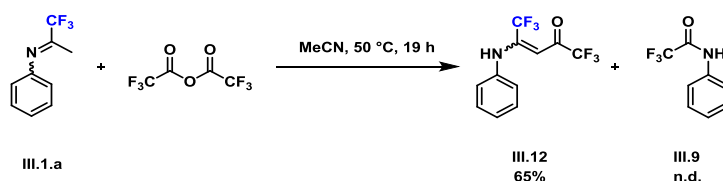
Table 11: Small screening of conditions for the reaction between ketimine III.1.aa and difluoroacetic anhydrides

Entry	Solvent	<i>t</i>	<i>T</i>	Base	Yields (%) (III.10:III.11)
1	DCM	19 h	-5 to 50 °C	Pyridine (1.5 equiv.)	traces:45
2		1.5 h	r.t.	Pyridine (1.5 equiv.)	29:64
3	MeCN	1.5 h	r.t.	DIPEA (2 equiv.)	Traces:47
4		1.5 h	r.t.	/	0:74
5		19 h	50 °C	/	0:98

**Scheme 74: Reaction between ketimine III.1.aa and fluorinated anhydrides**

On the other hand, the reaction between ketimine **III.1.a** and trifluoroacetic anhydride in MeCN at 50 °C gave rapidly access to 1,1,1,5,5,5-hexafluoro-4-(phenylamino)pent-3-en-2-one **III.12** in 65% yield (Table 9, Entry 5). The corresponding *N*-phenylacetamide **III.9** was always present as fraction after each purification (Scheme 75).

CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines



Scheme 75: Reaction between ketimine **III.1.a** and trifluoroacetic anhydride

The formation of traces of side-products was observed in certain cases in the reaction of **III.1.a** or **III.1.aa** with difluoroacetic anhydride. Compound **III.13** was corresponding to the non-rearomatized quinoline and **III.14-15** resulted from the attack of the starting ketimine on the fluorinated ketone released upon its hydrolysis (Figure 67).

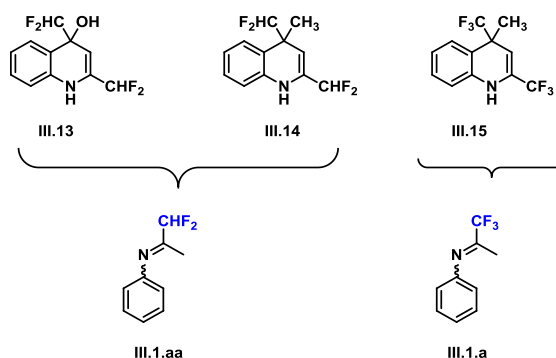
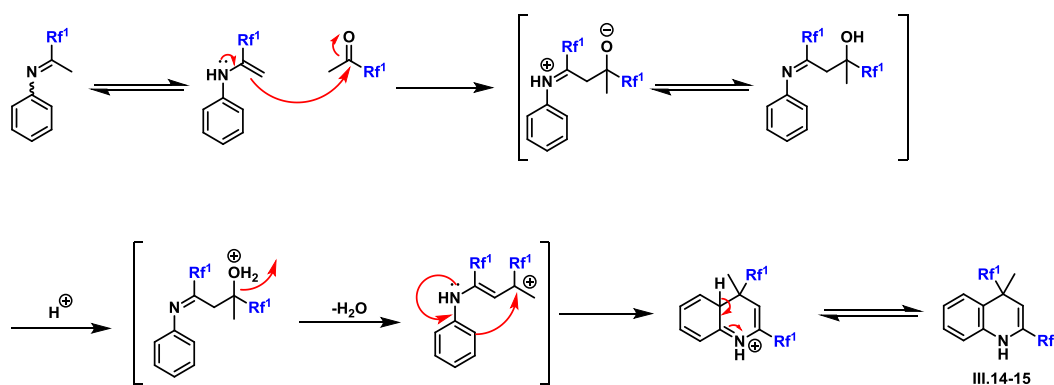


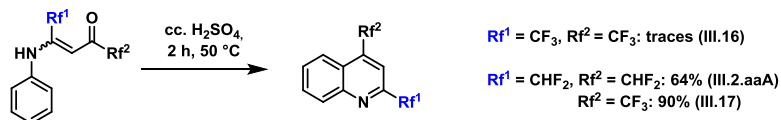
Figure 67: Observed side products in the reaction of **III.1.aa** and **III.1.a** with difluoroacetic anhydride

We postulated that traces of acid in difluoroacetic anhydride combined with trace of water in the ketimines were responsible for their hydrolysis to a small extent. The fluorinated ketone then formed can undergo a nucleophilic attack from the ketimine to form the corresponding fluorinated (phenylimino)pentanol. In presence of acid, the hydroxy moiety can be protonated and removed during the electrophilic aromatic substitution, which provided, after tautomerization, final products **III.14-15** (Scheme 76).



Scheme 76: Possible mechanism of the formation of compounds **III.14-15**

All intermediates **III.7**, **8**, **10**, **12**, **13** were difficult to obtain. Reactions were not reproducible, large amounts of waste were produced and the final quinoline was never obtained directly. Finally, in a third step, vinamides **III.8**, **10**, **12** were heated with concentrated H_2SO_4 . Quinolines **III.2.aaA**, **17** were obtained in good yields, while **III.16** was always obtained in traces amounts (Scheme 77).



Scheme 77: Formation of quinolines from the cyclization of vinamides in acidic medium

4.1.4 Conclusion

Herein, we developed a new method to synthesize quinoline derivatives based on FAR chemistry. These reactions, conceptually close to the Meth-Cohn and the Combes syntheses of quinolines, provided a new series of quinoline derivatives which possess similar or different fluorinated moieties in both 2 and 4 positions. They were obtained in only two steps, with good yields, under mild conditions, and with a total regioselectivity. On the other hand, the use of anhydrides as cyclization partners helped to confirm the superiority of FARs. Although anhydrides or acyl chlorides were synthetic assets, they did not allow to access to desired quinoline derivatives. In fact, the intermediate vinamides were hardly obtained and yields were not reproducible since the corresponding *N*-phenylacetamide was most of the time, the major product. When vinamides were nevertheless obtained, they were then submitted to a third reaction step in order to be converted into quinolines under harsh conditions. Accordingly, the FAR-based method proved to be much more efficient. The resulting quinolines were then submitted to further functionalization.

4.2 Introduction of new functionalities in position 8 by oxidation reactions³⁸⁸

Having in hand an efficient method to access 2,4-bis(fluoroalkyl)quinolines, we were interested in preparing derivatives bearing a carboxylic acid function in position 8 of quinoline. Indeed, two commercial quinoline-8-carboxylic acids, Quinclorac and Quinmerac showed some activities as selective herbicides. Quinclorac and Quinmerac are quinoline carboxylic acid developed by BASF in the early 1980s. They are used on cereals to control weeds growth.³⁹²⁻³⁹⁴ Thus, we were interested by introducing a carboxylic acid function at the same position on 2,4-bis(fluoroalkyl)quinolines. The aim was to test their potential activity as agrochemical ingredients (Figure 68).

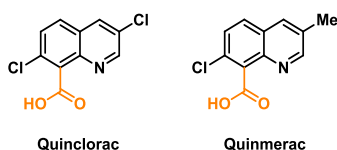
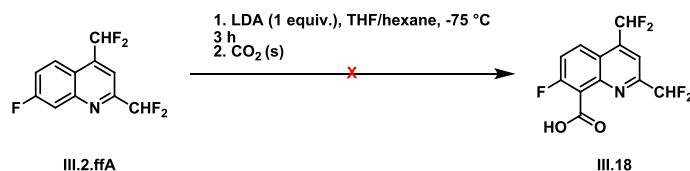


Figure 68: Molecular structures of Quinclorac and Quinmerac

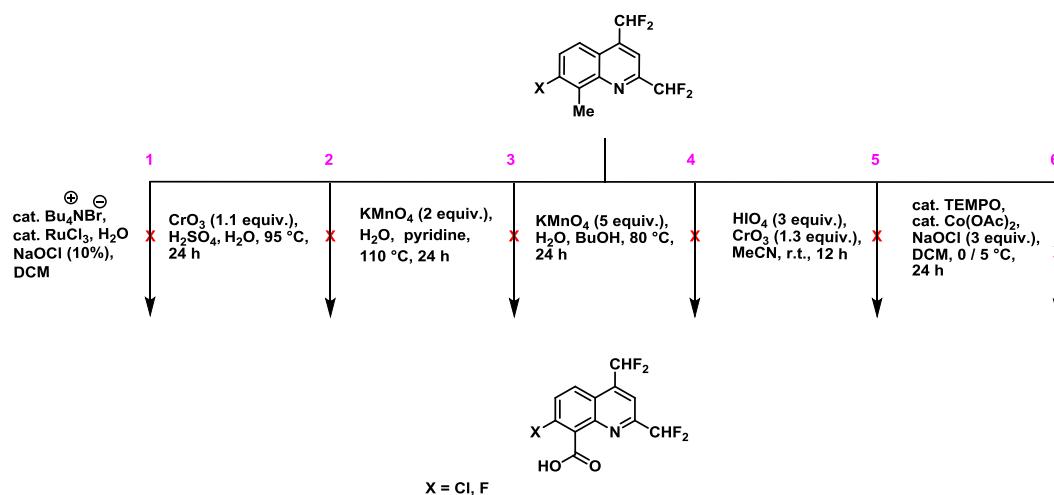
We first tried to introduce the carboxylic acid function directly by selective deprotonation of 2,4-bis(difluoromethyl)-7-fluoroquinoline **III.2.ffA** in *ortho*-position of nitrogen by using LDA in THF / hexane mixture at -75 °C,^{352, 354, 395-396} followed by trapping the organolithium species with dry ice to provide directly the desired acid **III.18**. The ¹H NMR spectrum of the reaction mixture revealed no formation of 2,4-bis(difluoromethyl)-7-fluoroquinoline-8-carboxylic acid **III.18**; a complex mixture was obtained instead (Scheme 78).



Scheme 78: Direct deprotonation using LDA and trapping with dry ice

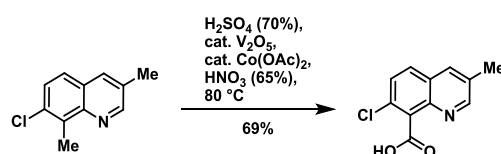
Next, an alternative strategy, based on the oxidation of a methyl group already present in position 8 was studied.

Conventional oxidation methods were evaluated to convert compounds **III.2.mmA** and **III.2.nnA** into their corresponding carboxylic acids following literature protocols. All reactions failed and the starting material was always completely recovered (Scheme 79).³⁹⁷⁻⁴⁰²



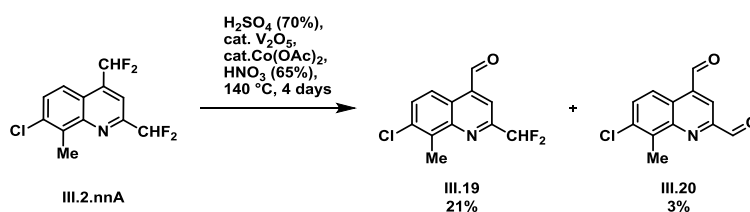
Scheme 79: Attempts to convert the methyl group in position 8 into its corresponding carboxylic acid

Hagen *et al.* described in 1988 the synthesis of 7-chloro-3-methylquinoline-8-carboxylic acid in 69% yield from 7-chloro-3,8-dimethylquinoline using a mixture of acids (H_2SO_4 and HNO_3) and two oxides in catalytic amount (Scheme 80).⁴⁰³



Scheme 80: Synthesis of 7-chloro-3-methylquinoline-8-carboxylic acid from 7-chloro-3,8-dimethylquinoline

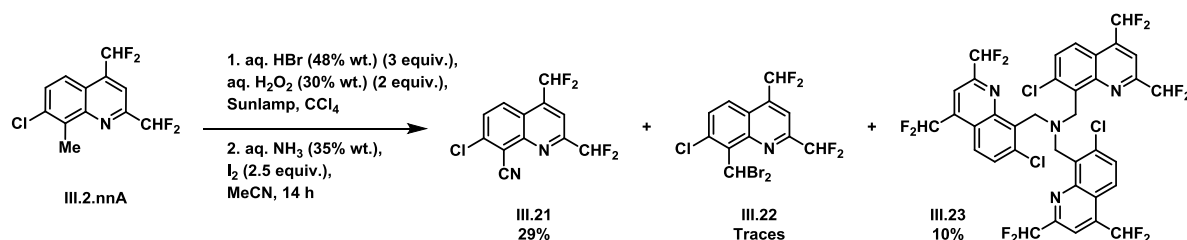
Reproducing the same reaction conditions on 7-chloro-2,4-bis(difluoromethyl)-8-methylquinoline **III.2.nnA** led to the formation of two undesired compounds **III.19** and **III.20** in 21% and 3% yield, respectively. A second attempt was carried out to confirm the formation of these products. They were obtained once again, but the yields were not increased (Scheme 81). In this reaction, acids are present in order to solubilize metal oxides such as vanadium (V) oxide which is not soluble in water. Metal oxides such as potassium permanganate should then act on the methyl moiety to convert it into a carboxylic acid. However, in this case the more electron-poor carbons of the difluoromethyl groups were more prone to be attacked. The presence of each metallic oxide is yet unclear. One probably oxidizes the carbon and the second one re-oxidizes the first metal to pursue the reaction.



Scheme 81: Reproduction of Hagen *et al.*'s procedure on 7-chloro-2,4-bis(difluoromethyl)-8-methylquinoline **III.2.nnA**

In parallel, we attempted the transformation of the methyl group in position 8 into nitriles and convert them finally into a carboxylic acid. The reaction was performed on 7-chloro-2,4-bis(difluoromethyl)-8-methylquinoline **III.2.nnA** in presence of an aqueous hydrobromic acid

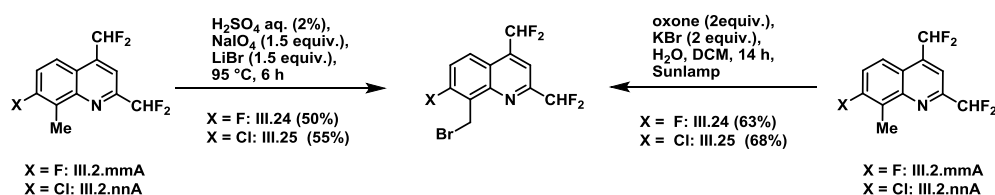
and an aqueous hydrogen peroxide in carbon tetrachloride under light; then aqueous ammonia and iodine were added in MeCN, according to the procedure by Togo *et al.*⁴⁰⁴ After 14 h under sunlamp irradiation three compounds were isolated after purification. The desired 7-chloro-2,4-bis(difluoromethyl)quinoline-8-carbonitrile **III.21** was obtained in 29% yield. Traces of 7-chloro-8-(dibromomethyl)-2,4-bis(difluoromethyl)quinoline **III.22** were obtained, as well as 10% of tris((7-chloro-2,4-bis(difluoromethyl)quinolin-8-yl)methyl)amine **III.23** formed during the radical process. Indeed, the plausible mechanism passes by a primary amine intermediate which can react with the radical quinoline-8-ylmethyl formed during the first step and provided **III.23** (Scheme 82).



Scheme 82: One-pot transformation of III.2.nnA into the corresponding quinoline-8-carbonitrile III.21

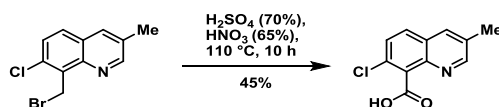
The yield of quinoline-8-carbonitrile **III.21** was not satisfying enough to perform the transformation into the corresponding carboxylic acid. Another procedure of Togo *et al.* described the conversion of a methyl group into a carboxylic acid under photochemical conditions.⁴⁰⁵ Following this procedure, the desired carboxylic acid should be obtained treating 8-methyl-2,4-bis(difluoromethyl)-7-halo-quinolines **III.2.mmA** or **III.2.nnA** with oxone® and potassium bromide in DCM / water media. Nevertheless, the reaction did not allow the access to the desired compounds but to 8-(bromomethyl)-2,4-bis(difluoromethyl)-7-halo-quinolines **III.24** (X = F) and **III.25** (X = Cl) in 63 and 68% yield, respectively.

The thermal procedure proposed by Sudalai *et al.* (aqueous sulfuric acid, sodium periodate and lithium bromide in the absence of solvent) gave the same results.⁴⁰⁶ Nonetheless, 8-(bromomethyl)-2,4-bis(difluoromethyl)-7-halo-quinolines **III.24** (X = F) and **III.25** (X = Cl) were obtained in 50 and 55% yield, respectively. As the photochemical procedure was easier to carry out and gave better results, it was preferred although slightly longer reaction time was required (Scheme 83).



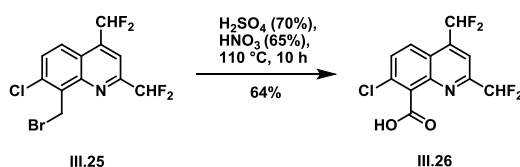
Scheme 83: Oxidative bromination of the methyl group in position 8 of III.2.mmA, nnA under photochemical vs. thermal conditions

In 1984, Hagen *et al.* performed the oxidation of 8-(bromomethyl)-7-chloro-3-methylquinoline into its corresponding carboxylic acid (Quinmerac) thanks to a mixture of concentrated acids at 110 °C (Scheme 84).³⁹³



Scheme 84: Synthesis of 7-chloro-3-methylquinoline-8-carboxylic acid according to the procedure of Hagen *et al.*

Using these conditions, 8-(bromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline **III.25** was efficiently converted into 7-chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid **III.26** which was obtained in 64% yield (Scheme 85).



Scheme 85: Oxidation of 8-(bromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline into 7-chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid III.26

The structure of the desired compound was confirmed by single-crystal X-ray diffraction studies, 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 69).

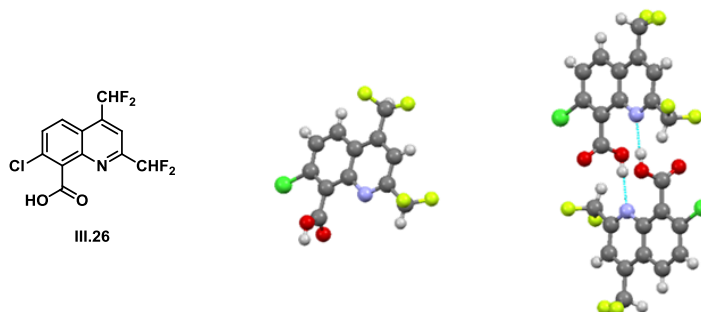
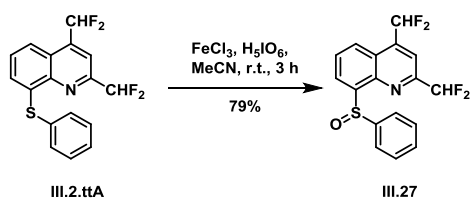


Figure 69: Crystallography analysis of III.26

As alternative strategy, we tried the oxidation of 2,4-bis(difluoromethyl)-8-(phenylsulfanyl)quinoline **III.2.ttA** following the procedure of Kim *et al.* using iron(III) chloride and periodic acid.⁴⁰⁷

Indeed, this compound would be a precursor for sulfoxide-metal exchange trapped by dry ice to provide the desired 7-chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid **III.26**. Sulfoxide **III.27** was obtained in 79% yield in a racemic mixture. The diastereotopic fluorine atoms were observed in ¹⁹F NMR and confirmed the presence of the stereogenic center on the molecule (the sulfone was not formed) (Scheme 86). By lack of time the sulfoxide-metal exchange was not attempted.



Scheme 86: Oxidation of 2,4-bis(difluoromethyl)-8-(phenylsulfanyl)quinoline III.2.ttA into sulfoxide III.27

This study revealed the resistance of compounds **III.2.mmA** and **III.2.nnA** toward oxidation. Indeed compounds which possess a methyl in position 8 were hardly oxidized, the carboxylic acid function was difficultly introduced and most reactions did not lead to the expected product, as attested by the need of harsh reaction conditions to afford final compounds in moderate yields only. It can be in part explained by the low electron-density of these bis(fluoroalkyl)quinolines.

To validate this hypothesis, we carried out electrochemical studies to determine the physico-chemicals properties of these new series of quinoline derivatives. In parallel, spectrofluorometric analyses were performed to study their spectrophotometric properties, since some compounds revealed themselves to be fluorescent yellow in solution; this kind of molecules can be interesting for further application in material science field.

4.3 Physico-chemical investigations on 2,4-bis(fluoroalkyl) quinoline derivatives

4.3.1 Spectrophotometric absorption properties

Several analyses were conducted on quinoline derivatives to better understand their physico-chemical properties. We started by absorption measures. Several effects might be observed as defined hereafter (Figure 70):

- **Bathochromic effect** (*red shift*) is the shift of an absorption maximum to a higher wavelength.
- **Hypsochromic effect** (*blue shift*) is the shift of an absorption maximum to a shorter wavelength.
- **Hyperchromic effect** is an effect which leads to an increase in absorption intensity.
- **Hypochromic effect** is an effect which leads to a decrease in absorption intensity.

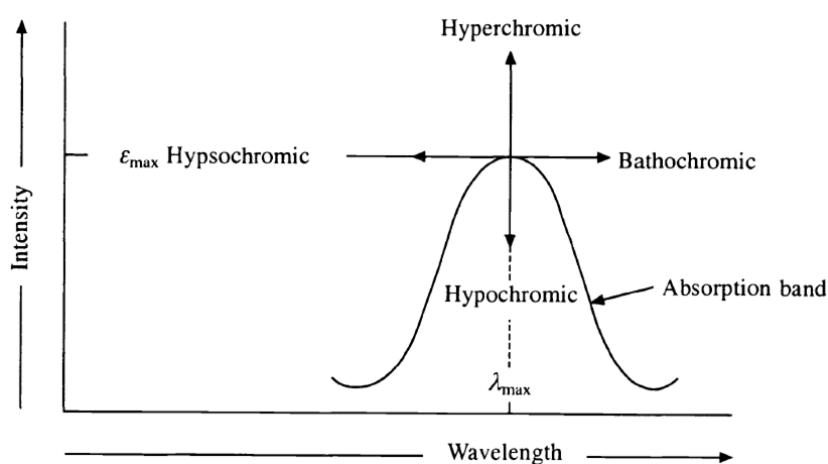


Figure 70: Definition of the visible effect in absorption

In literature, three types of absorption bands are reported for aromatic rings such as benzene or naphthalene, which all correspond to a π - π^* transition in the near UV region. These absorption bands are noted III, II, I and are ascribed to transitions from the ground state (1A_g) to 1L_a (II: broad absorption), to 1L_b (I: sharp absorption) and to 1B_b (III) excited states. The 1L_a excited state results from a HOMO-LUMO transition (Figure 71).⁴⁰⁸⁻⁴¹⁰

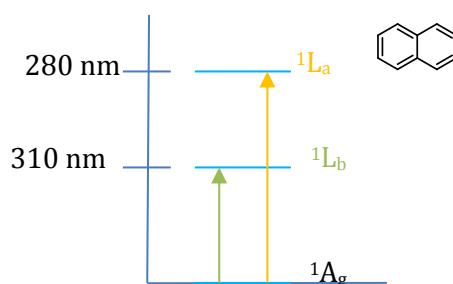


Figure 71: Electronic energy diagrams of naphthalene molecular orbitals for the two low absorption bands I and II

All carbocyclic aromatic systems depicted nearly the same absorption bands for π - π^* transition. Quinoline derivatives are heterocyclic analogues to naphthalene and similarly to it, their absorption spectra revealed the presence of three transitional bands (III, II, I).⁴¹¹ Considering bands III and I, one can notice the increase in intensity compared to naphthalene, while band II is almost at the same intensity level. On the other hand, the first 1L_b and second 1L_a absorption bands, that are more easily accessible in the UV-visible window of the spectrum, are poorly separated from each other. Concerning the expected n - π^* transition band characteristic of nitrogen heteroaromatic systems, it is masked here by the intense π - π^* transition band (Figure 72).

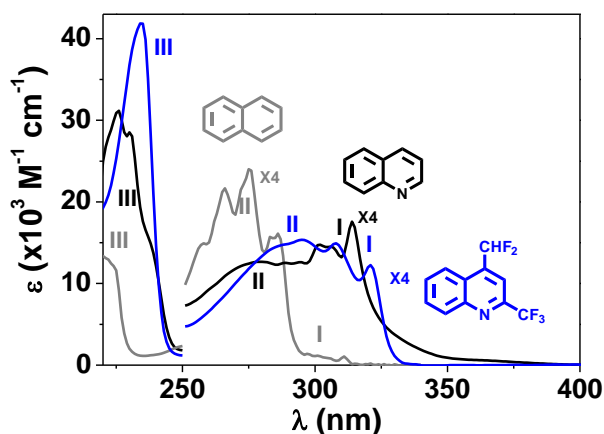


Figure 72: Comparison of the electronic absorption spectra of naphthalene (cyclohexane)⁴¹², quinoline (1,2-dichloroethane) and III.2.aA (1,2-dichloroethane) measured at 25 °C

Addition of fluoroalkyl substituents (*e.g.* CHF₂, CHFCl, CF₃ or CHF₂CF₃) in both 2 and 4 positions of quinoline derivatives (centred on the pyridyl subunit) does not affect so much the electronic absorption properties of the quinolines chromophores. It results in a weak bathochromic shift of the two π - π^* transitions conjugated to a hypo- and hyperchromic shift for band I and band II respectively, leading to a blend of the two sets of transitions compared to parent quinoline (Figure 73).

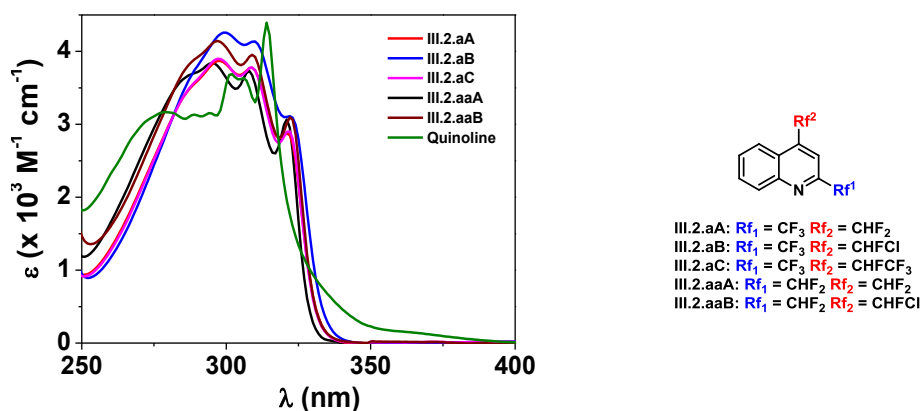


Figure 73: Electronic absorption spectra of fluorinated (CHF₂, CHFCl, CF₃ or CHF₂CF₃) quinolines substituted in C2 and C4 positions (III.2.aA, III.2.aB, III.2.aC, III.2.aaA and III.2.aaB). Solvent: 1,2-dichloroethane; T = 25 °C

On the other hand, no significant effect was observed with respect to the nature of substitution. Despite properties exerted by fluorine, increasing the number of fluorine atoms linked to the

same carbon in position 2 or 4 has only a minor effect on the absorption pattern of corresponding quinoline derivatives (Figure 73, Table 12).

Table 12: Absorption properties for quinoline and its derivatives substituted in C2 and C4 positions by fluorinated groups (quinoline, III.2.aA, III.2.aB, III.2.aC, III.2.aaA and III.2.aaB)

Compound	$\pi-\pi^*$	
	λ (nm)	ϵ ($\times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$)
quinoline	278	3.167
	289	3.134
	294	3.154
	302	3.688
	306	3.634
	314	4.395
III.2.aA	288	sh
	298	3.869
	309	3.777
	321	2.876
III.2.aB	289	sh
	299	4.256
	309	4.138
	322	3.112
III.2.aC	287	sh
	298	3.898
	309	3.778
	322	2.904
III.2.aaA	285	sh
	295	3.843
	308	3.732
	321	3.067
III.2.aaB	287	sh
	297	297
	309	309
	322	322

*sh: shoulder

The next step was the study of the effect of substitution on the benzene ring unit by electron-withdrawing groups (*i.e.* F, OCF₃) on **III.2.aA** and **III.2.aaA**. The chosen compounds bear fluorine and trifluoromethoxy moieties in three different positions:

- C6 position: **III.2.gA** and **III.2.ggA** for F and **III.2.jA** and **III.2.jjA** for OCF₃.
- C7 position: **III.2.fA** and **III.2.ffA** for F and **III.2.iA** and **III.2.iiA** for OCF₃.
- C8 position: **III.2.eA** for F and **III.2.hhA** for OCF₃.

In both series (**III.2.aA** and **III.2.aaA**), the introduction of fluorine or trifluoromethoxy on carbons C6 or C7 led to a significant hypochromic and hypsochromic shift of the $\pi-\pi^*$ transitional band III (Figure 74, Table 13).

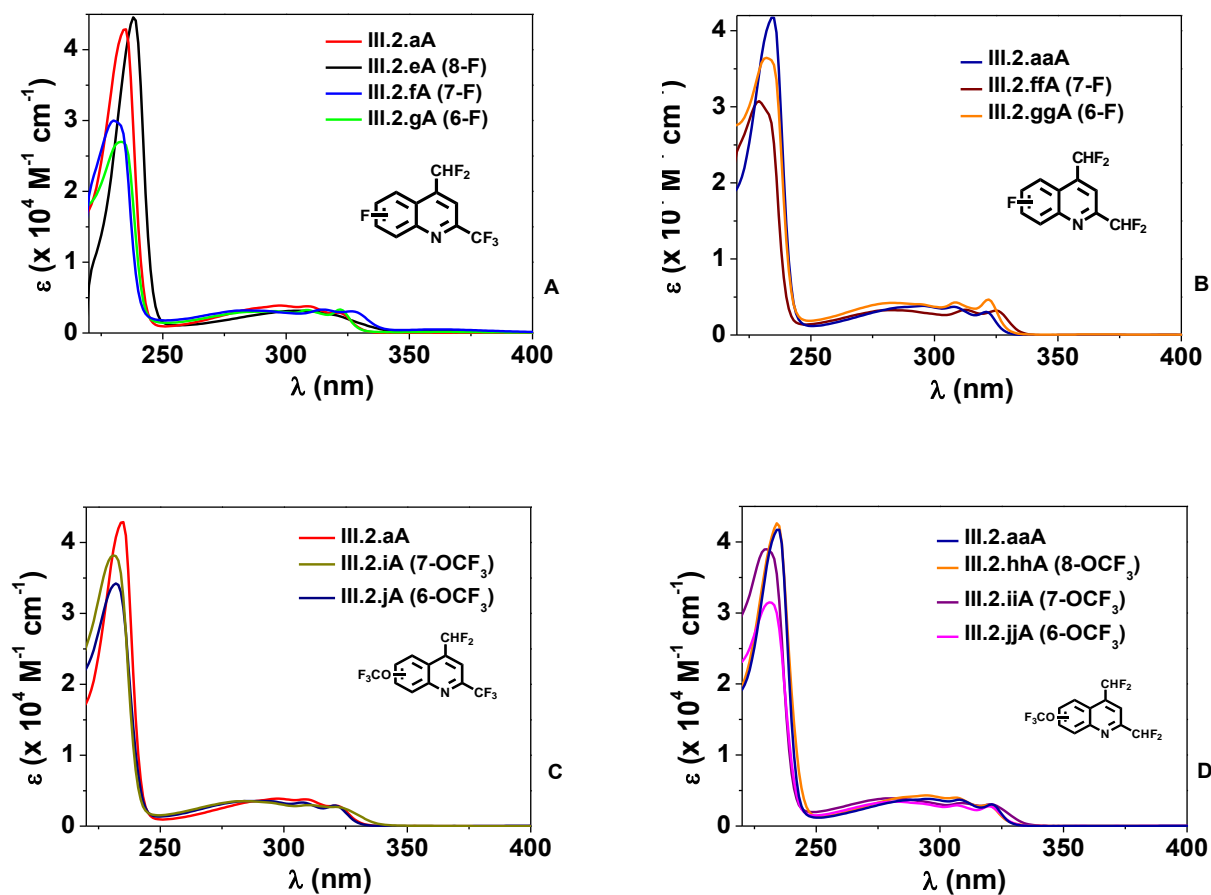


Figure 74: Influence of the F or CF_3 substituents on the electronic absorption spectra of quinolines substituted by either: A) a fluorine on C6 (III.2.gA), C7 (III.2.fA) or C8 (III.2.eA) and a CF_3/CHF_2 combination in C2/C4 positions; B) a fluorine on C6 (III.2.ggA) or C7 (III.2.ffA) and a $\text{CHF}_2/\text{CHF}_2$ combination in C2/C4 positions; C) a trifluoromethoxy on C6 (III.2.jA) or C7 (III.2.iA) and a CF_3/CHF_2 combination in C2/C4 positions; D) a trifluoromethoxy on C6 (III.2.jjA), C7 (III.2.iiA) or C8 (III.2.hhA) and a $\text{CHF}_2/\text{CHF}_2$ combination in C2/C4 positions. Solvent: 1,2-dichloroethane, $T = 25^\circ\text{C}$

CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

Table 13: Electronic absorption properties for quinoline derivatives III.2.aA and analogues substituted by a fluorine group on either C6 (III.2.gA), C7 (III.2.fA) or C8 (III.2.eA) [top left]; III.2.aaA and analogues substituted by a fluorine group on either C6 (III.2.ggA) or C7 (III.2.ffA) [bottom left]; III.2.aA and analogues substituted by a trifluoromethoxy group on either C6 (III.2.jA) or C7 (III.2.iA) [top right]; III.2.aaA and analogues substituted by a trifluoromethoxy group on either C6 (III.2.jjA), C7 (III.2.iiA) or C8 (III.2.hhA) [bottom right]. Solvent: 1,2-dichloroethane, T = 25.0 °C

Compound	Band III λ (ϵ)	Band I (1L_b) λ (ϵ)	Band II (1L_a) λ (ϵ)	Compound	Band III λ (ϵ)	Band I (1L_b) λ (ϵ)	Band II (1L_a) λ (ϵ)
F				OCF ₃			
III.2.aA	235 (4.29)	287 (0.347) 298 (0.387) 309 (0.378) 321 (0.287)		III.2.aA	235 (4.29)	287 (0.347) 298 (0.387) 309 (0.378) 321 (0.287)	
III.2.gA	233 (2.70)	283 (0.295) 295 (0.310) 309 (0.324) 322 (0.332)		III.2.jA	232 (3.422)	286 (0.355) 293 (0.354) 308 (0.333) 321 (0.291)	
III.2.fA	230 (3.00)	283 (0.318) 290 sh 315 (0.331) 327 (0.306)		III.2.iA	232 (3.422)	284 (0.352) 310 (0.296) 321 (0.271)	
III.2.eA	238 (4.458)	306 (0.315) 320 sh					
				III.2.aaA	234 (4.172)	284 sh 295 (0.383) 308 (0.372) 321 (0.306)	
III.2.aaA	234 (4.172)	284 sh 295 (0.383) 308 (0.372) 321 (0.306)		III.2.jjA	231 (3.148)	282 (0.344) 293 sh 307 (0.292) 320 (0.279)	
III.2.ggA	232 (3.645)	284 (0.422) 294 (0.403) 309 (0.428) 322 (0.467)		III.2.iiA	230 (3.897)	280 (0.391) 294 sh 309 (0.323) 321 (0.306)	
III.2.ffA	229 (3.074)	282 (0.326) 288 sh 312 (0.331) 325 (0.321)		III.2.hhA	234 (4.264)	284 sh 294 (0.431) 306 (0.401) 319 (0.297)	

Solvent: 1,2-dichloroethane; T = 25 °C; λ in nm; ϵ in $\times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$. The errors on λ and ϵ are given as ± 1 nm and 10%, respectively. sh=shoulder

A zoom on bands II and I of figure 75 allows to sharpen the interpretation of these effects. When placed in position C6, a fluorine substituent has only a weak effect on the position and the shape of absorption peaks (II and I); however a notable effect on the absorption of quinolines was observed since a hypo- or hyperchromic shift of absorption intensity is visible respectively for compounds **III.2.gA** and **III.2.ggA** vs. **III.2.aA** and **III.2.aaA**. A fluorine substituent in position C6 weakly influences either by induction or resonance effects the transitions I and II of quinoline chromophores. Nevertheless, C7 fluorine substitution led to a splitting of the two sets of

absorption transitions caused by a hypsochromic shift on 1L_a and a bathochromic shift on 1L_b . Indeed, a stabilization of the π - π^* bond transition (I) and a destabilization of the π - π^* bond transition (II) by the mesomeric electron-donor character of fluorine can be invoked. In the last case, fluorine in position C8 on quinoline derivatives led conversely to a blending of 1L_a and 1L_b transitions (Figure 75).

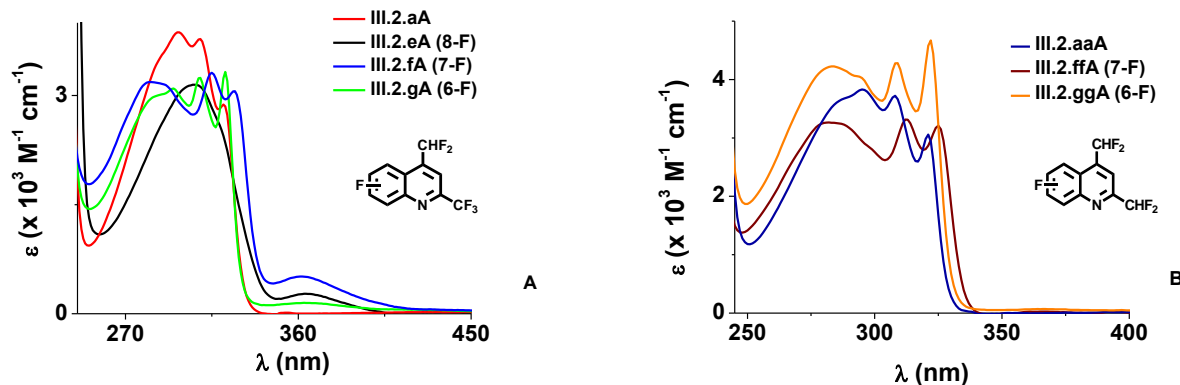


Figure 75: Zoom on the influence of the F or CF_3 substituents on the electronic absorption spectra of quinolines substituted by either: A) a fluorine on C6 (III.2.gA), C7 (III.2.fA) or C8 (III.2.eA) and a CF_3/CHF_2 combination in C2/C4 positions; B) a fluorine on C6 (III.2.ggA) or C7 (III.2.ffA) and a CHF_2/CHF_2 combination in C2/C4 positions. Solvent: 1,2-dichloroethane, T = 25 °C

Substitution in positions C6 or C7 by a trifluoromethoxy group (strong -I and weak +M effects) results in a hypsochromic shift of the 1L_a band while 1L_b remains unaffected. The substitution in position C8 has no effect and absorption patterns follow the one of III.2.aaA (Figure 76).

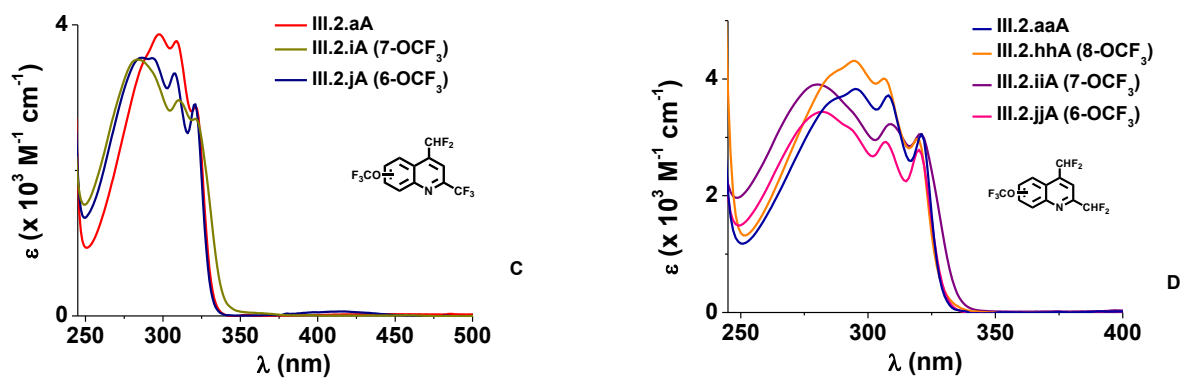


Figure 76: Zoom on the influence of the F or CF_3 substituents on the electronic absorption spectra of quinolines substituted by either: C) a trifluoromethoxy on C6 (III.2.jA) or C7 (III.2.iA) and a CF_3/CHF_2 combination in C2/C4 positions; D) a trifluoromethoxy on C6 (III.2.jjA), C7 (III.2.iiA) or C8 (III.2.hhA) and a CHF_2/CHF_2 combination in C2/C4 positions. Solvent: 1,2-dichloroethane, T = 25 °C

Another part of this study was to compare substituents effects – at the same position – on the electronic absorption properties of quinoline derivatives.

For the first comparison, we focused on compounds bearing electron-donating and electron-withdrawing groups in position C6 on the series of III.2.aA-type quinolines. As previously exposed, electron-withdrawing groups such as F or OCF_3 showed minor impacts on the shape and position of absorption peaks. Nevertheless, electron-donating substituents (OMe: III.2.dA and NMe_2 : III.2.kA) significantly alter absorption properties. A strong bathochromic shift of band III as well as a change in the shape and the position of bands II and I were observed.

Compound **III.2.kA** displayed a broad and intense absorption in the UV-visible region (406 nm corresponding to 1L_a ; one can notice the inversion of the respective positions of bands II and I due to the substituent-induced photobasicity [*i.e.* a molecule that becomes more basic in the excited state with respect to its ground state] (Figure 77, Table 14).⁴¹³⁻⁴¹⁷

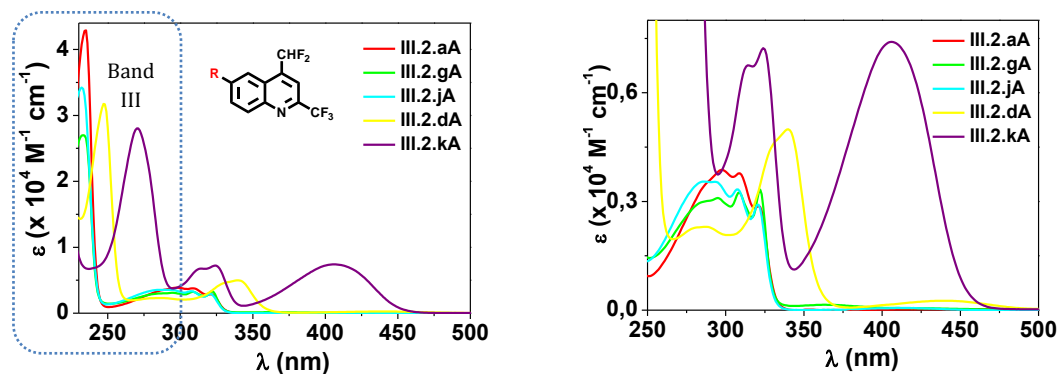


Figure 77: Influence on the absorption spectra of the substitution on the C6 position for quinoline derivatives bearing a CF_3 in C2 and a CHF_2 in C4 (derivative **III.2.aA** as a reference scaffold) [left: full spectrum; right: zoom on bands II and I spectra]. Solvent: 1,2-dichloroethane, $T = 25.0\text{ }^\circ\text{C}$

Table 14: Absorption properties of 6-substituted quinoline derivatives bearing a CF_3 in C2 position and a CHF_2 in C4 position

Compound	6-R	Band III	Band I (1L_b)	Band II (1L_a)
		λ (ϵ)	λ (ϵ)	λ (ϵ)
III.2.aA	H	235 (4.29)	287 (0.347)	
			298 (0.387)	
			309 (0.378)	
			321 (0.287)	
III.2.gA	F	233 (4.29)	283 (0.295)	
			295 (0.310)	
			309 (0.324)	
			322 (0.332)	
III.2.jA	OCF_3	232 (3.42)	285 (0.354)	
			294 (0.354)	
			307 (0.333)	
			321 (0.291)	
III.2.dA	OMe	247 (3.17)	287 (0.230)	
			330 (0.456)	440 (0.026)
			340 (0.499)	
III.2.kA	NMe_2	270 (2.8)	312 (0.664)	406 (0.740)
			324 (0.723)	

Solvent: 1,2-dichloroethane; $T = 25\text{ }^\circ\text{C}$; λ in nm; ϵ in $\times 10^4\text{ M}^{-1}\text{ cm}^{-1}$. The errors on λ and ϵ are given as ± 1 nm and 10%, respectively.

As complementary data on the series of C6-substituted analogues of **III.2.aA** in order to assess their electronic properties, a ^{13}C NMR study was carried out.

Figure 78 illustrates the variations of the chemical shifts of the quinoline carbons as a function of the nature of substitution at the C6 position of **III.2.aA**-derived quinolines (Figure 78, Table 15). The study of the chemical shift of carbons showed that globally no modification occurs on carbons far from position C6, *i.e.* those of the pyridine ring unit and the C8 position. However, neighbouring carbons C5 and C7 are fully impacted (shielding of carbons with respect to **III.2.aA**) by the presence of mesomeric electron-donating groups in C6 position. It is interesting to note that the trifluoromethoxy group behaves as a -I and +M group, very much like F, OMe and NMe₂ substituents although with a reduced amplitude. As expected, a deshielding of carbon C6 with respect to **III.2.aA** is observed due to the -I effect of the C6-substituents.

Concerning the most effective +M groups, namely OMe: **III.2.dA** and NMe₂: **III.2.kA** a more obvious shielding of carbons C2 and C4 suggests a resonance process along the aromatic system (more important than for F or OCF₃) which could explain the large bathochromic shifts of $^1\text{L}_a$ transitions. It is noteworthy that the C2 and C4 substitution with electron-withdrawing fluorinated functions exacerbates this electronic effect with respect to quinoline.

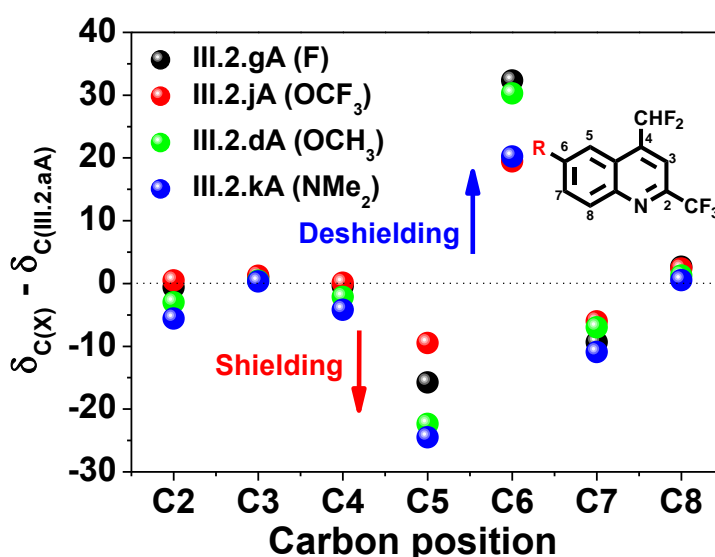


Figure 78: Variation of the ^{13}C NMR shifts of the quinoline carbons as a function of the nature of the substituent on position C6 in the **III.2.aA**-derived quinoline series. Solvent: CDCl_3 ; T = 298K

Table 15: ^{13}C NMR chemical shifts of 6-substituted quinoline derivatives bearing a CF_3 in C2 position and a CHF_2 in C4 position (**III.2.aA** series). Solvent: CDCl_3 ; T = 298 K

Compound	^{13}C δ (ppm)							
	6-R	C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈
III.2.aA	H	147.94	114.14	140.33	123.44	130.06	131.39	131.29
III.2.gA	F	147.31	115.09	139.92	107.68	162.40	122.01	133.96
III.2.jA	OCF ₃	148.41	115.36	140.46	113.97	149.50	125.35	133.66
III.2.dA	OMe	144.95	114.59	138.21	101.06	160.35	124.42	132.56
III.2.kA	NMe ₂	142.35	114.48	136.12	98.92	150.28	120.46	131.80

Compounds of the series **III.2.aaA** were also considered and the electronic absorption spectra of the C6-substituted derivatives were recorded (Figure 79, Table 16).

Overall, the absorption spectral variations shown for the **III.2.aaA** series also holds for the analogous **III.2.aaA**. The substitution pattern (CF₃ vs. CHF₂) on the pyridyl ring does not modify the spectral variations induced by the substituents at the C6 position.

Substituents exerting a rather electron-withdrawing effect (*i.e.* F and OCF₃) induced only minor modifications, while substituents having a stronger electron-donating influence than an electron-withdrawing one (*i.e.* OMe and NMe₂) led to a strong bathochromic shift of band ¹L_a (446 nm and 400 nm). It is noteworthy that the intensity of the ¹L_a absorbance peak is much weaker for OMe than for NMe₂ (in both series) suggesting a process controlled by both inductive and mesomeric effect for OMe and mostly mesomeric for NMe₂.

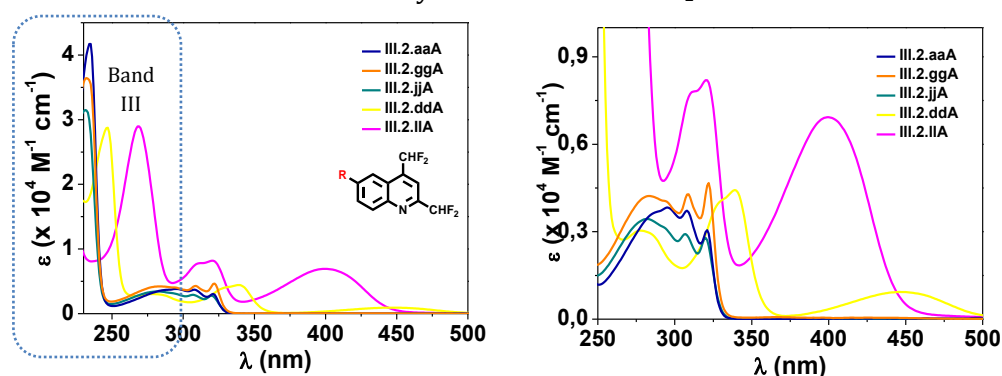


Figure 79: Influence on the electronic absorption spectra of the substitution in the C6 position for quinoline derivatives bearing a CHF₂ in C2 and C4 (derivatives **III.2.aaA** as reference scaffold). [left: full spectrum; right: zoom on bands II and I spectra]. Solvent: 1,2-dichloroethane, T = 25.0 °C

Table 16: Absorption properties for 6-substituted quinoline derivatives bearing CHF₂ groups in C2 and C4 positions. Solvent: 1,2-dichloroethane, T = 25.0 °C

Compound	6-R	Band III λ (ε)	Band I (¹ L _b) λ (ε)	Band II (¹ L _a) λ (ε)	
III.2.aaA	H	234 (4.172)		284 sh	
				295 (0.383)	
				308 (0.372)	
				321 (0.306)	
III.2.ggA	F	232 (3.645)		284 (0.422)	
				294 (0.403)	
				309 (0.428)	
				322 (0.467)	
III.2.jjA	OCF ₃	231 (3.140)		282 (0.344)	
				293 sh	
				307 (0.292)	
				320 (0.277)	
III.2.ddA	OMe	247 (2.874)		277 (0.303)	
				329 (0.402)	446 (0.093)
				339 (0.443)	
III.2.IIA	NMe ₂	269 (2.897)		311 (0.778)	
				321 (0.820)	400 (0.693)

Solvent: 1,2-dichloroethane; T = 25 °C; λ in nm; ε in x 10⁴ M⁻¹ cm⁻¹. The errors on λ and ε are given as ± 1 nm and 10%, respectively. sh=shoulder

The ^{13}C NMR investigation for the **III.2.aaA**-series which is variously substituted at the C6 position, led to the same outcomes than for **III.2.aaA** (*vide supra*) (Figure 80, Table 17). Inductive electronic (-I) effects are dominating for F and OCF_3 , while resonance effects (+M) are preponderant for OCH_3 and NMe_2 . Therefore, bands I, II and III are significantly affected with the two π electron-donating substituents (OCH_3 and NMe_2), while they are only slightly affected by the fluorinated groups (F and OCF_3).

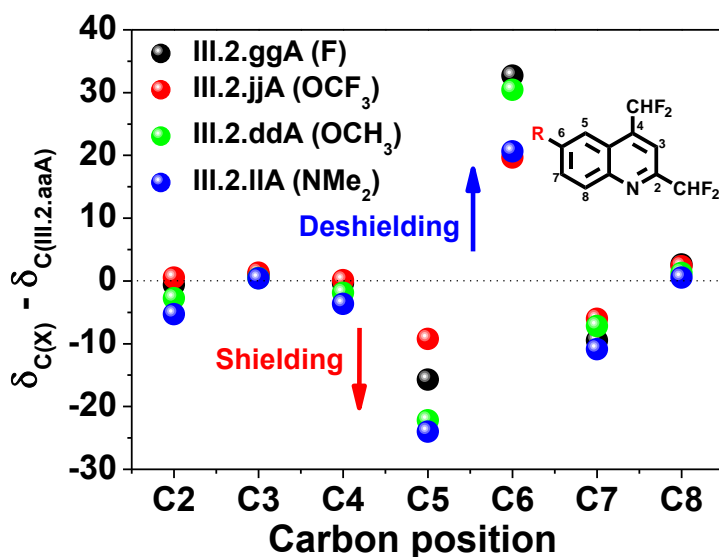


Figure 80: Variation of the ^{13}C NMR shifts of the quinoline carbons as a function of the nature of the substituent on position C6 in the **III.2.aaA** series. Solvent: CDCl_3 ; T = 298K

Table 17: ^{13}C NMR chemical shifts of 6-substituted quinoline derivatives bearing CHF_2 groups in C2 and C4 positions (**III.2.aaA** series). Solvent: CDCl_3 ; T = 298 K

Compound	^{13}C δ (ppm)							
	6-R	C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈
III.2.aaA	H	152.70	114.24	139.93	123.55	129.33	130.91	130.83
III.2.ggA	F	152.09	115.28	139.56	107.84	162.01	121.43	133.46
III.2.jjA	OCF_3	153.23	115.56	140.06	114.32	148.97	124.89	133.17
III.2.ddA	OMe	149.93	114.70	138.02	101.35	159.77	123.71	132.11
III.2.IIA	NMe_2	147.42	114.64	136.29	99.55	149.96	120.03	131.36

The latest figures illustrate the influence of substitution pattern at the C7 position. As previously demonstrated, electron-withdrawing groups (*i.e.* F and OCF_3) clearly generate a hypsochromic and a bathochromic shift on $^1\text{L}_a$ (II) and $^1\text{L}_b$ (I) respectively. As expected according to foregoing analysis, electron-donating groups induce an important bathochromic shift of the band III and II for NMe_2 . However, no obvious signal in the visible region was observed for compound **III.2.ccA**, unlike for its C6 substituted analogue **III.2.ddA**. But both **III.2.ccA** and **III.2.ddA** demonstrate a strong bathochromic shift of their $^1\text{L}_b$ transition (Figure 81, Table 18).

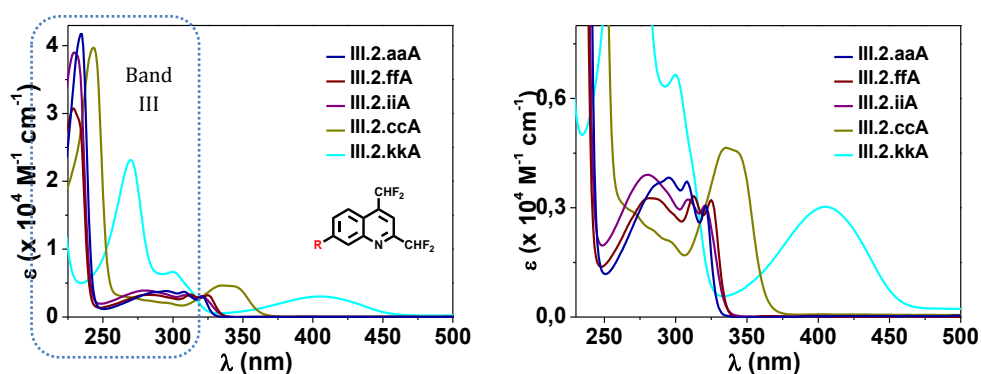


Figure 81: Influence on the electronic absorption spectra of the substitution in the C7 position for quinoline derivatives bearing CHF₂ groups in C2 and C4 positions (III.2.aaA as reference scaffold). Solvent: 1,2-dichloroethane, T = 25.0 °C

Table 18: Absorption properties for 7-substituted quinoline derivatives bearing CHF₂ groups in C2 and C4 positions. Solvent: 1,2-dichloroethane, T = 25.0 °C

Compound	7-R	Band III λ (ε)	Band I (¹ L _b) λ (ε)	Band II (¹ L _a) λ (ε)
III.2.aaA	H	234 (4.172)	284 sh	
			295 (0.383)	
			308 (0.372)	
			321 (0.306)	
III.2.ffA	F	229 (3.074)	282 (0.326)	
			289 sh	
			312 (0.331)	
			325 (0.321)	
III.2.iiA	OCF ₃	230 (3.896)	280 (0.391)	
			295 sh	
			309 (0.323)	
			321 (0.306)	
III.2.ccA	OMe	243 (3.968)	271 sh	
			295 sh	
			335 (0.464)	
			342 (0.456)	
III.2.kkA	NMe ₂	270 (2.316)	300 (0.665)	
			313 sh	
			405 (0.303)	

Solvent: 1,2-dichloroethane; T = 25 °C; λ in nm; ε in x 10⁴ M⁻¹ cm⁻¹. The errors on λ and ε are given as ± 1 nm and 10%, respectively. sh=shoulder

The ^{13}C NMR chemical shift distribution shows the same general feature than for C6-substituted quinolines. As expected C7 revealed a strong deshielding with a concomitant shielding of the C6 and C8 signals. It is noteworthy that C2 and C4 signals no more attested a shielding exacerbates by resonance induced by C7-substituent, whereas the signal of C3, borne by the pyridyl ring, did, especially with the electron-donating NMe_2 substituent (Figure 82, Table 19).

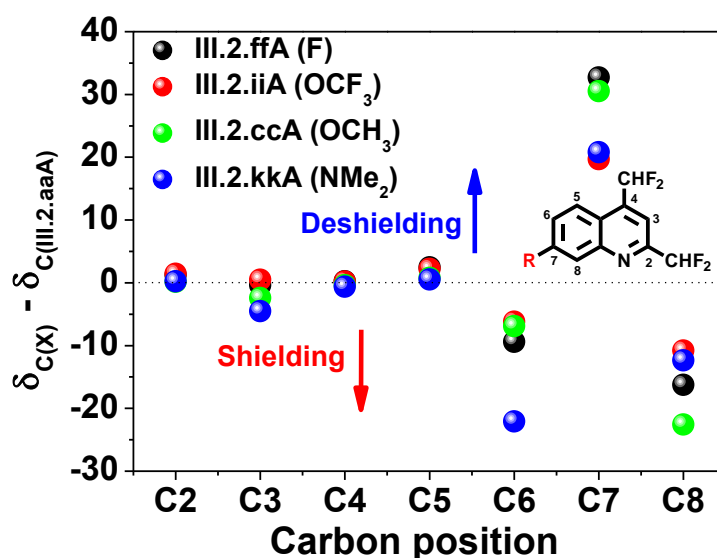


Figure 82: Variation of the ^{13}C NMR shifts of the quinoline carbons as a function of the nature of the substituent on position C7 in the (III.2.aaA series). Solvent: CDCl_3 ; T = 298K

Table 19: ^{13}C NMR chemical shifts of 7-substituted quinoline derivatives bearing CHF_2 groups in C2 and C4 positions (III.2.aaA series). Solvent: CDCl_3 ; T = 298 K

Compound	7-R	^{13}C δ (ppm)						
		C ₂	C ₃	C ₄	C ₅	C ₆	C ₇	C ₈
III.2.aaA	H	152.70	114.24	139.93	123.55	129.33	130.91	130.83
III.2.ffA	F	153.93	113.86	140.17	126	119.91	163.60	114.58
III.2.iiA	OCF_3	154.12	114.72	140.14	125.76	123.13	150.58	120.02
III.2.ccA	OMe	152.86	111.80	139.56	124.33	122.45	161.45	108.24
III.2.kkA	NMe_2	152.95	109.73	139.30	124.08	107.26	151.69	118.49

Thus, this first study of spectrophotometric absorption and ^{13}C NMR study highlighted the electronic inductive and mesomeric effects of substituents [F and OCF_3 (strong -I, weak +M) and NMe_2 and OMe (weak -I, strong +M)] on the absorption pattern of quinoline chromophores. The $^1\text{L}_a$ excited state results from the HOMO→LUMO transitions are very sensitive to the substituent present on the quinoline derivatives and the energy gap (linked to a bathochromic shift) seems to be significantly decreased with the presence of electron-donating groups (facilitating oxidation reactions).

4.3.2 Spectrofluorimetric properties

Some selected compounds revealed fluorescence. To completely study these quinoline chromophores, further investigations were performed to put in light fluorescence properties. Quinoline derivatives substituted by fluoroalkyl groups in positions C2 and C4 show very weak emission signals after excitation ($\lambda_{\text{exc}} = 314\text{-}322\text{ nm}$) of their $\pi\text{-}\pi^*$ transition with maxima ranging from 360 nm to 425 nm, close the parent unsubstituted quinoline (Figure 83).⁴¹⁸ Such as for the absorption, addition and modification of fluoroalkyl groups on the pyridyl unit has only a low impact on the emission properties of the quinoline derivatives.

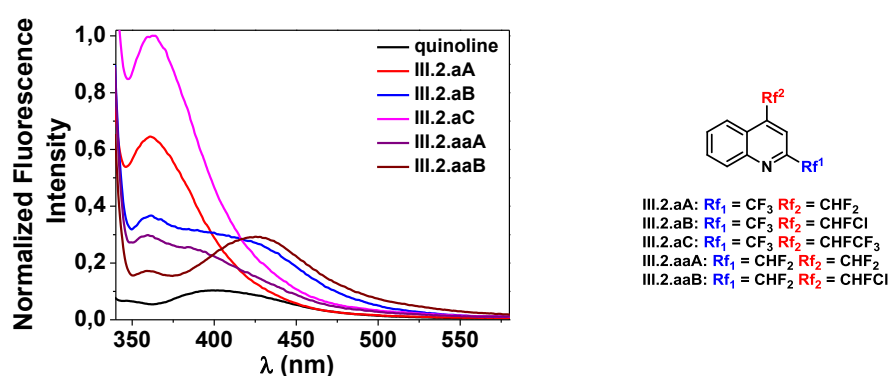


Figure 83: Fluorescence emission spectra of quinolines substituted by CHF_2 , CHFCI , CF_3 or CHF_2CF_3 groups in C2 and C4 positions (III.2.aA, III.2.aB, III.2.aC, III.2.aaA and III.2.aaB). Solvent: 1,2-dichloroethane; $T = 25\text{ }^\circ\text{C}$. Emission and excitation band widths = 15 and 20 nm, respectively. Emission intensities have been normalized with respect to absorbances of the quinoline solutions and therefore reflect the relative quantum yields. Absorbances at excitation wavelength are always below 0.1 to prevent inner filter effects

The substitution in positions C6 and C7 of the benzene ring by fluorine in the III.2.aA series or by trifluoromethoxy in the III.2.aaA series has a weak influence on the position, shape and intensity of emission signals of the quinoline derivatives. However, substitution at the C8 position drastically changes the recorded emission signal. A shift to the red region and an important increase in intensity were observed (Figure 84).

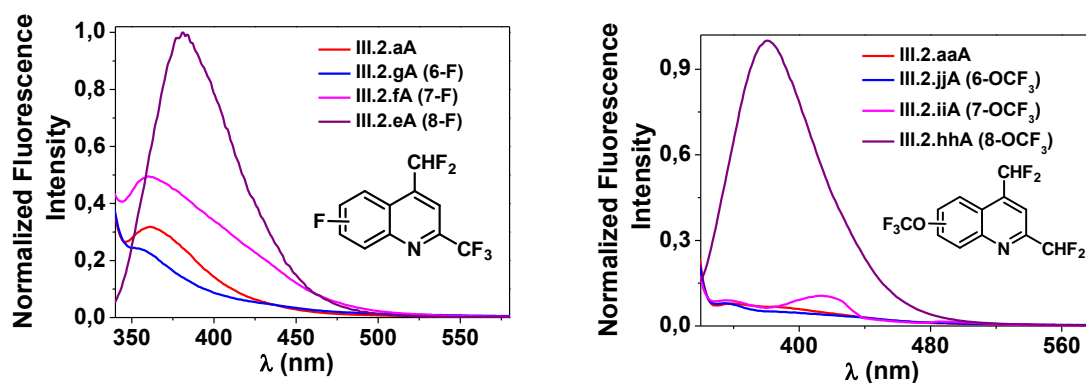


Figure 84: Influence on the emission spectra of quinoline substitution by either: a fluorine on C6 (III.2.gA), C7 (III.2.fA) or C8 (III.2.eA) and a CF_3/CHF_2 combination in C2/C4 positions (left); a trifluoromethoxy on C6 (III.2.jjA), C7 (III.2.iiA) or C8 (III.2.hhA) and a $\text{CHF}_2/\text{CHF}_2$ combination in C2/C4 positions (right). Solvent: 1,2-dichloroethane; $T = 25\text{ }^\circ\text{C}$. Emission and excitation band widths = 15 and 20 nm, respectively. Emission intensities have been normalized with respect to absorbances of the quinoline solutions and therefore reflect the relative quantum yields. Absorbances at excitation wavelength are always below 0.1 to prevent inner filter effects

Compounds substituted by F or Cl groups in position C7 and a methyl in position C8 also demonstrated a clear modification of their emission spectra with respect to quinoline **III.2.aaA** and an intense hyperchromic emission peak was recorded (Figure 85, Figure 86).

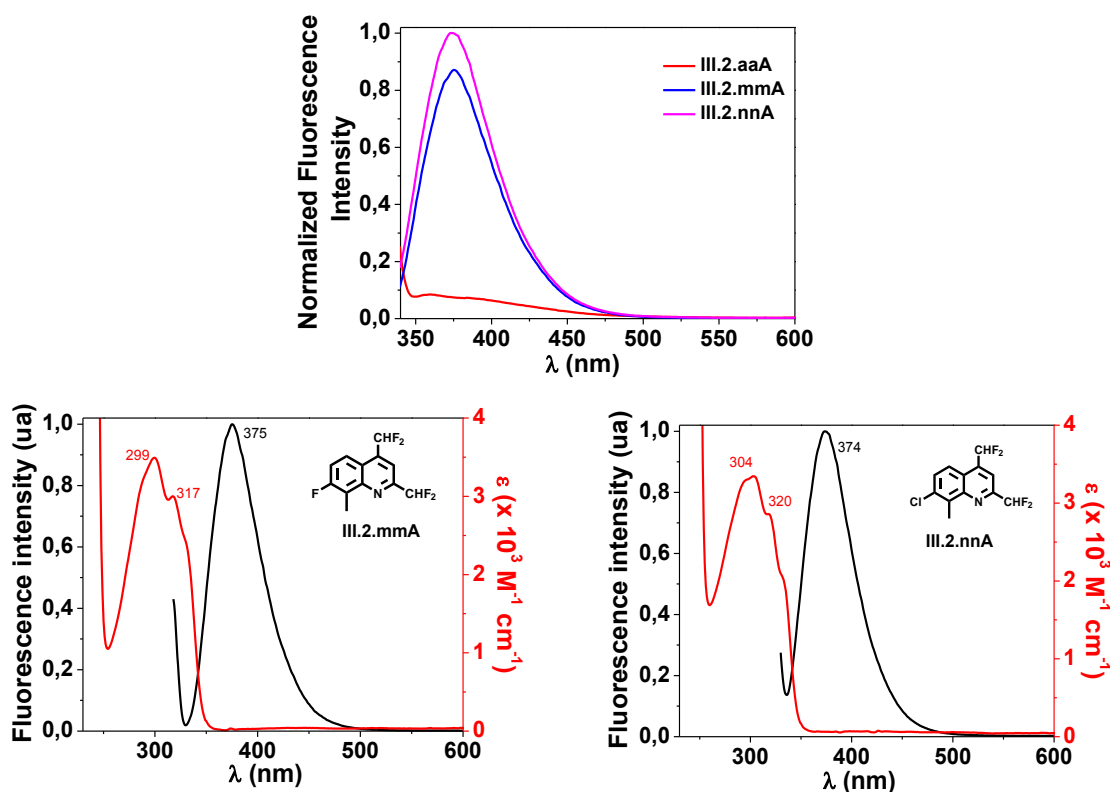


Figure 85: Influence on the emission spectra of the C7- and C8-substitution (III.2.mmA; III.2.nnA) of a quinoline derivative bearing CHF₂ groups in C2 and C4 positions (III.2.aaA as a reference scaffold). Solvent: 1,2-dichloroethane; T = 25 °C. Emission (black) and excitation (red) band widths = 15 and 20 nm, respectively.

Emission intensities have been normalized with respect to absorbances of the quinoline solutions and therefore reflect the relative quantum yields. Absorbances at excitation wavelength are always below 0.1 to prevent inner filter effects

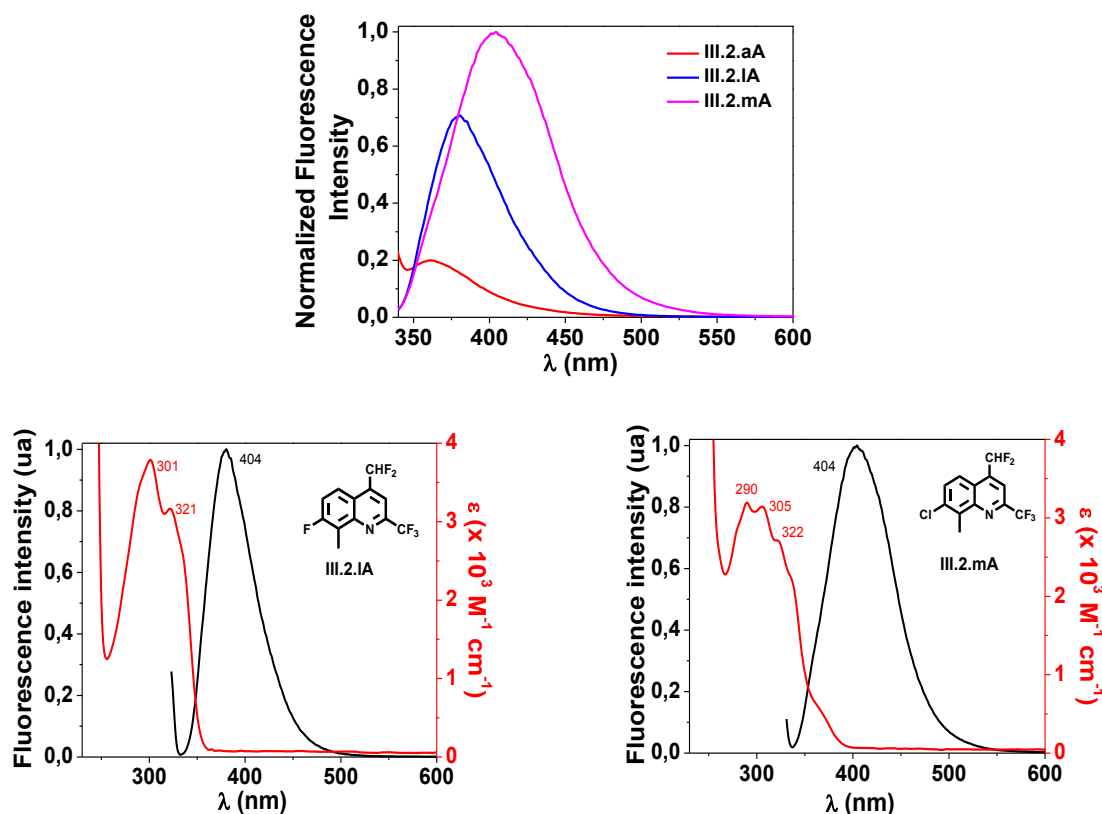


Figure 86: Influence on the emission spectra of the C7- and C8-substitution (**III.2.1A**; **III.2.mA**) of a quinoline derivative bearing a CF_3 in C2 and a CHF_2 in C4 (**III.2.aA** as a reference scaffold). Solvent: 1,2-dichloroethane; $T = 25^\circ\text{C}$. Emission (black) and excitation (red) band widths = 15 and 20 nm, respectively. Emission intensities have been normalized with respect to absorbances of the quinoline solutions and therefore reflect the relative quantum yields. Absorbances at excitation wavelength are always below 0.1 to prevent inner filter effects

We then focused on the effect of OMe or NMe_2 substitution on the emission properties of fluorinated quinolines **III.2.aA** and **III.2.aaA** (Table 20).

Substitution by a methoxy group (exerting -I and +M effects) on the quinoline core at C6 or C7 positions increases the intensity of the emission band but has no effect on its position (Figure 87-A/B, Table 20).

By comparison, addition of a dimethylamino group at C6 or C7 positions drastically alters both the intensity, which significantly increases (hyperchromic shift) and the position (bathochromic shift of *ca.* 100 nm with respect to **III.2.aA**, **III.2.aaA** and OMe-substituted quinolines **III.2.dA**, **III.2.cA**, **III.2.ddA**, **III.2.ccA**) (Figure 87-C/D, Table 20).

As already observed in absorption spectroscopy, substituents able to exert strong mesomeric effects markedly impacted both the absorption (*i.e.* substantial influence on the $^1\text{L}_a$ – HOMO→LUMO – transitions which undergo strong bathochromic shifts) and the emission properties (bathochromic shift and enhancement of the fluorescence quantum yields) of quinoline derivatives.

By contrast, strong inductive electron-withdrawing groups (F, OCF_3) did not induce major variations on spectroscopic properties. Nevertheless, the methoxy group remains a singular substituent since it displays a specific feature due to its mesomeric donor (+M) effect countered by its inductive (-I) electronic effect.

Similarly to 8-fluoro or 8-trifluoromethoxy quinolines **III.2.eA** and **III.2.hhA**, 8-methoxy quinolines **III.2.bA** and **III.2.bbA** demonstrated a prominent increase of $\text{S}^1\text{-S}^0$ radiative

deactivation emission¹ signal associated to a bathochromic shift (*ca.* 50-60 nm with respect to **III.2.eA** and **III.2.hhA**) in the 430-440 nm region (Figure 87-A/B, Table 20).

Table 20: Emission properties in 1,2-dichloroethane of the substituted quinoline derivatives.

Compound			λ_{em} (nm)	Intensity
Rf ¹	R			
	Quinoline		399	weak
CF ₃		III.2.aA	361	weak
CHF ₂	H	III.2.aaA	360	weak
			422 sh	
CF ₃	6-F	III.2.gA	355	weak
	7-F	III.2.fA	361	weak
	8-F	III.2.eA	381	strong
CHF ₂	6-OCF ₃	III.2.jjA	355	weak
	7-OCF ₃	III.2.iiA	356	weak
	8-OCF ₃	III.2.hhA	412	strong
CF ₃	7-F, 8-CH ₃	III.2.lA	375	strong
	7-Cl, 8-CH ₃	III.2.mA	373	strong
CHF ₂	7-F, 8-CH ₃	III.2.mmA	381	strong
	7-Cl, 8-CH ₃	III.2.nnA	405	strong
CF ₃	6-OCH ₃	III.2.dA	383	strong
	7-OCH ₃	III.2.cA	390	strong
	8-OCH ₃	III.2.bA	439	strong
CHF ₂	6-OCH ₃	III.2.ddA	379	strong
	7-OCH ₃	III.2.ccA	381	strong
	8-OCH ₃	III.2.bbA	432	strong
CF ₃	6-NMe ₂	III.2.kA	478	strong
CHF ₂	6-NMe ₂	III.2.lIA	472	strong
	7-NMe ₂	III.2.kkA	492	strong

Solvent: 1,2-dichloroethane, T = 25.0 °C. sh=shoulder

¹ The observed quinoline-centered emission originates from the S¹→S⁰ radiative deactivation corresponds to the relaxation of the molecule from its excited state to its fundamental state. It is related to the ¹L_a absorption (HOMO→LUMO transitions).

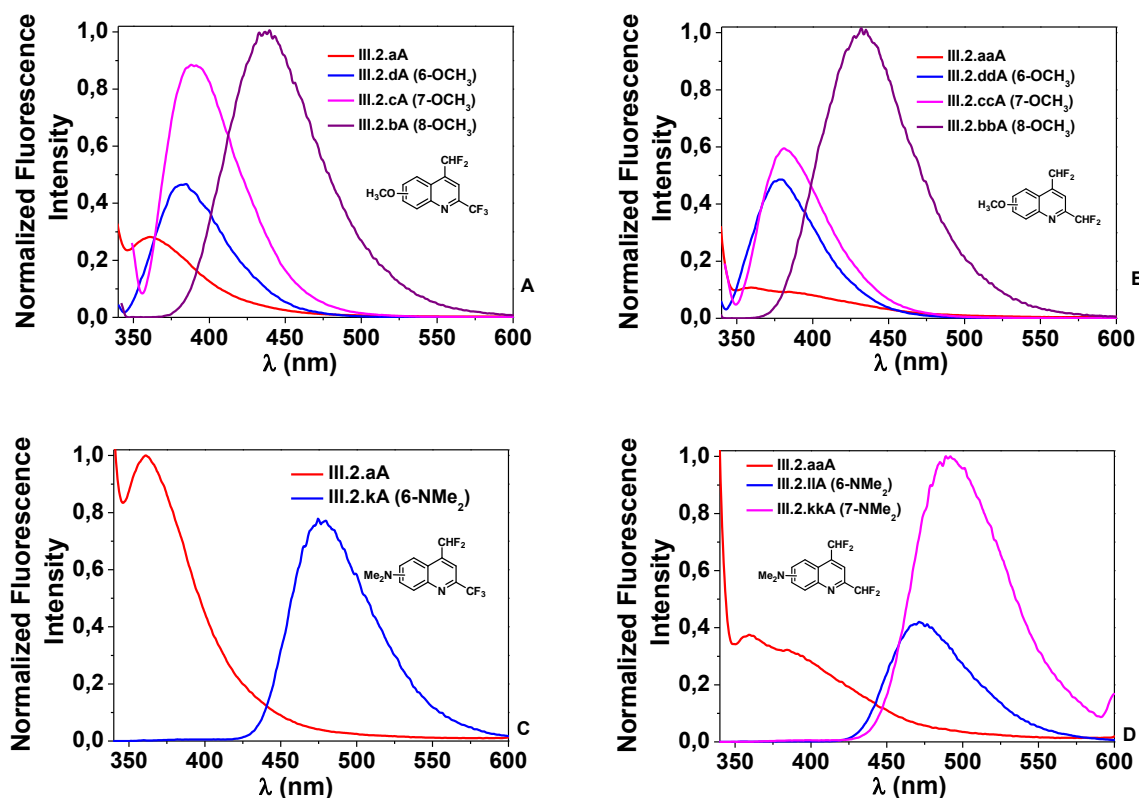


Figure 87: Influence on the emission spectra of quinolines by either: A) a methoxy on C6 (III.2.dA), C7 (III.2.cA) or C8 (III.2.bA) and a CF₃/CHF₂ combination in C2/C4 positions; B) a methoxy on C6 (III.2.ddA), C7 (III.2.ccA) or C8 (III.2.bbA) and a CHF₂/CHF₂ combination in C2/C4 positions; C) a dimethylamino on C6 (III.2.kA) and a CF₃/CHF₂ combination in C2/C4 positions; D) a dimethylamino on C6 (III.2.lA) or C7 (III.2.kkA) and a CHF₂/CHF₂ combination in C2/C4 positions. Solvent: 1,2-dichloroethane, T = 25 °C. Emission intensities have been normalized with respect to absorbances of the quinoline solutions and therefore reflect the relative quantum yields. Absorbances at excitation wavelength are always below 0.1 to prevent inner filter effects

Figure 88 presented hereafter, summarizes the effect of the substitution at the C6 or C7 position for **III.2.aA** and **III.2.aaA** series on emission properties of quinoline derivatives (Figure 88).

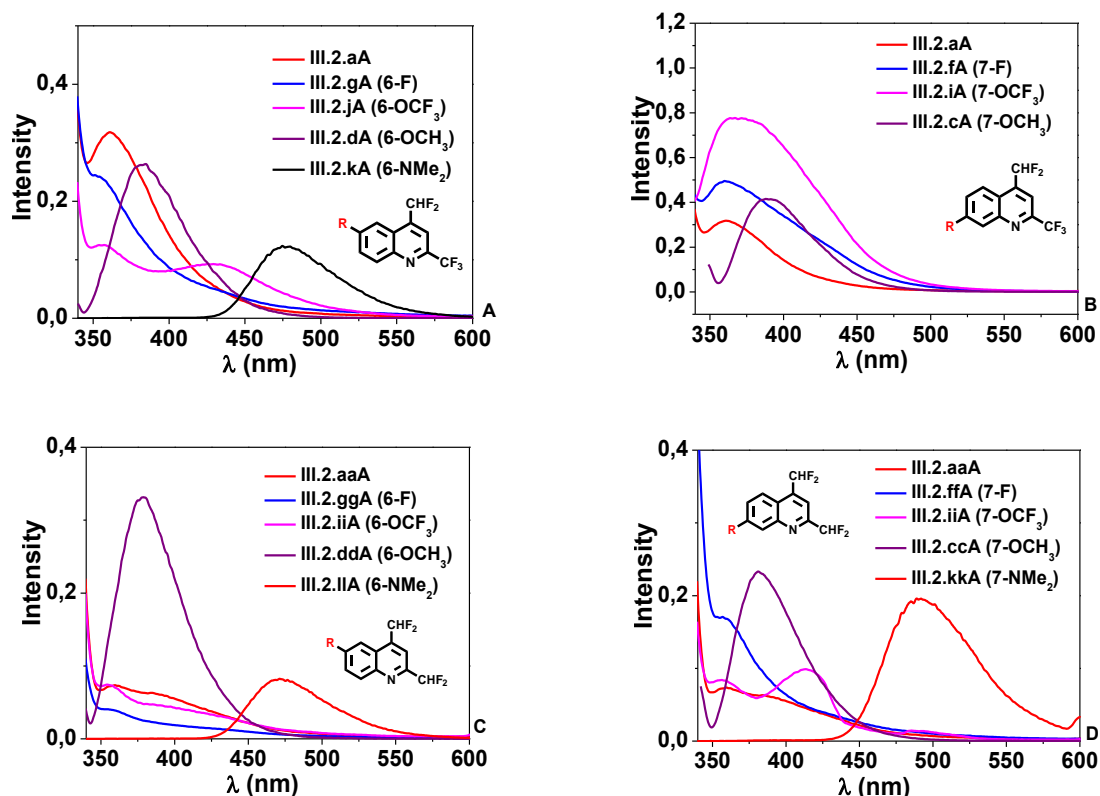


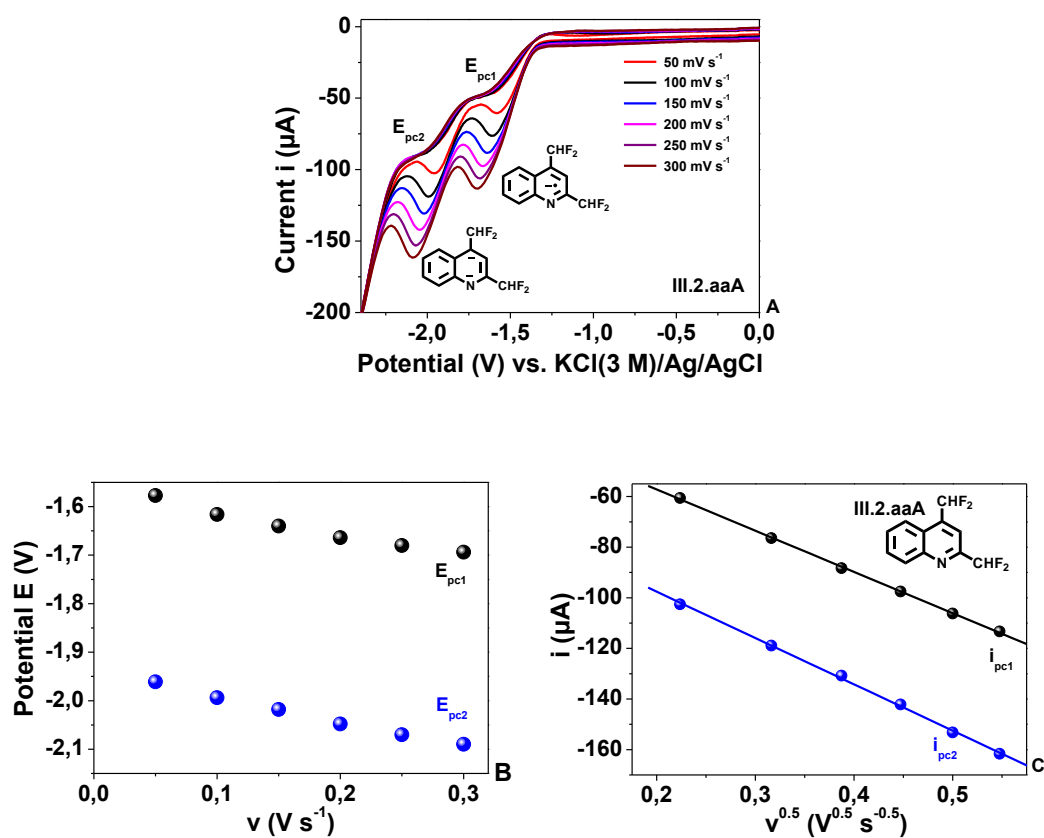
Figure 88: Influence on the emission spectra of the substitution on the: A) C6 position for quinoline derivatives bearing a CF_3 in C2 and a CHF_2 in C4 (derivative **III.2.aA as a reference scaffold); B) C7 position for quinoline derivatives bearing a CF_3 in C2 and a CHF_2 in C4 (derivative **III.2.aA** as a reference scaffold); C) C6 position for quinoline derivatives bearing CHF_2 in C2 and C4 positions (derivative **III.2.aaA** as a reference scaffold); D) C7 position for quinoline derivatives bearing CHF_2 in C2 and C4 positions (derivative **III.2.aaA** as a reference scaffold). Solvent: 1,2-dichloroethane, $T = 25^\circ\text{C}$. Emission intensities have been normalized with respect to absorbances of the quinoline solutions and therefore reflect the relative quantum yields. Absorbances at excitation wavelength are always below 0.1 to prevent inner filter effects**

4.3.3 Electrochemical properties

As a last part of this work, we finally turned our interest toward quinoline derivatives bearing a CHF_2 moiety in both 2 and 4 positions. The purpose was to carry out electrochemical studies and evaluate the influence of the substitution pattern at the benzene- and/or pyridyl ring as well as the behaviour of compounds toward oxidation and reduction (Table 21).

Redox potentials of quinoline derivatives were measured by cyclic voltammetry (CV) at 25 °C. They were recorded at different scan rates (50 $\text{mV}\cdot\text{s}^{-1}$ to 300 $\text{mV}\cdot\text{s}^{-1}$) in the potential range from -2.5 V to +2.5 V (Figure 89-A).

All compounds exhibited two well defined cathodic reduction peaks in the potential range -1.5 V – 2 V, with most of the time no evidence for anodic oxidation peaks (Figure 90).



Under these experimental conditions, degradation of compounds can be discarded since measures were reproducible. The two observable reduction peaks were corresponding to the successive formation of the monoradical-anion (1st step) and the dianion (2nd step) respectively.

Figure 89: (A) Cyclic voltammograms of III.2.aaA as a function of the sweep rate; (B) Variation of the cathodic potentials as a function of the sweep rate demonstrating the irreversible character of the two successive one-electron transfers; (C) Variation of the cathodic current intensities as a function of the square root of the scan rate indicating diffusion controlled redox processes. Solvent: 1,2-dichloroethane; T = 25.0 °C; I = 0.1 M (NBu_4BF_4); reference electrode = KCl (3 M)/Ag/AgCl; working electrode = glassy carbon disk of 0.07 cm^2 area

Electrochemical studies of quinolines were reported in literature and showed that the first step is corresponding to a reversible one-electron transfer, while the second is corresponding to an irreversible one-electron process.⁴¹⁹⁻⁴²¹

Under our conditions, the two reduction steps were attributed to an irreversible one-electron-transfer. This conclusion is supported by the fact that no reverse signal scan was observed and by the acquisition of a linear dependence of the cathodic potentials (E_{pc}) as a function of the scan rate (v) [two horizontal lines should have been obtained if the system was reversible] (Figure 89-B).

Furthermore, a linear dependence of the peak current (i_{pc}) of the two cathodic signals of **III.2.aaA** on the square root of the sweep rate ($v^{0.5}$) was obtained. This parallelism depicts the diffusion-controlled electron processes, meaning that only electrodes are implied in the reduction process and no external elements act on it (implication of external interaction would lead to the acquisition of crossed lines). More specifically, quinoline derivatives are not subjected to inter- or intramolecular proton transfer and electrochemical properties are strictly associated to the successive formation of the two anionic reduced species (the monoradical anion related to E_{pc1} and the dihydroquinoline dianion related to E_{pc2}) (Figure 89-C).

An important feature of analysed quinoline derivatives is their wide range of redox inertness. Indeed, no redox reactions occur for potential values ranging from +2.5 V to \approx -1.4 V [the more reduction occurs far from 0, the more the molecule is inert toward reduction, likewise for oxidation reactions].

Another interesting point is that substituents seem to have the same electronic effects either on the starting quinoline or on its one-electron reduced species.

On figure 90-A, the cyclic voltammetry measures of compounds **III.2.aA** and **III.2.aaA** revealed the preservation of the two successive irreversible one-electron transfers, whatever the substitution pattern on the pyridyl unit. However, one can discern a shift of the 1st reduction peak of about 120 mV between **III.2.aA** and **III.2.aaA**, while the position and shape of the 2nd reduction peak is conserved (Figure 90-A). This feature agrees with the stronger electron-withdrawing effect of CF_3 compared to CHF_2 and suggests that the separation between the two reduction waves is intrinsically dependent on the pyridyl ring substitution.

To discuss the influence of substituents, we will consider the analysis of the first one-electron transfer associated to the E_{pc1} values (Table 21).

Addition of fluorine on the benzene ring clearly induces an anodic shift of the 1st and the 2nd reduction peaks (*ca.* 80 mV for F at the C6 position and 120 mV for F at the C7 position) (Figure 90-B). The electron-withdrawing capacity of fluorine decreases the electronic density of the electroactive quinoline **III.2.aaA**. Consequently, quinolines bearing a fluorine at C6 as well as at C7 positions are more prone to reduction. This is particularly true for F at the C7 position since the anodic signal shift is higher than for F at the C6 position. Accordingly, to absorption and emission data fluorine substitution mainly acts as an inductive electron-withdrawing rather than electron π -donor on quinoline derivatives.

Introduction of a CH_3 moiety at the position C8 increases the reduction inertness of the molecule and decreases its oxidant character due to the inductive effect reinforcement by the latter substituent. Moreover, no dehalogenation was observed during the electrochemical study (Figure 90-F). Indeed, it was reported that during such analysis halogeno-aryls may suffer from the cleavage of the C-halogen bond allowing for the formation of the monoradical anion intermediate.⁴²² It seems that in our case, the stability of the fluorinated azaheteroaromatic

monoradical anion was higher than for comparable fluoro-substituted arenes preventing dehalogenation pathways.^{419, 421}

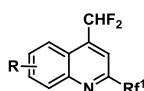
OCF₃-substituted quinoline derivatives **III.2.jjA** and **III.2.iiA** led to the most oxidant compounds of the series due to the greater electron-withdrawing properties of this substituent (Figure 90-C). One can notice the presence of a third irreversible reduction peak at ≈ -2.2 V as well as an irreversible oxidation peak around 1.30-1.40 V. We postulated that the third reduction peak was caused by the dissociation of $\cdot\text{CF}_3$ radical releasing a phenolic unit that can give rise to an oxidation signal.

The same behaviour was not observed for quinolines substituted by an OMe moiety (Figure 90-D). Indeed, only a weak cathodic shift of the 1st reduction peak was observed because of its inductive electron-withdrawing and mesomer electron-donating properties.

The NMe₂ substitution (strong mesomeric donor and weak inductive acceptor) at the C6 or C7 positions of quinoline derivatives led to the strongest cathodic shift of the two successive reduction peaks (Figure 90-E). A higher cathodic shift was measured for the C6-substituted (*ca.* 100 mV) than for the C7-substituted (*ca.* 40 mV) compounds.

In conclusion, it was shown during this study that the reactivity of quinoline derivatives can be tuned by adding electron-releasing or withdrawing substituents at C6, C7 or C8 positions. It was also suggested that the observed variation of the electronic properties of quinoline derivatives are solely influenced by inductive or mesomeric electronic effects whatever the position of substitution (C6, C7 or C8) on the benzene-type ring. Electron-withdrawing substituents decrease the electronic density of the quinoline unit and render these compounds “more oxidant” (easier to be reduced), while electron-donating substituents increase the electronic density and thereby decrease the propensity of the corresponding redox compounds to be reduced (“less oxidant”; enhancement of their ability to be oxidized).

Table 21: Electrochemical data (1st and 2nd reduction processes) measured using cyclic voltammetry (CV) for all the substituted quinolines of the III.2.aaA series



Compound			E_{pc1} (V)	E_{pc2} (V)	$E_{pc1}-E_{pc2}$ (V)
Rf ¹	R				
CF ₃	H	III.2.aA	-1.52	-2.00	0.48
		III.2.aaA	-1.64	-2.01	0.37
	6-F	III.2.ggA	-1.56	-1.92	0.36
	7-F	III.2.ffA	-1.52	-1.87	0.35
	6-OCF ₃	III.2.jjA	-1.48	-1.83	0.35
CHF ₂	7-OCF ₃	III.2.iiA	-1.45	-1.79	0.34
	6-OCH ₃	III.2.ddA	-1.67	-2.00	0.33
	7-OCH ₃	III.2.ccA	-1.66	-2.03	0.37
	6-NMe ₂	III.2.llA	-1.74	-2.11	0.37
	7-NMe ₂	III.2.kkA	-1.68	-2.00	0.32
	7-F, 8-CH ₃	III.2.mmA	-1.60	-1.94	0.34
	7-Cl, 8-CH ₃	III.2.nnA	-1.54	-1.88	0.34

Solvent: 1,2-dichloroethane; T = 25.0 °C; I = 0.1 M (NBu₄BF₄); ν = 200 mV s⁻¹; reference electrode = KCl (3 M)/Ag/AgCl; working electrode = glassy carbon disk of 0.07 cm² area; auxiliary electrode = Pt wire.

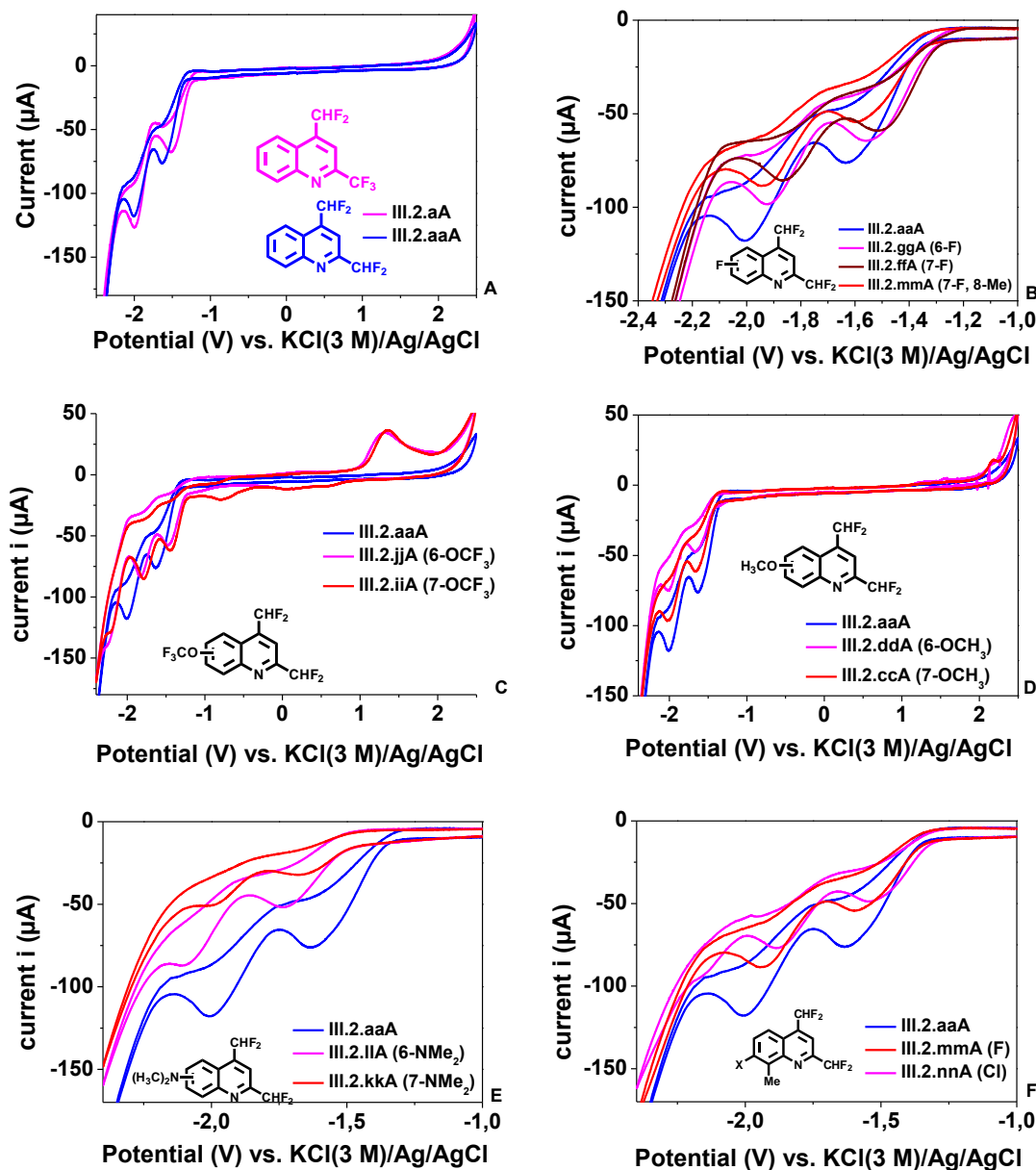


Figure 90: A) Cyclic voltammograms of III.2.aa and III.2.aaA measured at a sweep rate of 200 mV s^{-1} ; B) Influence on the cyclic voltammograms of the fluorine substitution at the C6 (III.2.ggA) and C7 (III.2.ffA) positions of a quinoline bearing CHF_2 groups in C2 and C4 positions (III.2.aaA as a reference scaffold) as well as of the introduction of a methyl group at the C8 position (III.2.mmA); C) Influence on the cyclic voltammograms of the trifluoromethoxy substitution at the C6 (III.2.jjA) and C7 (III.2.iiA) positions of a quinoline bearing CHF_2 groups in C2 and C4 positions (III.2.aaA as a reference scaffold); D) Influence on the cyclic voltammograms of the methoxy substitution at the C6 (III.2.ddA) and C7 (III.2.cca) positions of a quinoline bearing CHF_2 groups in C2 and C4 positions (III.2.aaA as a reference scaffold); E) Influence on the cyclic voltammograms of the dimethylamino substitution at the C6 (III.2.lla) and C7 (III.2.kk) positions of a quinoline bearing CHF_2 groups in C2 and C4 positions (III.2.aaA as a reference scaffold); F) Influence on the cyclic voltammograms of the halogen substitution (F, III.2.mmA and Cl, III.2.nnA) at the C6 positions of a quinoline bearing CHF_2 groups in C2 and C4 positions and a CH_3 group at the C8 position (III.2.aaA as a reference scaffold). $v = 200 \text{ mV s}^{-1}$. Solvent: 1,2-dichloroethane; $T = 25.0 \text{ }^\circ\text{C}$; $I = 0.1 \text{ M (NBu}_4\text{BF}_4)$; reference electrode = $\text{KCl}(3 \text{ M})/\text{Ag}/\text{AgCl}$; working electrode = glassy carbon disk of 0.07 cm^2 area

Thanks to these electrochemical measurements, we were furthermore able to locate the position of the LUMO orbital by determination of the onset point on the 1st reduction peak (Figure 91, Table 22). The position of the HOMO can be calculated afterwards by a simple formula implying $\Delta E_{\text{gap}}^{\text{meas.}}$ (between HOMO and LUMO), which was determined thanks to λ_{max} of the 1L_a absorption peak: $[\Delta E_{\text{gap}} = \frac{1209}{\lambda_{\text{max}}}]$. In our case 1L_a was not always well defined and it was hard to exactly found the position of this onset.

Up to now the position of the HOMO orbital was not determined, however, DFT calculations are ongoing to complete this physico-chemical analysis of quinoline derivatives.

Table 22: Determination of the position of the LUMO for selected compounds

Compound	E_{pc1} (V)	E_{pc2} (V)	$E_{\text{pc1}}^{\text{onset}}$ (V)	$E_{\text{LUMO}}^{\text{meas.}}$ (V)
III.2.aA	-1.52	-2.00	-1.26	-3.14
III.2.aaA	-1.64	-2.01	-1.36	-3.04
III.2.ggA	-1.56	-1.92	-1.31	-3.09
III.2.ffA	-1.52	-1.87	-1.29	-3.11
III.2.jjA	-1.48	-1.83	-1.24	-3.16
III.2.iiA	-1.45	-1.79	-1.25	-3.15
III.2.ddA	-1.67	-2.00	-1.41	-2.99
III.2.ccA	-1.66	-2.03	-1.41	-2.99
III.2.llA	-1.74	-2.11	-1.51	-2.89
III.2.kkA	-1.68	-2.00	-1.46	-2.94
III.2.mmA	-1.60	-1.94	-1.35	-3.05
III.2.nnA	-1.54	-1.88	-1.31	-3.09

$$E_{\text{LUMO}}^{\text{meas.}} = -(E_{\text{pc1}}^{\text{onset}} + 4.4 \text{ eV}) ; E_{\text{HOMO}}^{\text{calc.}} = E_{\text{LUMO}}^{\text{meas.}} - \Delta E_{\text{gap}}^{\text{meas.}}$$

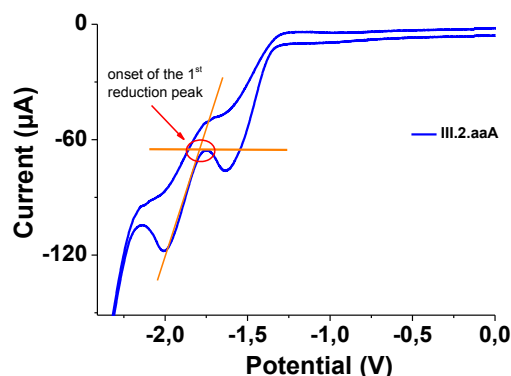


Figure 91: Determination of the onset point on a CV voltammograms

4.3.4 Conclusion

To conclude, we established a structure-physico-chemical activity relationship of quinoline derivatives. We correlated the observed absorption and emission properties and the electronic effects of the substituents. It was clear that more electron-withdrawing groups decrease the electronic density, which increases the HOMO-LUMO gap, while more electron-donating groups have the opposite effect. A small energy gap between orbitals facilitates electron transfer and redox reactions. Moreover, specific emissions or absorptions (almost in the visible region) were measured especially for quinolines bearing OMe or NMe₂ groups giving to these compounds a particular interest for further applications.

The electrochemical study moreover demonstrated that these compounds are inert in a large range of potentials, which correlates with our observation in synthetic chemistry. Indeed, between +2.5 V to \simeq -1.4 V neither oxidation nor reduction reactions are visible. Increasing the potential was not a guaranty to observe oxidation and enhance the risk to perform side reactions.

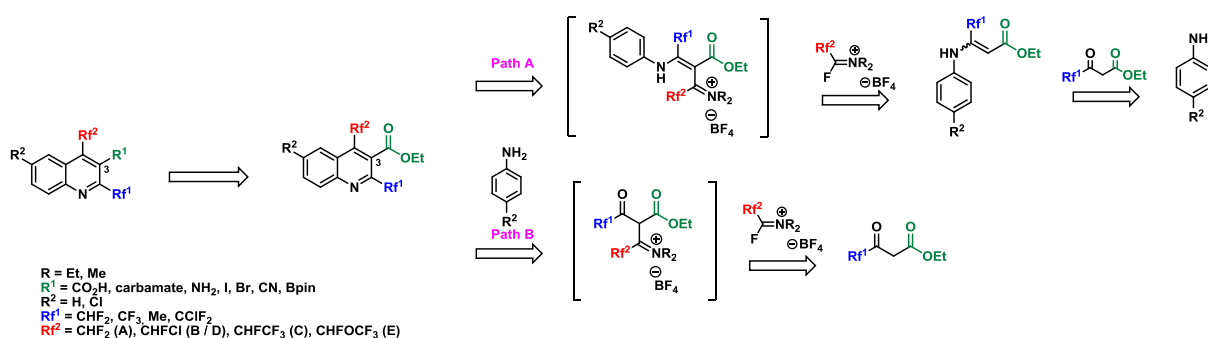
This work give us some clues on which kind of substituent it would be interesting to add on the quinoline scaffold to favour its reduction, however nothing prove that they will be easier to oxidize.

4.4 Synthesis of quinoline derivatives functionalized in position 3

4.4.1 Objective and methodology

Quinoline derivatives functionalized in position 3 have been identified by Bayer CropScience with interesting agrochemical activity.

Therefore, the purpose of this study was to design new quinolines which possess various substituents in position 3. They will serve as platform for further functionalization towards agrochemical ingredients. Two available methods can be employed to reach the desired compounds. One can use the same synthetic pathway as for quinolines **III.2** (Path A) or one can follow path B. The first step of path B corresponds to a reaction between activated FARs and alkyl acetoacetates, a reaction already developed in our laboratory by Dr. F. Giornal. Next the resulting α -fluoroalkylaminoalkylidene- β -fluoroalkylacetoacetate is condensed on aniline derivatives. Both pathways A and B lead to the same quinoline-3-carboxylates, whose carboxyl group would serve as an entry towards various substituents (Scheme 87).



Scheme 87: Methodology to provide the desired 3-substituted quinoline derivatives

4.4.2 Development of a new series of quinoline derivatives

To access the desired quinoline-3-carboxylates, we chose to follow path A, as it was a logical continuation of the synthesis of quinolines from *N*-aryl fluoroacetimines (See section 4.1). All quinolines were obtained first by condensation of fluoroacetoacetate onto aniline derivatives to provide the corresponding enamine. In a second step, nucleophilic attack of enamines onto activated FARs, should lead to final quinoline derivatives substituted in position 3.

4.4.2.1 Synthesis of enamine derivatives

All compounds **III.28** (Scheme 88) were prepared from the condensation of anilines on ethyl acetoacetates. They were obtained under enamine form exclusively, in comparison with compounds **III.1** (Scheme 64), which were obtained under imine form.

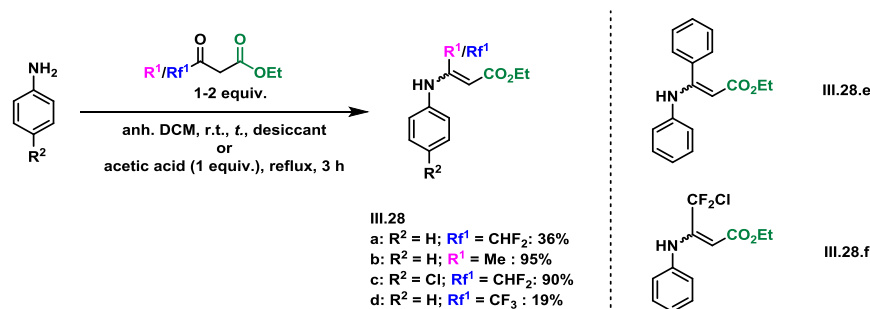
Compounds **III.28.b, c** were obtained in almost quantitative yields. They were not purified since we noticed that, in certain cases, purification could lead to degradation of the desired enamine.

The synthesis of (fluoroalkyl)phenylaminobutanoates **III.28.a, d** was carried out according to the conditions of Perrone *et al.*³⁸⁹ The reaction led to a mixture containing the desired compound and unidentified fluorinated species, even after purification by distillation of the starting fluoroacetoacetate which can contain degradation products. We attempted to purify the crude material on column chromatography. The pure desired compound was collected, but we also faced the recovery of a non-negligible quantity of degraded product, which considerably decreased the yield of the reaction. The first attempt on the synthesis of **III.28.d** led to the formation of the desired compound in only small amount. The starting aniline, ethyl trifluoromethylacetoacetate and degradation products were often recovered. The starting trifluoroacetoacetate is under enol form in majority, which impedes aniline condensation.

Sagar *et al.* described the synthesis of ethyl 4,4,4-trifluoro-3-(phenylamino)but-2-enoate **III.28.d** in refluxing acetic acid.⁴²³ In our hands, only 19% yield of the final product was obtained and increasing the scale of the reaction led to 8% yield only, in comparison with the 63% of literature. The analysis of **III.28.d** by ¹H NMR showed the formation of an imine-enamine mixture. However, the imine form was unstable and rapidly converted into the enamine.

We attempted to synthesize the cinnamate derivative **III.28.e** but both starting materials were recovered. Indeed, the phenyl group stabilizes the electrophilic carbon of the carbonyl by resonance. The carbon becomes less prone to be attacked by nucleophiles.

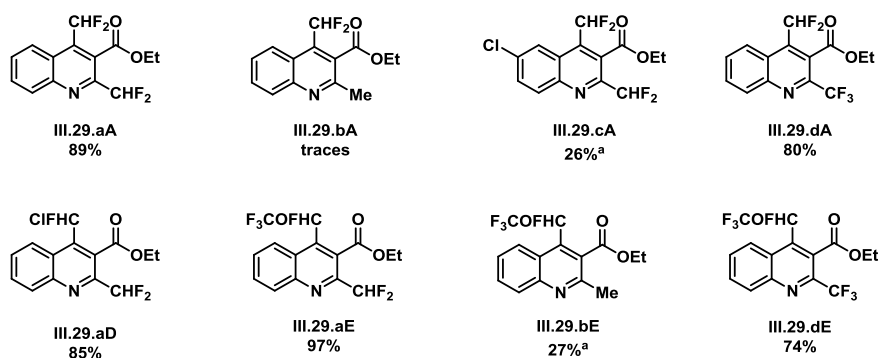
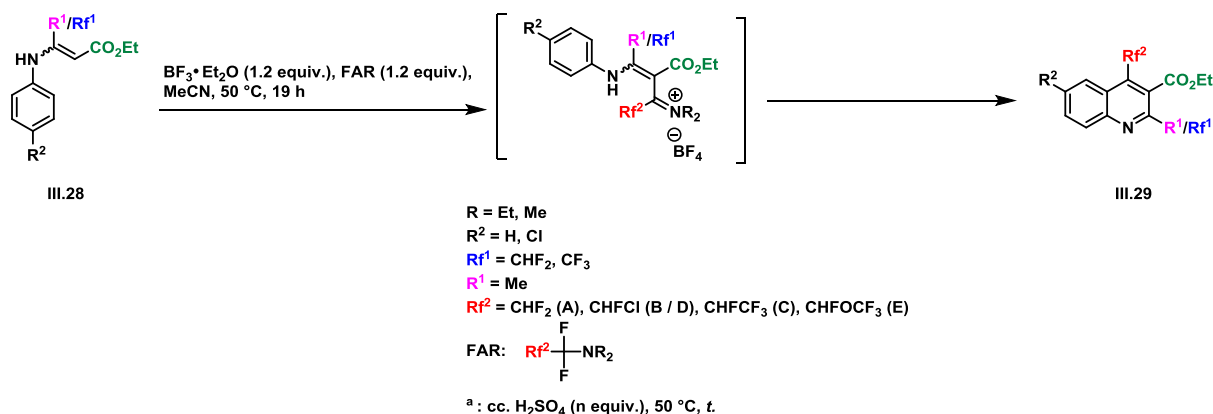
Similarly to **III.28.d**, we attempted to synthesize **III.28.f**. Here again, the starting perhalogenated acetoacetate undergoes a keto-enol equilibrium which disturbs the condensation of the aniline. By lack of time, further investigation on these two reactions could not be carried out, but the synthesis of compounds **III.28.e, f** must be optimized to complete the series of target compounds (Scheme 88).



Scheme 88: Synthesis of (phenylamino)butanoates **III.28**

4.4.2.2 Synthesis of quinoline derivatives bearing an ester function in position 3

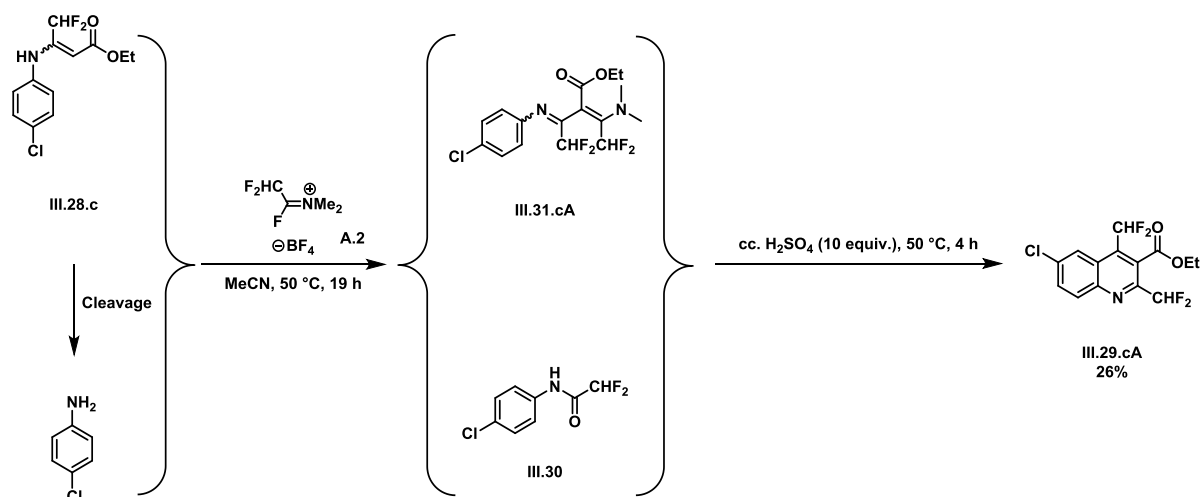
Enamines **III.28** react as nucleophiles on activated FARs to afford quinoline derivatives **III.29**. Compounds **III.29.aA**, **dA**, **aE**, **dE** bearing either a CHF₂ or a CHFOCF₃ moiety in position 4 were obtained in good yields ranging from 74 to 97% after *in situ* cyclization and purification by column chromatography (Scheme 89).



Scheme 89: Synthesis of quinoline derivatives **III.29 bearing a carboxylate group in position 3**

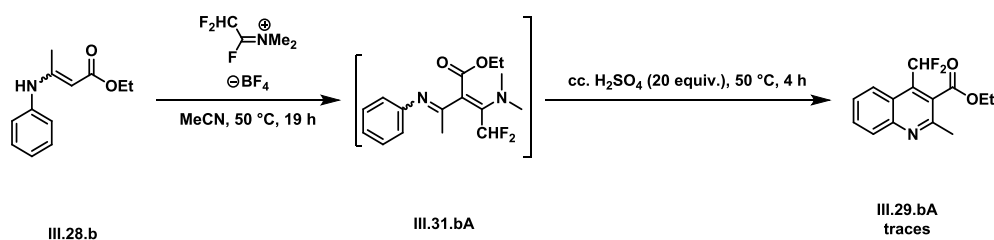
The first synthesis of **III.29.cA** led to the formation of only traces of the desired product. After purification, according to GCMS and ¹H NMR analysis a mixture of the corresponding acetamide **III.30** and vinamidine **III.31.cA** was observed. Compound **III.30** results from the reaction between chloroaniline released by the cleavage of enamine **III.28.c** and activated TFEDMA (**A.2**). Compound **III.31.cA** is the uncyclized intermediate towards quinoline **III.29.cA**.

Consequently, the mixture of **III.30** and **III.31.cA** was directly taken up in concentrated H₂SO₄ to facilitate the cyclization and finally quinoline **III.29.cA** was observed. Its separation from the two intermediates being difficult, we directly added 10 equivalents of acid to the reaction mixture in order to complete the conversion. The yield increased up to 26% of final quinoline. Nevertheless, a non-negligible fraction corresponding to the mixture of **III.30** and **III.31.cA** was once again recovered. It seems effectively that 10 equivalents were not enough to complete this reaction, which must be optimized by using stronger acids or increasing the reaction time (Scheme 90).



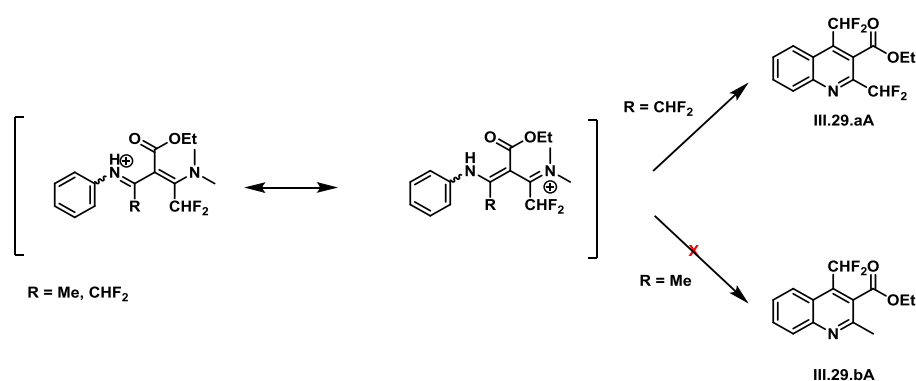
Scheme 90: Synthesis of III.29.cA

The synthesis of **III.29.bA** led to the acquisition of only traces of the product, supposedly formed by cyclization of intermediate **III.31.bA** during column chromatography, upon acidic catalysis by silica. **III.31.bA** was observed in the reaction mixture by ^1H NMR analysis, but its isolation remained unsuccessful. To confirm the result, we next added directly 20 equivalents of H_2SO_4 , as 10 seemed to be not enough, to favour the cyclisation of vinamidinium **III.31.bA**. But once again, only traces of **III.29.bA** were recovered (Scheme 91).



Scheme 91: Attempt to synthesize compound III.29.bA

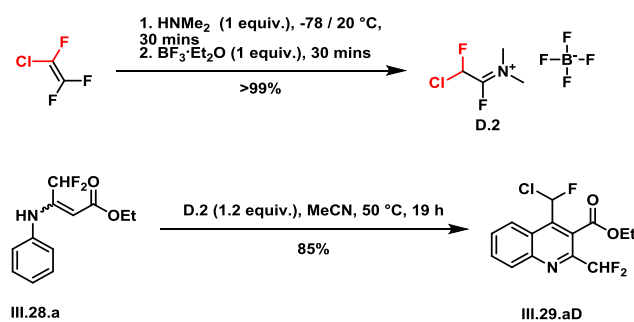
These results can be explained by electronic effects induced by the R^1 or Rf^1 substituent (Scheme 89 and Scheme 92) located in α position with regard to the aniline nitrogen. When this substituent is a CHF_2 group, its attractive inductive effect increases the electrophilic character of the distal carbon undergoing nucleophilic attack, therefore favouring the Friedel-Crafts-type cyclization. Conversely, an inductively electron-donating methyl group decreases the electrophilic character of this distal carbon and slows down the cyclisation. The size between CHF_2 and CH_3 moieties can also favoured a blending of the vinamidinium intermediate which can facilitate the cyclization (Scheme 92).



Scheme 92: Electronic effect of the substituents on the nucleophilic attack for activated FAR

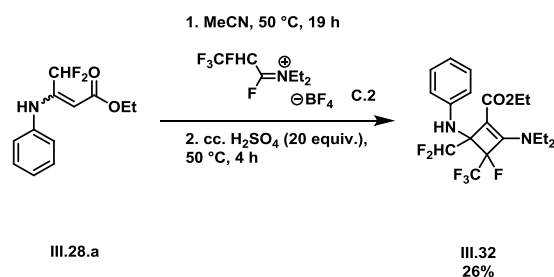
Nevertheless, 27% yield could be reached for compound **III.29.bE** when the activated OCF₃-FAR (**E.2**) was used.

The synthesis of **III.29.aD** was originally performed using the Yarovenko reagent (**B.1**). However, the reaction led mostly to the degradation of starting materials and to the recovery of the hydrolysed FAR (**B.3**). In order to determine if this lack of reactivity of activated FAR **B.1** was due to the steric hindrance and the strongest inductive effect of diethyl groups with respect to dimethyl groups (which reduce its reactivity), we performed the synthesis of **III.29.aD** by using the *N,N*-dimethyl analogue **D.2** of the activated Yarovenko reagent. **D.2** was freshly prepared *in situ* according to the procedure developed in our laboratory.³⁸⁵ It was directly engaged into the second step to afford the desired quinoline **III.29.aD** in 85% yield (Scheme 93).



Scheme 93: Synthesis of III.29.aD from analogue D.2 of the activated Yarovenko reagent (B.2)

When the activated Ishikawa reagent **C.2** was used with **III.28.a**, a cyclobutene **III.32** was formed by serendipity in 26% yield (Scheme 94) as confirmed by the single-crystal X-ray diffraction study (Figure 92). This study revealed the presence of an intramolecular hydrogen bonding between the NH and the oxygen O2. Both enantiomers are present in the crystallographic mesh (S,R : R,S). The reaction was performed twice to confirm that the cyclobutene rearrangement could effectively occur under acidic conditions. Indeed, in Dr. E. Schmitt's PhD thesis, the formation of such compounds was already observed under basic conditions.⁴²⁴



Scheme 94: Cyclobutene rearrangement

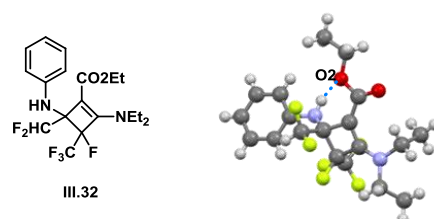
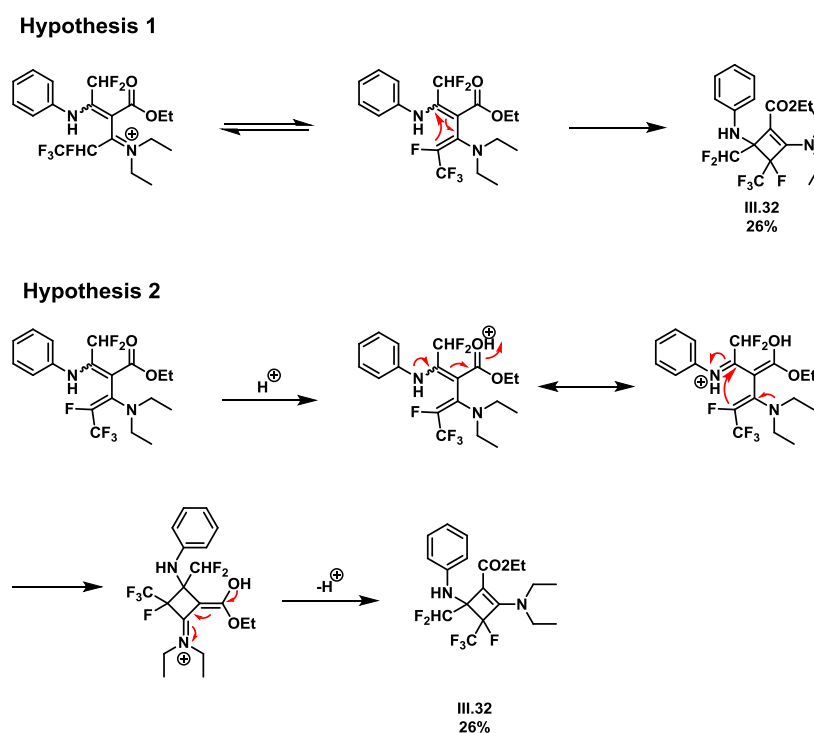


Figure 92: Crystallography analysis of compound III.32

We propose two possible mechanisms for the cyclobutene formation. In a first hypothesis, the hydrogen release allows an imine-enamine equilibrium and the formation of a conjugated diene system. Additionally, the presence of the large trifluoromethyl moiety, combined with that of the rather bulky diethylamino group, provokes a steric compulsion which twists the conjugated diene system and favours a [2+2] electrocycisation, providing cyclobutene **III.32**.

The second possibility is an activation of the carboxyl group by the acidic medium, leading to a conjugated iminium intermediate. Then, its intramolecular attack by the enamine provides compound **III.32** (Scheme 95).



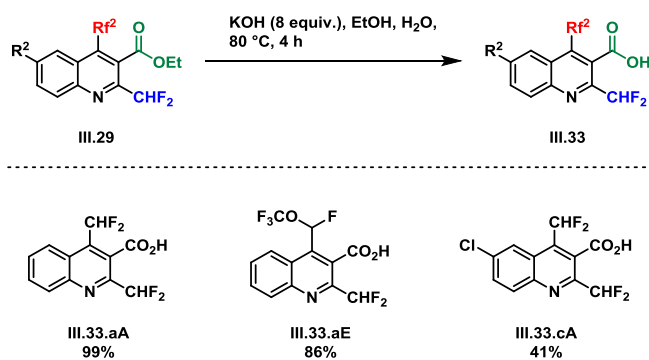
Scheme 95: Mechanistic postulates for cyclobutene formation

Since our main objective was the synthesis of quinolines, we did not dedicate more efforts in the study of cyclobutenes; nonetheless, it would be interesting to understand how they can be formed under either acidic or basic conditions.

In the end, in order to access the desired ethyl 2-CHF₂-4-CHF₂-3-quinolinecarboxylate, the use of the *N,N*-dimethyl analogue of Ishikawa's reagent (**F.1**) could be a solution, since this strategy proved efficient in the case of the Yarovenko reagent.

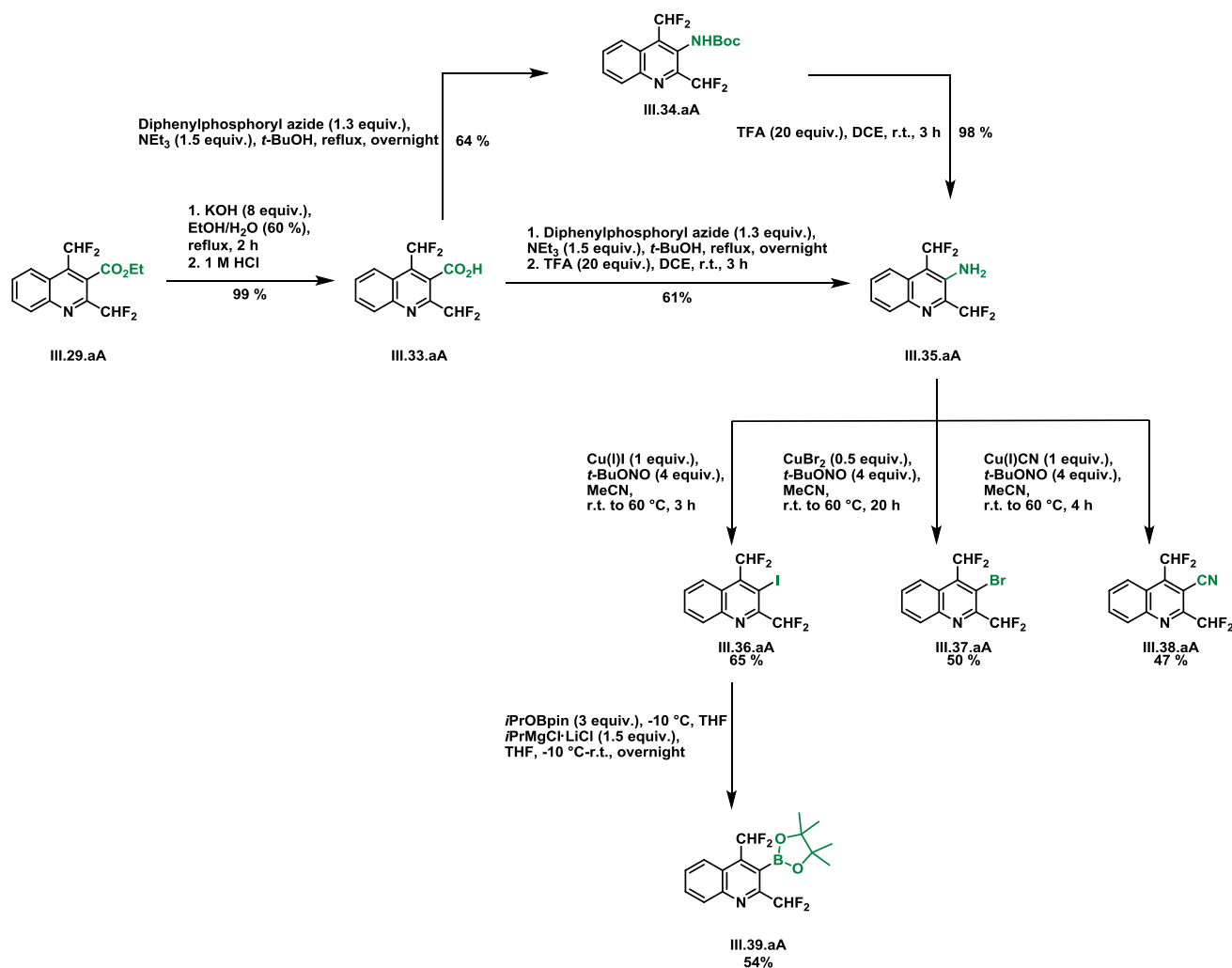
4.4.3 C3-Derivatization of quinoline-3-carboxylates

We first performed the saponification of selected compounds **III.29.aA**, **aE**, **cA** using potassium hydroxide in ethanol at 80 °C (Scheme 96). Compounds **III.33.aA**, **aE** were obtained in good yields, unlike **III.33.cA** (41% yield only). Extraction of the supernatant with various organic solvents did not allow recovering more of the desired compound. We suspected degradation of the product during the reaction, but by lack of time we could not perform other attempts.



Scheme 96: Saponification of selected esters

We were then interested in the post-functionalization of quinoline derivatives in position 3 (Scheme 97).



Scheme 97: Post-functionalization of compound III.29.aA

As a model quinoline we have chosen ethyl 2,4-bis(difluoromethyl)quinoline-3-carboxylate **III.29.aA**. After saponification into 2,4-bis(difluoromethyl)quinoline-3-carboxylic acid **III.33.aA**, we performed a Curtius rearrangement in presence of diphenylphosphoryl azide (DPPA). The formed isocyanate intermediate was trapped by *t*-BuOH, which provided the corresponding *t*-butyl (2,4-bis(difluoromethyl)quinolin-3-yl)carbamate **III.34.aA** in 64% yield.

In a second step, the amine function was then deprotected in acidic medium using TFA, and 2,4-bis(difluoromethyl)quinolin-3-amine **III.35.aA** was obtained in a quantitative yield. The reaction was also performed in one-pot following the procedure of Miller *et al.*⁴²⁵ The final compound was obtained in 61% over two steps. The formation of unprotected amines can allow other post-functionalizations by performing peptide couplings for example. However, we were interested in introducing a larger variability at position C3 of quinoline derivatives and Sandmeyer reactions were then attempted.

Following the procedure of Bui *et al.*⁴²⁶ using sodium nitrite and a mixture of copper bromide and hydrobromic acid, only the starting material was recovered. However, performing the same reaction in presence of *t*-butyl nitrite following the procedure of Boezio *et al.*⁴²⁷ allowed to access to 2,4-bis(difluoromethyl)-3-iodoquinoline **III.36.aA**, 3-bromo-2,4-bis(difluoromethyl)quinoline **III.37.aA** and 2,4-bis(difluoromethyl)quinoline-3-carbonitrile **III.38.aA** in moderate yields.

Finally, a boronic ester moiety was introduced by halogen-metal exchange using *i*PrMgCl•LiCl and *in situ* trapping with *isopropoxy*pinacolborane to form 2,4-bis(difluoromethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline **III.39.aA** following the procedure of Demory *et al.* (Scheme 97).⁴²⁸

Final compounds were obtained in six or seven steps with an overall yield comprised between 7 and 13%. All reactions were relatively easy to handle, except the formation of **III.39.aA** which can lead to the formation of the corresponding hydrolysed compound **III.2.aaA**.

To summarize, we validated the strategy for the functionalization of position C3 of quinolinecarboxylate **III.29.aA**. We can now imagine to post-functionalize the entire series of esters by following the same procedures and have access to a large scope of compounds substituted in position 3 and bearing fluoroalkylated substituents in both 2 and 4 positions.

4.4.4 Functionalization of difluoromethyl groups on quinoline derivatives

Besides functionalization of the C3 position of quinolines, we were also willing to study the possibility to derivatize CHF₂ substituents in positions 2 or 4. To do so, we imagined a deprotonation of the difluoromethyl group followed by trapping with an electrophile. By studying the literature, few publications depicted the isolation of CF₃⁻ or CHF₂⁻ species.

Chupp *et al.* described in 1989 the deprotonation reaction of a CHF₂ moiety linked to a penta-substituted pyridine. The use of bases (*e.g.* LDA, LiTMP), allow him to perform the introduction of numerous electrophiles (Figure 93).⁴²⁹

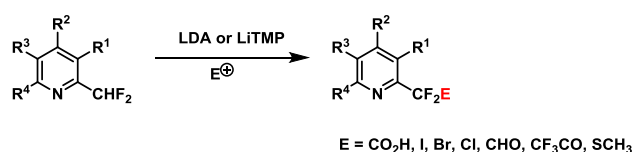


Figure 93: Chupp *et al.* reaction, functionalization of CHF₂ moiety

Grushin *et al.* reported the deprotonation of fluoroform from the formation of a copper complex obtained by deprotonation using copper chloride and *t*-BuOK. He then performed the introduction of a methyl group as electrophile in 28% yield (Figure 94).⁴³⁰⁻⁴³⁵

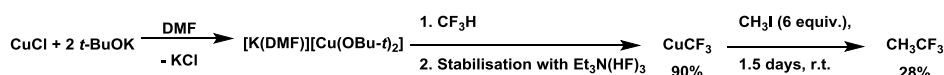


Figure 94: Grushin *et al.* reaction, TMSCl introduction

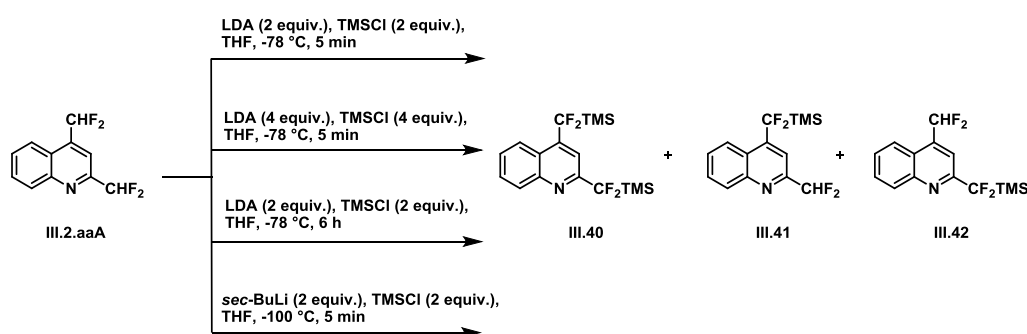
The stability and the reactivity of the CF_3^- anion was studied by Prakash *et al.*⁴³⁶ It presented an acceptable stability at -78°C and reacted with subsequent electrophiles, but what about the stability of the CHF_2^- anion? It is described that CHF_2^- is more stable than CF_3^- ,⁴³⁷⁻⁴³⁸ however, in order to avoid fluorine elimination and the formation of the difluoromethyl carbene, *in situ* trapping reaction was attempted using TMSCl. This reaction will allow the access to very interesting compounds which can become a potential mild source of quinolinedifluoromethynide anion, analogue of the Ruppert-Prakash reagent. These compounds may open the access to a new series of agrochemical ingredients. Indeed, once developed, this reaction may allow the insertion of multitude of electrophiles such as halogens (*e.g.* iodine), carbonyls, carbinols or alkyl moieties.

Accordingly, we first performed an *in situ* trapping reaction with TMSCl as the electrophile, starting from 2,4-bis(difluoromethyl)quinoline **III.2.aaA**. Introduction of the trimethylsilyl moiety on the fluorinated carbon(s) worked quite well. Indeed, the reaction was fast but the resulting compound was not stable. A stoichiometric amount of base was firstly tested, however, mixed compounds were obtained. To compensate the formation of complex mixture we decided to increase the quantity of base. We observed that under our conditions —excess of base and of electrophile— bis-silylation occurred first and the final compound rapidly underwent degradation during work-up (Scheme 98; Table 23).

We attempted to isolate 2,4-bis(difluoro(trimethylsilyl)methyl)quinoline **III.40**, by purification on column chromatography. Unfortunately, the compound demonstrated sensitivity toward silica gel and degraded.

Nevertheless, during the purification 4-difluoro(trimethylsilyl)methyl-2-(difluoromethyl)quinoline **III.41** was isolated and characterized. Sometimes traces of 2-difluoro(trimethylsilyl)methyl-4-(difluoromethyl)quinoline **III.42** were also observed.

To confirm the position of the silyl moiety and the formation of **III.41**, 2D NMR and ^1H NMR experiments were carried out. We observed effectively the disappearance of the corresponding 4- CHF_2 triplet. Yields were not determined for this study.



Scheme 98: *In situ* trapping reaction using TMSCl as electrophile

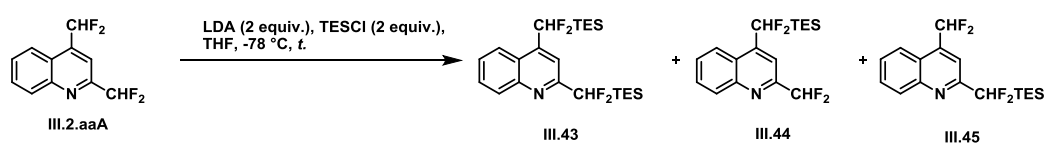
Table 23: Ratio of trimethylsilylated difluoromethylquinoline derivatives before and after work-up

Entry	Bases (n equiv.)	TMSCl (n equiv.)	t.	Conversion (%)	Ratio Before work-up (III.40:III.41)	Ratio After work-up (SM:III.40:III.41:III.42)
1	LDA (2 equiv.)	2 equiv.	5 min	100	89:11	Traces:80:16:4
2	LDA (4 equiv.)	4 equiv.	5 min	100	93:7	Traces:37.8:62:0.2
3	LDA (2 equiv.)	2 equiv.	6 h	96	35:61	Traces:12:82
4	<i>s</i> -BuLi (2 equiv.)	2 equiv.	5 min	0	/	/

We tried to selectively remove one of the two trimethylsilyl groups by trituration of the mixture in highly diluted acidic media or just water. All in all, we have never been able to control the regioselectivity of the TMS removal as results were not reproducible.

Although these results are interesting, the bis-silylated product was unstable and easily degraded with no control of regioselectivity. To palliate this problem, we decided to perform the reaction using a bulkier silicon electrophile such as TESCl, to improve the stability of the resulting difluoromethylsilyl group.

Similarly to TMSCl, the introduction of TESCl under *in situ* trapping conditions worked well and final compounds were obtained in almost quantitative yields (ratio determined by ¹H NMR). The reaction was complete in 2 minutes (Scheme 99; Table 24). However, the bis-silylated product was always accompanied by some mono-silylated compound **III.44** and traces of the other regioisomer 2-difluoro(triethylsilyl)methyl-4-(difluoromethyl)quinoline **III.45** were always observed in the reaction mixture.



Scheme 99: In situ trapping reaction using TESCl as electrophile

Table 24: Study of reaction duration and influence on completion

Entry	Conversion (%)	t (min)	Ratio before work-up ^(a)		
			III.43 :	III.44 :	III.45
1		2	97 :	3 :	
2	100	5	94 :	6 :	traces
3		10	95 :	5 :	
4		340	93 :	7 :	

(a): Determined by ¹H NMR

As compounds **III.43–45** could not be separated by conventional methods, more efforts must be dedicated to the selective formation of one or the other isomer of the mono-silylated products, or to the selective mono-desilylation of **III.43**. Despite selectivity issues that we must solve, these results confirmed the possibility to introduce silylated groups onto difluoromethyl substituents of quinoline derivatives.

Interestingly, this work also demonstrated that deprotonation occurs always on the CHF₂ moiety, revealing that these protons are probably more acidic than those of the benzo and pyrido subunits of the molecule, although the proton in position 3 might be difficultly accessible by the base, which artificially decreases its acidity.

5 CONCLUSION

Due to the combination of a new synthetic method and the reactivity of FARs, a series of 2,4-bis(fluoroalkyl)quinoline derivatives was obtained in moderate to good yield, under mild conditions, with a complete regioselectivity. This process requires only two steps, while three were needed when carboxylic anhydrides were used instead as reagents. FARs proved their superiority in the introduction of fluorinated moieties on the quinoline scaffold, whereas, using anhydrides, we faced irreproducible reactions, low yields of non-cyclized intermediates or, even worse, no reaction at all, and no direct formation of quinoline derivatives. (Figure 95). Starting from substituted anilines increased the scope and gave access to a multitude of compounds bearing either electron-donating or electron-withdrawing groups.

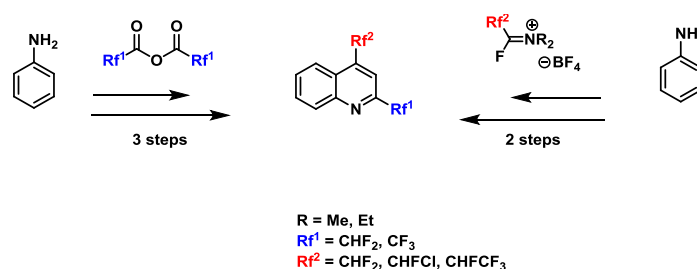
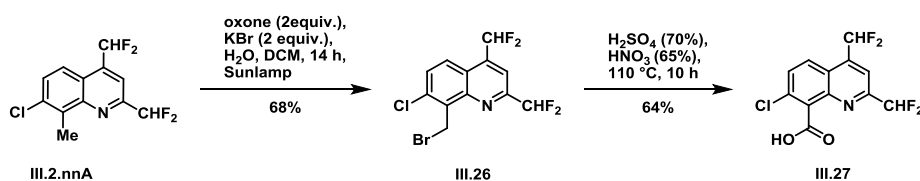


Figure 95: FARs vs. carboxylic anhydrides in the access to 2,4-bis(fluoroalkyl)quinolines

Having unlocked the access to a series of 2,4-bis(fluoroalkyl)quinolines, we then studied them following 4 approaches.

First, we tackled the access to quinoline-8-carboxylates. The direct introduction of a carboxy group by lithiation and trapping with CO_2 failed and complex mixtures were recovered. Then, the last-stage functionalization in position 8 by oxidation of a methyl substituent was attempted and proved difficult. Indeed, most of the time, partial oxidation products were obtained instead of the final compound. While no reaction was observed when standard oxidants were used, we finally managed to synthesize the desired 7-chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid **III.27** in two steps in an acceptable 64% yield under harsh conditions (Scheme 100).



Scheme 100: Formation of 7-chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid (**III.28**) by oxidation

This led us to study, in a second part, the electro-chemical and spectroscopic properties of variously decorated 2,4-bis(fluoroalkyl)quinolines and understand why they were insensitive toward oxidation.

Third, we realized the synthesis of 2,4-bis(fluoroalkyl)quinoline-3-carboxylates to be used as platform for further functionalization. The formation of the desired quinolines was sometimes not as easy as in the case of *N*-aryl ketimines, and the use of concentrated acid was needed in some cases to complete the cyclization. We noticed that the use of non-fluorinated *N*-aryl β -

aminoacrylate starting materials hampers the reaction, since the absence of an electron-withdrawing group makes the intermediate vinamidinium less prone to cyclization. Moreover, to access the β -aminoacrylates required for cyclization, the use of acetoacetates as starting material sometimes proved inefficient, probably due to the keto-enol equilibrium. We also confirmed the urgent need to develop FARs in the *N,N*-dimethylamino series to increase their reactivity and allow the formation of the desired quinolines.

Then, the post-functionalization of these quinolinecarboxylates in position 3 was carried out using known methodologies, and allowed the introduction of various groups such as carboxylic acid, halogen, nitrile, amine, amide, and boronic ester. Compounds were obtained in moderate to excellent yield and open a new route to further derivatization.

Fourth, we carried out preliminary investigations on the functionalization of the fluorinated carbons of 2,4-bis(difluoromethyl)quinoline. We managed to introduce trialkylsilyl groups by means of double deprotonation under *in situ* trapping conditions. For mono-silylation, the control of regioselectivity of the reaction remains to be studied. Furthermore, the nature of the silyl group appeared critical for the stability of the $\text{CF}_2\text{-Si}$ bond.

Finally, several quinoline derivatives obtained during this study were submitted to biological evaluations, but no significant activities were detected so far.

6 PERSPECTIVES

We established a robust FAR-based methodology to synthesize bis(fluoroalkyl)quinoline derivatives, which allowed the formation of many compounds with diverse substitution pattern in 3,6–8 positions of the quinoline scaffold. The development of new FARs would permit the introduction of more fluorinated groups in position 4, and the use of various ketones or fluoalkylacetoacetates will allow variability in position 2.

Moreover, building up on our work on the introduction of an ester moiety between the two fluoroalkyl groups, the formation of several derivatives variously functionalized in position 3 becomes possible. For example, peptide coupling could be performed, starting from quinolines bearing either a carboxylic acid group or an amine moiety in position 3 (Figure 96).

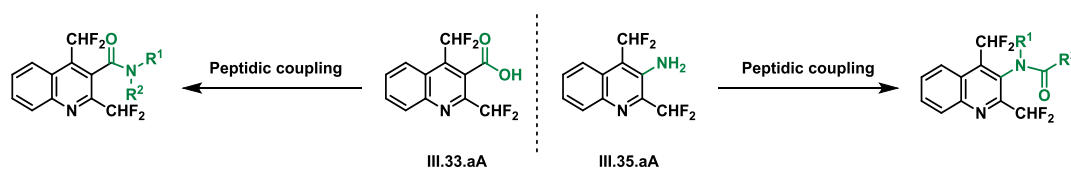


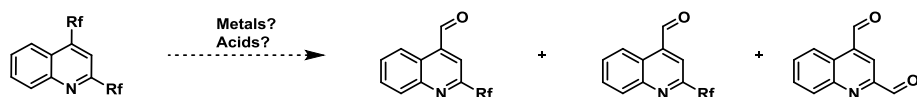
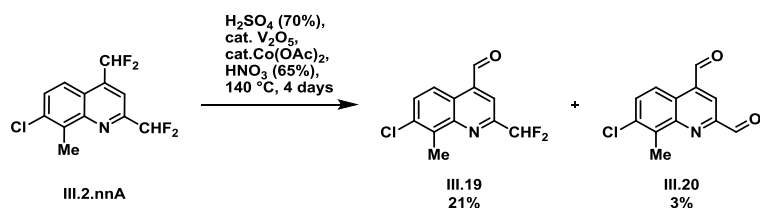
Figure 96: Peptide coupling from III.33.aA and III.35.aA

Additionally, 3-haloquinolines, obtained from the 3-carboxylates, could undergo nucleophilic aromatic substitutions, palladium-catalysed couplings —such as Suzuki, Heck, Stille couplings and so on—, or electrophilic trapping after generation of a carbanion upon halogen–metal exchange using organolithium or -magnesium reagents.

Yet another application of compounds obtained from quinoline-3-carboxylates could be the introduction of an azide function thanks to a Sandmeyer reaction. This could allow the formation of triazoles, which are important bioactive moieties and constitute a very useful means of derivatization or tethering to other bioactive ingredients, by click chemistry according to Sharpless' principles.⁴³⁹

During our attempts to oxidize a methyl substituent in position 8 of bis(fluoroalkyl)quinolines, under harsh reaction conditions, in presence of mixtures of concentrated acids at 140 °C for four days, two aldehydes **III.19** and **III.20** were isolated in various yields,. It would be interesting to perform the study on the C-F activation of the difluoromethyl group, as it remains hard to perform in aliphatic systems due to the low reactivity of this bond. This study should also solve the regioselectivity issues observed during the formation of aldehydes, and would include the detailed investigation on metals and acids used to perform the reaction (Scheme 101).⁴⁴⁰⁻⁴⁴¹

CHAPTER III: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

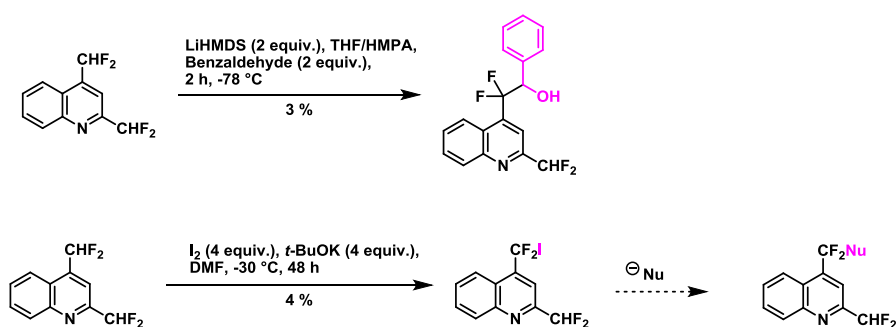


Scheme 101: Study of the C-F activation of difluoromethyl substituents

As another means to functionalize the difluoromethyl group, we performed the introduction of silylated moieties and we noticed the low stability of the resulting compounds. Moreover, the *in situ* trapping has its limitation since few electrophiles are compatible with LDA as base.

As additional preliminary results, we attempted the *in situ* trapping by iodine and benzaldehyde, following a procedure of Prakash *et al.*⁴⁴²⁻⁴⁴³ The reaction was not as faster as in the case where LDA was used as base, but both compounds were obtained with a symbolic low yield (~3-4%).

These two first trials were encouraging and should, after optimization, open the route to the introduction of a multitude of electrophiles, thus allowing access to new emergent fluorinated substituents (Scheme 102).



Scheme 102: Deprotonation of CHF_2 moiety and *in situ* trapping with benzaldehyde and iodine as a possible route towards new emergent fluorinated substituents

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General Conclusion and Perspectives

CONCLUSION

During this PhD thesis two projects were conducted.

The first one was dedicated to the synthesis of α,α -difluoro- β -hydroxy ketones. These compounds are interesting since they present potential activity as GABA receptor agonist. They are destined to serve as insecticides and more specifically to act on the CNS of insects (Figure 97).

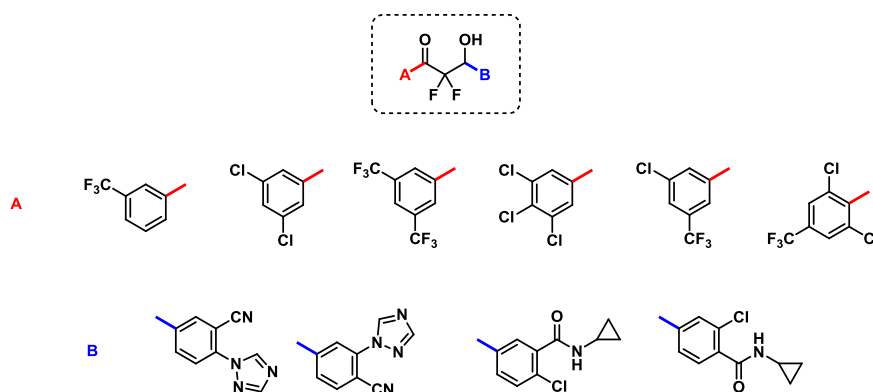


Figure 97: Defined substituents in the design of the target molecule

The synthesis of two key intermediates coupled in the last step was needed to get the target compounds.

Intermediates **1** were obtained in three steps to provide α,α -difluoro- β -trifluoromethyldihydroxy ketones **II.4** with an overall yield over three steps ranging 50 to 93%.

Intermediates **2** were obtained in one or four steps for the first family (compounds **II.5**) and in two steps for the second (compounds **II.11**).

The synthesis of **II.5** consisted in a nucleophilic aromatic substitution of fluorine by triazole moiety. Formation of 4-formyl-2-(1*H*-1,2,4-triazol-1-yl)benzotrile **II.5.b** needed a protection and a deprotection step to allow the introduction of the triazole moiety due to a less efficient stabilization of the intermediate carbanion by the formyl group in *meta* position.

The second family of compounds can be obtained accordingly to two pathways. A halogen-metal exchange followed by a peptide coupling (path a) or by a peptide coupling followed by a halogen-metal exchange (path b). In both cases the halogen-metal exchange reaction was not easy to control. Conversion of compounds did not reach more than 50% and several side-reactions were observed leading to the formation of unidentified impurities. By contrast to path a, pathway b gave access to compounds in slightly higher overall yields, although the limiting step remains the halogen-metal exchange (Figure 98).

General Conclusion and Perspectives

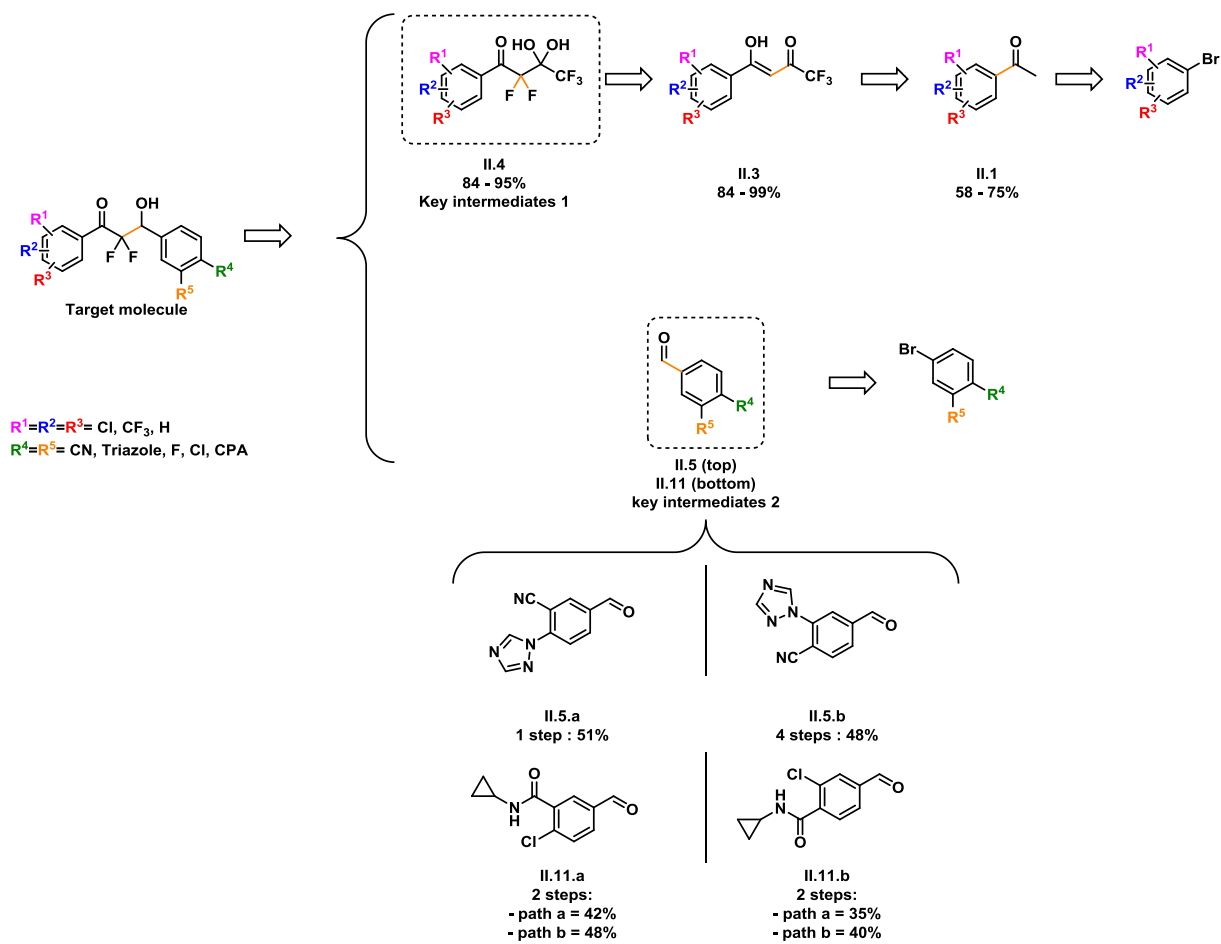


Figure 98: Summary of the synthesis of α,α -difluoro- β -hydroxy ketones

Up to now, twenty-four molecules bearing a α,α -difluoro- β -hydroxy ketone motif were synthesized. Biological analysis highlighted a specific family of compound and a pro-drug approach has started to tune their structure and find a hit.

General Conclusion and Perspectives

The second project was dedicated to the development of a new series of fluorinated quinolines substituted in both 2 and 4 positions (Figure 99).

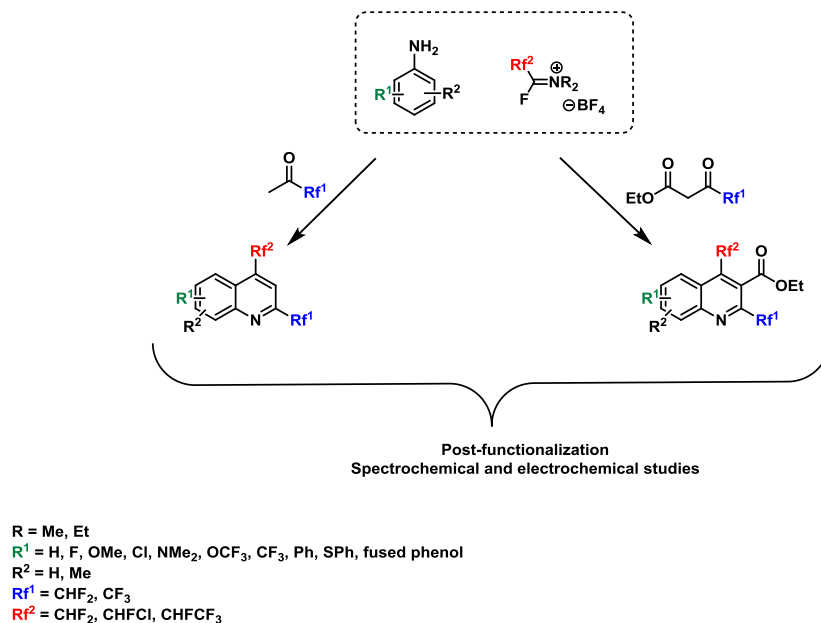


Figure 99: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines

A series of 2,4-bis(fluoroalkyl)quinoline derivatives was obtained in moderate to good yield, under mild conditions, with a complete regioselectivity in two steps only. The quinoline formation occurred in analogy to the Combes and the Meth-Cohn reactions and uses highly reactive Fluoroalkyl Amino Reagents (FARs) activated by Lewis acids. Competition between the reactivity of FARs and anhydrides was tested, proving the incredible advantage to use FARs in the development of new quinolines which allow the insertion of emergent fluorinated groups in both 2 and 4 positions (Figure 100).

Already marketed herbicides possessing a quinoline core inspired the last stage functionalization in position 8 in order to introduce a carboxylic acid function. Oxidation reactions did not work so well, however, they allowed the formation of several interesting side products. We finally managed to synthesise one bis(fluoroalkyl)quinoline 8-carboxylic acid in two steps in an acceptable 64% yield. These reactions pointed out the difficulty to oxidize these bis(fluoroalkyl)quinolines.

Spectrophotometric and electrochemical studies were realized in order to understand their electronical properties induced by the fluoroalkyl substituents present on the molecule.

We then performed the synthesis of 2,4-bis(fluoroalkyl)quinoline derivatives functionalized in position 3 by a carboxylate moiety to be used as platform for further functionalization. Following the same protocol as in the first part, the synthesis of quinoline derivatives obtained from fluorinated acetoacetate must be optimized for several cases. Likewise, it seems to be primordial to develop new FARs bearing a dimethylamino moiety instead of a diethylamino to increase their reactivity and allow the formation of multiple new quinolines.

The last part of this project was dedicated to the post-functionalization of these quinoline derivatives in position 3. Different standard reactions were applied to increase the scope of the

General Conclusion and Perspectives

reaction and allow the introduction of various groups which will open the route for further derivatization.

Biological evaluations were performed on quinoline derivatives but no significant activities were detected so far (Figure 100).

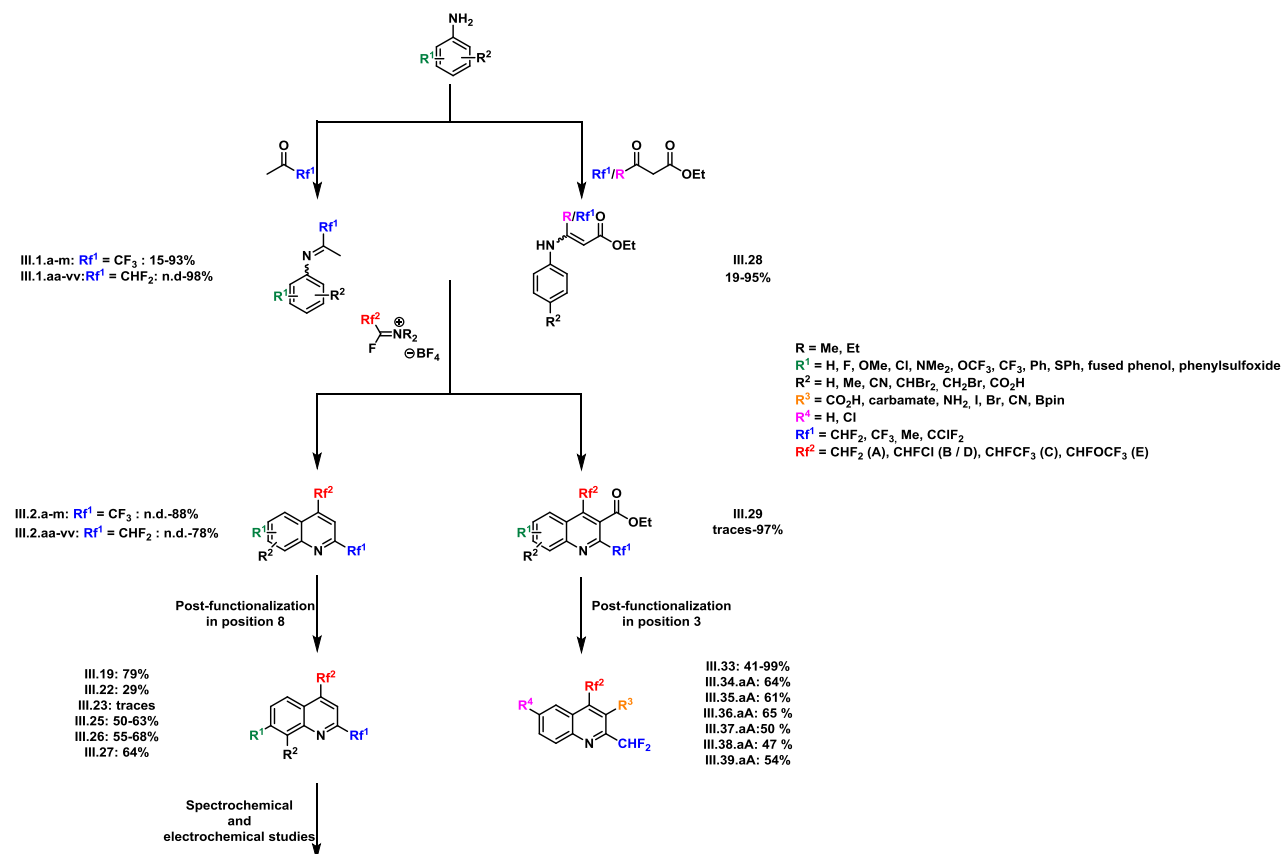


Figure 100: Summary of the synthesis of 2,4-bis(fluoroalkyl)quinoline derivatives

PERSPECTIVES

1 SYNTHESIS OF α,α -DIFLUORO- β -HYDROXY KETONES

A pro-drug approach has been started to fine-tune the activity of the molecules and improve their *in vitro* and *in vivo* activities. The purpose is to increase the bioavailability of them using several methodologies (Figure 101).

- Replacing the hydroxyl group by a fluorine atom can increase the metabolic stability by blocking oxidative degradation.
- Lipophilicity of the molecule can be modified by performing *O*-alkylation or *O*-acylation reactions allowing a better passage through cell membranes and enhancing the probability to reach the CNS of insects.
- Separation of diastereoisomers can be envisaged as well as the synthesis of enantiopur compounds, which can give clues on chirality and its effect on the biological activity.
- Studying the effect of fluorine on a series of compounds containing various number of fluorine atom can help the tunability of the molecule. The modification of the number of fluorine atoms on the molecule can influence its pKa, by acting on the acidity and the basicity of proximate groups (OH, carbonyl, etc.)

Previous aspects presented to modify the properties of the molecule might be applied for compounds bearing one or zero fluorine atoms in the α -position.

- Finally, we may proceed to the inversion of both aromatic rings which may modify the interactions between the molecule and the active site and enhance the biological activities of the compounds.

General Conclusion and Perspectives

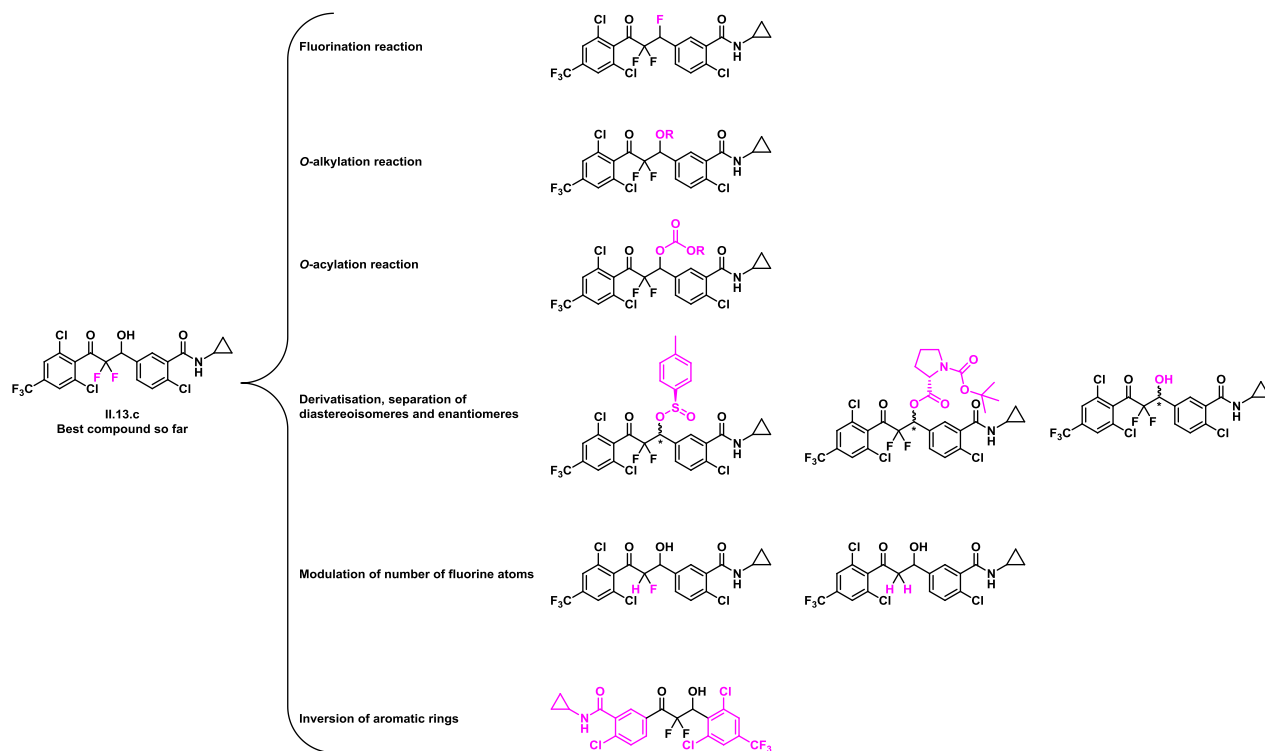


Figure 101: Examples of reaction to tune compound II.13.c (Pro-drug approach)

2 SYNTHESIS OF QUINOLINE DERIVATIVES

The development of quinoline derivatives remains at the backbone of scientific research since the 19th century.

Indeed, their valuable skeleton has demonstrated to be biologically active in various fields (from agrochemical to pharmaceutical industries through material science).

In this manuscript, we described a new method to synthesized quinolines bearing two fluorinated groups in both 2 and 4 positions based on the use of FARs.

Development of new FARs as well as the use of various fluorinated ketones or fluoalkylacetoacetates would increase the scope of existing quinoline derivatives since numerous emergent fluorinated substituents will be introduced.

Electrochemical studies revealed that oxidation reactions on these quinolines to introduce carboxylic acid function were hard to perform due to their inertness towards oxidation.

On the other hand, compounds that bear a carboxylate moiety in position 3 were easily synthesized (in specific cases) and gave access to a multitude of derivatives. The introduction of further functional groups allows the access to more complex molecules. The presence of substituents like halogens may allow:

- Substitution reactions.
- Metallo-catalyzed coupling reactions.
- Halogen-metal exchange reactions.

The introduction of azide or terminal alkenes might be considered for the formation of triazoles by click chemistry. It was described in the literature that quinolines can exhibit vascular disrupting effects.^{229, 444-445} We can thus imagine to combine them with a photosensitizer like phthalocyanines useful in photodynamic therapy (PDT) which will present a dual effect for anti-tumoral purpose.⁴⁴⁶

It would be interesting to study the C-F activation. Indeed, under harsh conditions we noticed the transformation of the CHF₂ into formyl moiety (without regioselectivity). The selective removal of fluorine (onto CF₃) and the introduction of various functionalities can be studied.

Finally, the selective insertion of electrophiles by deprotonation of the CHF₂-group will be a good alternative in the development of new emergent fluorinated substituents. We noticed that the action of bases onto quinolines selectively attacks the CHF₂-group allowing the introduction of two TMS or TES moieties. The major problem was the instability of these molecules in addition to the limitations of the *in situ* trapping reaction. However, it proves that only CHF₂-groups are impacted by strong bases and opens an encouraging route to the development of new compounds.

Stronger bases as well as electrophiles must be systematically tested. Direct deprotonation reactions must be optimized to palliate the *in situ* trapping reaction limitation.

Both developments including selective electrophile introduction and C-F activation reactions will be major advances in the development of new emergent fluorinated substituents (Figure 102).

General Conclusion and Perspectives

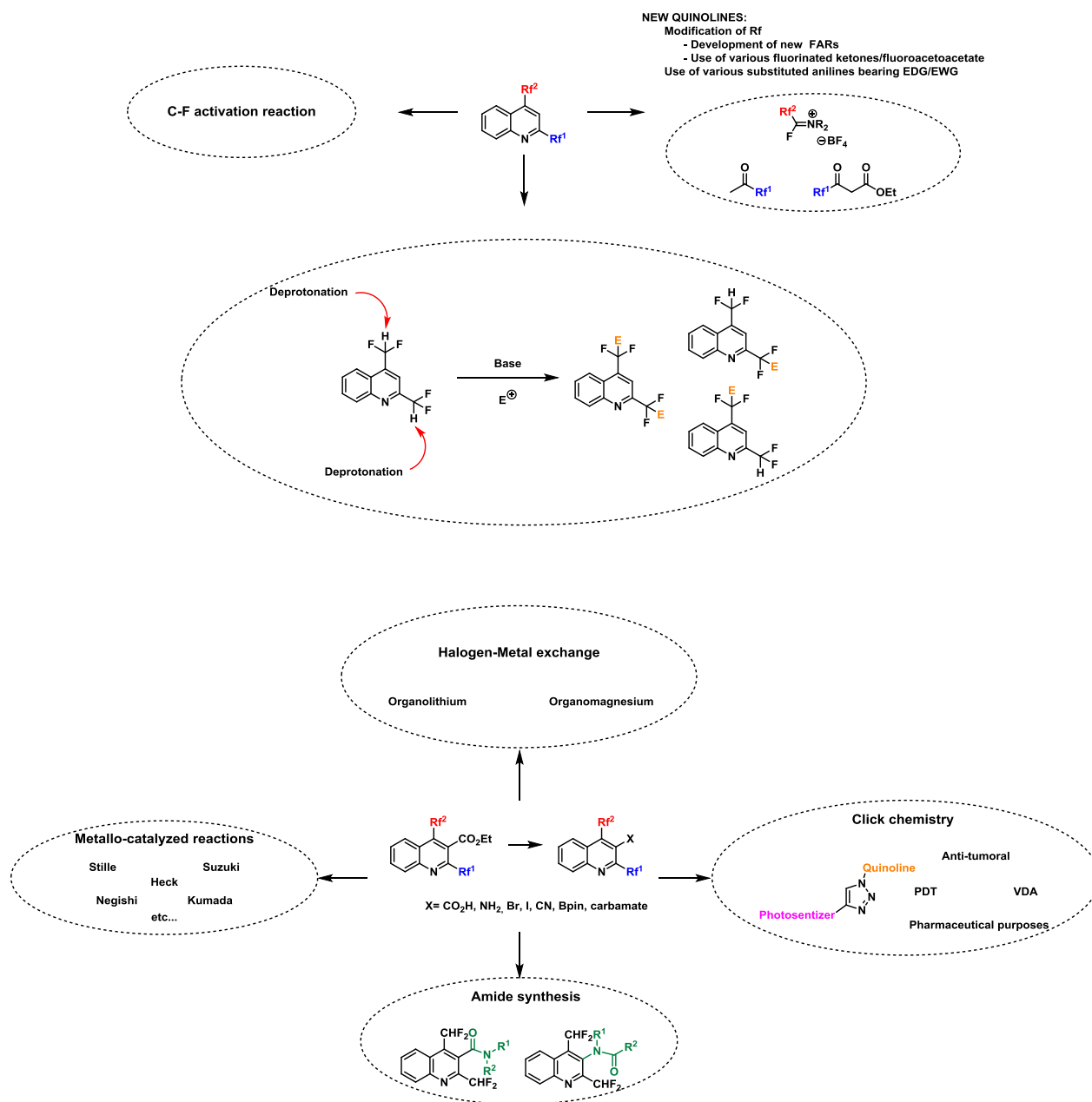


Figure 102: Example of possible ameliorations or modifications onto quinoline derivatives

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LIST OF SCIENTIFIC CONTRIBUTIONS

Publication:

Aribi, F.; Schmitt, E.; Panossian, A.; Vors, J.-P.; Pazenok, S.; Leroux, F. R., A new approach toward the synthesis of 2,4-bis(fluoroalkyl)-substituted quinoléine derivatives using fluoroalkyl amino reagent chemistry. *Org. Chem. Front.* **2016**, *3*, 1392-1415. (Inside Front cover picture.)

Commare, B.; Schmitt, E.; Aribi, F.; Panossian, A.; Vors, J.-P.; Pazenok, S.; Leroux, F. R., Fluoroalkyl Amino Reagents (FARs): A General Approach towards the Synthesis of Heterocyclic Compounds Bearing Emergent Fluorinated Substituents. *Molecules* **2017**, *22*, 977-1003.

Patent:

Leroux, F. R.; Aribi, F.; Schmitt, E.; Panossian, A.; Vors, J.-P.; Pazenok, S., Process for the preparation of Polyfluoroalkylated Quinolines, BCS153082 (Bayer CropScience AG / CNRS / Strasbourg University; filed 21/01/2016).

Posters:

Poster ISFC 2015 (International Symposium on Fluorine Chemistry): "A general approach towards NH pyrazoles bearing diverse fluoroalkyl groups by means of fluorinated iminium salts.", Schmitt, E.; Aribi, F.; Landelle, G.; Pazenok, S.; Lui, N.; Vors, J.-P.; Leroux, F.R.. ISFC 2015, Como, Italy, August 23-28, 2015.

Poster CFCF 2017 (Colloque français de chimie du fluor): "Synthesis of 2,4-bis(fluoroalkyl)-substituted quinolines.", Aribi, F.; Schmitt, E.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F.R.. CFCF 2017, Murol, France, May 15-18, 2017. Best poster prize.

Oral communication:

Oral Communication: "New approaches toward fluorinated building blocks for crop-protection products: Synthesis of 2,4-bis(fluoroalkyl)-substituted quinoléines."; Aribi, F.; Schmitt, E.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F.R..

JCO - Journée de Chimie Organique, Palaiseau, France, September 7-9, 2016. Best oral communication prize.

JDC - Journée des Doctorants en Chimie, Strasbourg, France, November 2, 2016.

EXPERIMENTAL PART

Material and Methods

All reactions were performed in flame-dried glassware using Schlenk techniques for reactions needed anhydrous conditions. Liquids and solutions were transferred with syringes. Air- and moisture-sensitive materials were stored and handled under an atmosphere of argon. Solvents were purified and dried following standard procedures: Dichloromethane (DCM) and Tetrahydrofuran (THF) were 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, Acetone-d₆ and DMSO-d₆ on Bruker AV 400 instruments (¹H: 400 MHz, ¹⁹F: 376 MHz, ¹³C: 101 MHz). Chemical shifts are reported in parts per million (ppm) and are referenced to the residual solvent resonance as the internal standard (chloroform (δ [¹H] = 7.26 and accordingly δ [¹³C] = 77.16 ppm). Data are reported as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, qd = quadruplet of doublets, td = triplet of doublets, dd = doublet of doublets, dq = doublet of quadruplets), coupling constant (Hz) and integration. 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.

Electrochemical and spectrophotometric studies were performed according following descriptions:

- ➔ **Absorption studies.** The UV-visible absorption spectra were recorded from 220 to 800 nm with an AGILENT CARY 5000 spectrophotometer maintained at 25.0(2) °C by the flow of a CARY VARIAN Dual Cell Peltier accessory. Quartz optical cells with pathlength of 1 cm were used for these measurements.
- ➔ **Emission studies.** The fluorescence emission spectra were recorded from 300 to 800 nm on a PERKIN-ELMER LS-50B maintained at 25.0(2) °C by the flow of a Haake FJ thermostat. The light source was a pulsed xenon flash lamp with a pulse width at half-peak height <10 μ s and power equivalent to 20 kW. The slit width was adjusted for both the excitation and the emission to reach the maximum of intensity. The spectrofluorimetric signal of the S₁→S₀ transitions were measured at absorbances <0.1 to minimize reabsorption processes.
- ➔ **Electrochemistry.** The redox potentials of the fluorinated quinoline derivatives were measured by cyclic voltammetry (CV) in 1,2-dichloroethane solvent. Cyclic voltammetry of the quinolines (~ mM solutions) was carried out using a Voltalab 50 potentiostat/galvanostat (RADIOMETER ANALYTICAL MDE15 polarographic stand, PST050 analytical voltammetry and CTV101 speed control unit) controlled by the VOLTAMASTER 4 electrochemical software. A conventional three-electrode cell (10 mL) was employed in our experiments with a glassy carbon disk (GC, $s = 0.07 \text{ cm}^2$) set into a Teflon rotating tube as a working electrode, a Pt wire as a counter electrode, and KCl(3 M)/Ag/AgCl reference electrode (+210 mV vs NHE). Prior to each measurement, the surface of the GC electrode was carefully polished with 0.3 μ m aluminium oxide suspension (ESCIL) on a silicon carbide abrasive sheet of grit 800/2400. Thereafter, the GC electrode was copiously washed with water and dried with paper towel and argon. The electrode was installed into the voltammetry cell along with a platinum wire counter electrode and the reference. The solutions containing *ca.* 10⁻³ M of the quinoline derivatives were vigorously stirred and purged with O₂-free (SIGMA OXICLEAR cartridge) argon for 15 minutes before the voltammetry experiment was initiated, and maintained under an argon atmosphere during the measurement procedure. The voltammograms (cyclic voltammograms - CV-) were recorded at room temperature (23(1)°C) in 1,2-dichloroethane with 100 mM tetra-*n*-butylammonium tetrafluoroborate (ALFA AESAR, +99%) as supporting and inert electrolyte. The voltage sweep rate was varied from 50 to 300 mV s⁻¹ and several cyclic voltammograms were recorded from +2.5 V to -2.5 V. Peak potentials were measured at a scan rate of 200 mV s⁻¹ unless otherwise indicated. Redox potentials were determined from oxidation and reduction potentials.

Chapter II: Synthesis of α,α -difluoro- β -hydroxy ketones

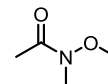
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1 KEY INTERMEDIATES 1

1.1 Preparation of *N*-methoxy-*N*-methylacetamide¹⁶⁶

To a stirred suspension of *N*-methoxymethylamine hydrochloride salt (1 equiv., 20 g, 205 mmol) in DCM (500 mL) at 0 °C was slowly added NEt₃ (2 equiv., 57 mL, 410 mmol). Acetyl chloride (1 equiv., 14.6 mL, 205 mmol) was then added dropwise to the solution. The solution was then allowed to warm to room temperature and stirred for 2 h before quenching the reaction with saturated aqueous NaHCO₃ solution. The two layers were separated and the organic phase was washed with 1 M HCl, brine and dried over sodium sulphate (Na₂SO₄) before being concentrated under vacuum. *N*-methoxy-*N*-methylacetamide was obtained as colourless oil after distillation in 96% yield (20.3 g). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 3.65 (s, 3H, OCH₃), 3.14 (s, 3H, NCH₃), 2.09 (s, 3H, CH₃) ppm.

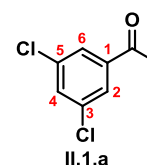


Chemical Formula: C₄H₉NO₂
Exact Mass: 103,06 g/mol
Colourless oil

1.2 Typical procedure A for the preparation of ketones synthesis (II.1) and preparation of compound (II.2)

1-(3,5-Dichlorophenyl)ethan-1-one II.1.a¹⁶⁸

A dry and argon-flushed Schlenk-flask, was charged with the 1-bromo-3,5-dichlorobenzene (1 equiv., 2.09 g, 9.26 mmol) and THF (19.9 mL). The solution was cooled to 0 °C and *i*PrMgCl.LiCl complex solution 1.3 M in THF (1.2 equiv., 1.3 M, 8.2 mL, 11.1 mmol) was added. The reaction mixture is stirred for 5 h before *N*-methoxy-*N*-methylacetamide (2 equiv., 1.97 mL, 18.5 mmol) was added at 0 °C. The temperature was heated to room temperature and the mixture was stirred for 10 h. 1 M hydrochloric acid (HCl) was added to quench the reaction and the organic layer was extracted with AcOEt, dried over Na₂SO₄ and concentrated under vacuum. The reaction mixture was purified on column chromatography using a gradient of AcOEt in cyclohexane (0-5%) to provide the desired 1-(3,5-dichlorophenyl)ethan-1-one **II.1.a** as a clear oil in 68% yield (1.19 g). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 7.80 (d, ⁴*J*_{H-H} = 1.9 Hz, 2H, C_{2,6}H), 7.54 (t, ⁴*J*_{H-H} = 1.9 Hz, 1H, C₄H), 2.58 (s, 3H, CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 195.39 (s, CO), 139.51 (s, C₁), 135.75 (s, C_{3,5}), 132.85 (s, C₄), 126.87 (s, C_{2,6}), 26.72 (s, CH₃) ppm. GCMS: for C₈H₆Cl₂O: m/z (%) 188 (3.3) [C₈H₅Cl₂O], 173 (100) [C₇H₃Cl₂O]⁺, 145 (4.3) [C₆H₃Cl₂]⁺.



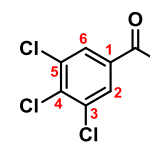
Chemical Formula: C₈H₆Cl₂O
Exact Mass: 187,98 g/mol
Clear oil

The following experiments were carried out according to **Typical Procedure A**. Data are reported as: a) Commercially available bromo benzene; b) THF; c) *i*PrMgCl.LiCl complex solution 1.3 M in THF; d) *N*-methoxy-*N*-methylacetamide; e) purification; and f) yield and aspect.

Individual analysis for each compound (**II.1.a-c**) is given below.

1-(3,4,5-Trichlorophenyl)ethan-1-one II.1.b

a) 5-Bromo-1,2,3-trichlorobenzene (1 equiv., 1.48 g, 5.69 mmol); b) THF (12.8 mL); c) *i*PrMgCl.LiCl complex solution 1.3 M in THF (1.2 equiv., 1.3 M, 5.25 mL, 6.83 mmol); d) *N*-methoxy-*N*-methylacetamide (2 equiv., 1.21 mL, 11.4 mmol); e) AcOEt in cyclohexane (5-20%). and d) 1-(3,4,5-trichlorophenyl)ethan-1-one **II.1.b** was obtained as a colourless solid in 58% yield (731 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.92$ (s, 2H, $\text{C}_{2,6}\text{H}$), 2.58 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 194.71$ (s, CO), 136.60 (s, C_4), 136.33 (s, C_1), 135.07 (s, $\text{C}_3, 5$), 128.36 (s, $\text{C}_{2,6}$), 26.60 (s, CH_3) ppm. IR ν (cm^{-1}): 3068 (Csp_2H); 1688 ($\text{C}=\text{O}_{\text{ketone}}$); 1547-1374 cm^{-1} ($\text{C}=\text{C}_{\text{aro}}$). GCMS: for $\text{C}_8\text{H}_5\text{Cl}_3\text{O}$: m/z (%) 222 (30) [$\text{C}_8\text{H}_5\text{Cl}_3\text{O}$], 207 (100) [$\text{C}_7\text{H}_2\text{Cl}_3\text{O}$] $^+$, 179 (37) [$\text{C}_6\text{H}_2\text{Cl}_3$] $^+$. MP: 71.9-72.3 $^{\circ}\text{C}$.

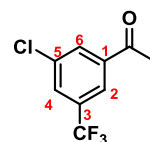


II.1.b

Chemical Formula: $\text{C}_8\text{H}_5\text{Cl}_3\text{O}$
Exact Mass: 221,94 g/mol
Colourless solid

1-[3-Chloro-5-(trifluoromethyl)phenyl]ethan-1-one II.1.c

a) 1-Bromo-3-chloro-5-(trifluoromethyl)benzene (1 equiv., 0.874 mL, 5.78 mmol); b) THF (13.5 mL); c) *i*PrMgCl.LiCl complex solution 1.3 M in THF (1.2 equiv., 1.3 M, 5.34 mL, 6.94 mmol); d) *N*-methoxy-*N*-methylacetamide (2 equiv., 1.23 mL, 11.6 mmol); e) AcOEt in cyclohexane (0-10%). and d) 1-[3-chloro-5-(trifluoromethyl)phenyl]ethan-1-one **II.1.c** was obtained as a clear oil in 58% yield (747 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.08$ (s, 1H, C_6H), 8.05 (s, 1H, C_2H), 7.78 (s, 1H, C_4H), 2.63 (s, 3H, CH_3) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -63.01$ (s, CF_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 195.22$ (s, CO), 139.23 (s, C_1), 135.92 (s, C_5), 132.92 (q, $^2J_{\text{C-F}} = 33.6$ Hz, C_3), 131.73 (q, $^5J_{\text{C-F}} = 0.5$ Hz, C_6), 129.74 (q, $^3J_{\text{C-F}} = 3.7$ Hz, C_4), 123.37 (q, $^3J_{\text{C-F}} = 3.7$ Hz, C_2), 123.01 (q, $^1J_{\text{C-F}} = 273.1$ Hz, C_3CF_3), 26.67 (s, CH_3) ppm. GCMS: for $\text{C}_9\text{H}_6\text{ClF}_3\text{O}$: m/z (%) 222 (23) [$\text{C}_9\text{H}_6\text{ClF}_3\text{O}$], 207 (100) [$\text{C}_8\text{H}_3\text{ClF}_3\text{O}$] $^+$, 179 (63.3) [$\text{C}_7\text{H}_3\text{ClF}_3$] $^+$.

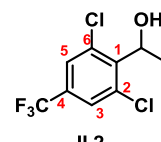


II.1.c

Chemical Formula: $\text{C}_9\text{H}_6\text{ClF}_3\text{O}$
Exact Mass: 222,01 g/mol
Clear oil

1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)ethan-1-ol II.2

In a solution of 4-bromo-3,5-dichlorobenzotrifluoride (1 equiv., 1.09 mL, 6.81 mmol) in anhydrous Et_2O (20 mL), was added *n*-BuLi (1 equiv., 1.59 M, 4.28 mL, 6.81 mmol). The reaction mixture was stirred for 2 h at -78 $^{\circ}\text{C}$ then acetaldehyde (1.5 equiv., 0.573 mL, 10.2 mmol) was added. The mixture was stirred for an additional 3 h before to be warm slowly to room temperature. Brine solution was added and organic layer was extracted with AcOEt, dried over Na_2SO_4 and concentrated under vacuum. 1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)ethan-1-ol **II.2** was obtained without any purification as a yellow oil in 99% yield (1.75 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.56$ (s, 2H, $\text{C}_{3,5}\text{H}$), 5.62 (dq, $^3J_{\text{H-OH}} = 9.7$, $^3J_{\text{H-H}} = 6.9$ Hz, 1H, CHOH), 2.83 (d, $^3J_{\text{OH-H}} = 9.9$ Hz, 1H, OH), 1.66 (d, $^3J_{\text{H-H}} = 6.9$ Hz, 3H, CH_3) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -63.09$ (s, CF_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 142.67$ (s, C_1), 134.77 (s, $\text{C}_{2,6}$), 131.39 (q, $^2J_{\text{C-F}} = 34.3$ Hz, C_4), 126.44 (q, $^3J_{\text{C-F}} = 3.7$ Hz, $\text{C}_{3,5}$), 122.58 (q, $^1J_{\text{C-F}} = 273.7$ Hz, C_4CF_3), 68.30 (s, COH), 21.30 (s, CH_3) ppm. IR ν (cm^{-1}): 3370 (OH), 2979-2931 (Csp_2H), 1459-1437 ($\text{C}=\text{C}_{\text{aro}}$).

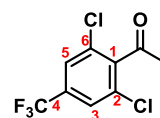


II.2

Chemical Formula: $\text{C}_9\text{H}_7\text{Cl}_2\text{F}_3\text{O}$
Exact Mass: 257,98 g/mol
Yellow oil

1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)ethan-1-one II.1.d

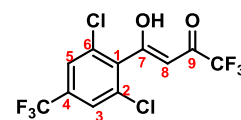
To a solution of 1-(2,6-dichloro-4-(trifluoromethyl)phenyl)ethan-1-ol (**II.2**) (1 equiv., 1.27 g, 4.91 mmol) in water (6 mL) and Et₂O (3 mL) was added concentrated sulphuric acid (H₂SO₄) (1 mL), the reaction mixture stirred for 5 min. Sodium dichromate (Na₂Cr₂O₇) was then added in one pot (0.4 equiv., 0.515 g, 1.97 mmol), the brown reaction mixture was stirred at room temperature for 4 h. The ethereal layer was separated and the aqueous layer was extracted with Et₂O. The combined extracts were dried over Na₂SO₄ and concentrated under vacuum. 1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)ethan-1-one **II.1.d** was obtained as a colourless oil in 75% yield (0.943 g) was obtained as a colourless oil. ¹H NMR (400 MHz, CDCl₃) δ_{H} = 7.59 (s, 2H, C_{3,5}H), 2.58 (s, 3H, CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_{F} = -63.17 (s, CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 198.56 (s, CO), 143.18 (s, C₁), 133.17 (q, ²J_{C-F} = 34.2 Hz, C₄), 131.29 (s, C_{2,6}), 125.42 (q, ³J_{C-F} = 3.7 Hz, C_{3,5}), 122.37 (q, ¹J_{C-F} = 273.7 Hz, C₄CF₃), 30.90 (s, CH₃) ppm. IR ν (cm⁻¹): 2968-2931 (Csp₂H), 1724 (C=O_{ketone}), 1560-1458 (C=C_{aro}). GCMS: for C₉H₅F₃ClO: m/z (%) 256 (10) [C₉H₅F₃ClO], 241 (100) [C₈H₂F₃ClO]⁺, 213 (23) [C₇H₂F₃Cl]⁺.

**II.1.d**

Chemical Formula: C₉H₅Cl₂F₃O
Exact Mass: 255.97 g/mol
Colourless oil

1.3 Typical procedure B for the preparation of compounds from Claisen condensation (II.3)**(Z)-4-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-1,1,1-trifluoro-4-hydroxybut-3-en-2-one II.3.a**

To a -30 °C solution of HMDS (1.5 equiv., 0.522 mL, 2.46 mmol) in THF (3.30 mL) was added *n*-BuLi (1.5 equiv., 1.59 M, 1.54 mL, 2.46 mmol). The mixture was stirred for 20 min at -30 °C, and 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]ethan-1-one **II.1.d** (1 equiv., 421 mg, 1.64 mmol) was added dropwise. After 4 h at -30 °C, 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (1.5 equiv., 0.329 mL, 2.46 mmol) was added dropwise and stirred for 4 h at the same temperature. The reaction mixture was quenched with 1 M H₂SO₄ and stirred for an additional 1 h. The resultant mixture was extracted with DCM. The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum to provide the desired (3Z)-4-[2,6-dichloro-4-(trifluoromethyl)phenyl]-1,1,1-trifluoro-4-hydroxybut-3-en-2-one **II.3.a** as a clear oil in 84% yield (0.486 g). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 7.66 (s, 2H, C_{3,5}H), 6.16 (s, 1H, C₈H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_{F} = -63.35 (s, C₄CF₃), -76.13 (s, CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 186.38 (s, C₇), 174.33 (q, ²J_{C-F} = 37.5 Hz, C₉), 137.48 (s, C₁), 134.38 (q, ²J_{C-F} = 34.6 Hz, C₄), 133.79 (s, C_{2,6}), 125.68 (q, ³J_{C-F} = 3.7 Hz, C_{3,5}), 122.21 (q, ¹J_{C-F} = 274.7 Hz, C₄CF₃), 117.13 (q, ¹J_{C-F} = 281.7 Hz, CF₃), 99.39 (q, ³J_{C-F} = 2.2 Hz, C₈) ppm. HRMS (ESI negative) for C₁₁H₃Cl₂F₆O₂ [M⁻]: calcd 350.9420, found 350.9419.

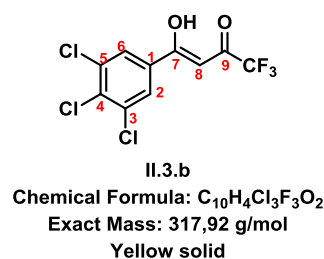
**II.3.a**

Chemical Formula: C₁₁H₄Cl₂F₆O₂
Exact Mass: 351.95 g/mol
Clear oil

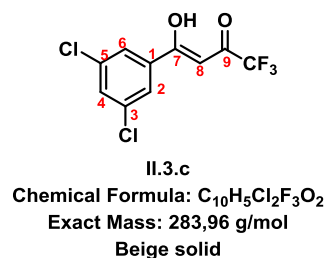
The following experiments were carried out according to **Typical Procedure B**. Data are reported as: a) HMDS; b) THF; c) *n*-BuLi; d) Commercially available ketones or ketones (**II.1**); e) 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate; and f) yield and aspect. Individual analysis for each compound (**II.3**) is given below.

(Z)-1,1,1-Trifluoro-4-hydroxy-4-(3,4,5-trichlorophenyl)but-3-en-2-one II.3.b

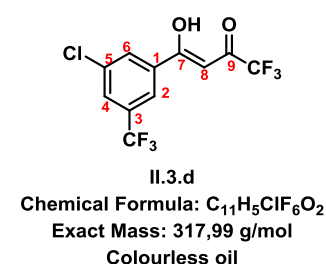
a) HMDS (1.5 equiv., 0.294 mL, 1.38 mmol); b) THF (4.5 mL); c) *n*-BuLi (1.5 equiv., 1.57 M, 0.88 mL, 1.38 mmol); d) 1-(3,4,5-Trichlorophenyl)ethan-1-one **II.1.b** (1 equiv., 206 mg, 0.923 mmol); e) 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (1.5 equiv., 0.185 mL, 1.38 mmol); and f) (Z)-1,1,1-Trifluoro-4-hydroxy-4-(3,4,5-trichlorophenyl)but-3-en-2-one **II.3.b** was obtained as a yellow solid in 93% yield (272 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 14.76$ (s, 1H, OH), 7.93 (s, 2H, $\text{C}_{2,6}\text{H}$), 6.51 (s, 1H, C_8H) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -76.42$ (s, CF_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 182.55$ (s, C_7), 177.80 (q, $^2J_{\text{C-F}} = 37.0$ Hz, C_9), 137.41 (s, C_1), 135.62 (s, $\text{C}_{3,5}$), 132.76 (s, C_4), 127.40 (s, $\text{C}_{2,6}$), 117.03 (q, $^1J_{\text{C-F}} = 283.4$ Hz, CF_3), 93.00 (q, $^3J_{\text{C-F}} = 2.0$ Hz, C_8) ppm. $\text{C}_{10}\text{H}_4\text{Cl}_3\text{F}_3\text{O}_2$ (317): calcd (%) N 0, C 37.59, H 1.26, found N 0, C 38.01, H 1.46. MP: 98.5-98.7 °C.

**(Z)-4-(3,5-Dichlorophenyl)-1,1,1-trifluoro-4-hydroxybut-3-en-2-one II.3.c**

a) HMDS (1.5 equiv., 0.836 mL, 3.94 mmol); b) THF (13.4 mL); c) *n*-BuLi (1.5 equiv., 1.64 M, 2.4 mL, 3.94 mmol); d) 1-(3,5-Dichlorophenyl)ethan-1-one **II.1.a** (1 equiv., 0.496 g, 2.63 mmol); e) 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (1.5 equiv., 0.527 mL, 3.94 mmol); and f) (Z)-4-(3,5-Dichlorophenyl)-1,1,1-trifluoro-4-hydroxybut-3-en-2-one **II.3.c** was obtained as a beige solid in 99% yield (741 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 14.80$ (s, 1H, OH), 7.79 (s, 2H, $\text{C}_{2,6}\text{H}$), 7.59 (s, 1H, C_4H), 6.51 (s, 1H, C_8H) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -76.47$ (s, CF_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 183.19$ (s, C_7), 177.92 (q, $^2J_{\text{C-F}} = 36.9$ Hz, C_9), 136.26 (s, $\text{C}_{3,5}$), 135.90 (s, C_1), 133.63 (s, C_4), 126.01 (s, $\text{C}_{2,6}$), 117.04 (q, $^1J_{\text{C-F}} = 283.3$ Hz, CF_3), 93.10 (q, $^3J_{\text{C-F}} = 2.0$ Hz, C_8) ppm. HRMS (ESI negative) for $\text{C}_{10}\text{H}_5\text{Cl}_2\text{F}_3\text{O}_2$ [M^-]: calcd 282.9635, found 282.9542. MP: 47.9-50.5 °C.

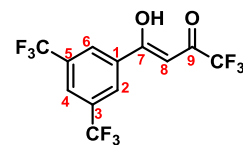
**(Z)-4-(3-Chloro-5-(trifluoromethyl)phenyl)-1,1,1-trifluoro-4-hydroxybut-3-en-2-one II.3.d**

a) HMDS (1.5 equiv., 1.14 mL, 5.39 mmol); b) THF (17 mL); c) *n*-BuLi (1.5 equiv., 1.58 M, 3.42 mL, 5.39 mmol); d) 1-[3-Chloro-5-(trifluoromethyl)phenyl]ethan-1-one **II.1.c** (1 equiv., 800 mg, 3.59 mmol); e) 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (1.5 equiv., 0.722 mL, 5.39 mmol); and f) (Z)-4-(3-chloro-5-(trifluoromethyl)phenyl)-1,1,1-trifluoro-4-hydroxybut-3-en-2-one **II.3.d** was obtained as colourless oil in 96% yield (1.1 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 14.74$ (s, 1H, OH), 8.08 (s, 1H, C_6H), 8.05 (s, 1H, C_2H), 7.85 (s, 1H, C_4H), 6.57 (s, 1H, C_8H) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -63.04$ (s, C_5CF_3), -76.52 (s, CF_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 182.71$ (s, C_7), 178.32 (q, $^2J_{\text{C-F}} = 36.9$ Hz, C_9), 136.44 (s, C_1), 135.67 (s, C_5), 133.45 (q, $^2J_{\text{C-F}} = 33.9$ Hz, C_3), 130.85 (s, C_6), 130.48 (q, $^3J_{\text{C-F}} = 3.6$ Hz, C_4), 122.83 (q, $^1J_{\text{C-F}} = 273.7$ Hz, C_3CF_3), 122.60 (q, $^3J_{\text{C-F}} = 3.7$ Hz, C_2), 117.00 (q, $^1J_{\text{C-F}} = 283.8$ Hz, CF_3), 93.18 (q, $^3J_{\text{C-F}} = 2.0$ Hz, C_8) ppm. $\text{C}_{11}\text{H}_5\text{ClF}_6\text{O}_2$ (318): calcd (%) N 0, C 41.47, H 1.58, found N 0, C 41.34, H 1.84.



(Z)-4-(3,5-Bis(trifluoromethyl)phenyl)-1,1,1-trifluoro-4-hydroxybut-3-en-2-one II.3.e

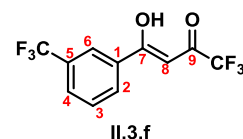
a) HMDS (1.5 equiv., 1.24 mL, 5.86 mmol); b) THF (8 mL); c) *n*-BuLi (1.5 equiv., 1.54 M, 3.8 mL, 5.86 mmol); d) 1-(3,5-Bis(trifluoromethyl)phenyl)ethan-1-one (1 equiv., 0.704 mL, 3.9 mmol); e) 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (1.5 equiv., 0.784 mL, 5.86 mmol); and f) (Z)-4-[3,5-bis(trifluoromethyl)phenyl]-1,1,1-trifluoro-4-hydroxybut-3-en-2-one **II.3.e** was obtained as a yellow oil in 98% yield (1.35 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 14.33 (s, 1H, OH), 8.37 (s, 2H, $\text{C}_{2,6}\text{H}$), 8.12 (s, 1H, C_4H), 6.65 (s, 1H, C_8H) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -63.35 (s, $\text{C}_3, {}_5\text{CF}_3$), -76.52 (s, CF_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 182.33 (s, C_7), 178.72 (q, ${}^2J_{\text{C-F}}$ = 37.2 Hz, C_9), 135.31 (s, C_1), 133.19 (q, ${}^2J_{\text{C-F}}$ = 34.2 Hz, $\text{C}_3, {}_5$), 127.62 (q, ${}^3J_{\text{C-F}}$ = 3.0 Hz, $\text{C}_2, {}_6$), 127.10 (m, C_4), 122.94 (q, ${}^1J_{\text{C-F}}$ = 273.7 Hz, $\text{C}_3, {}_5\text{CF}_3$), 117.04 (q, ${}^1J_{\text{C-F}}$ = 283.4 Hz, CF_3), 93.27 (q, ${}^3J_{\text{C-F}}$ = 2.0 Hz, C_8) ppm. HRMS (ESI negative) for $\text{C}_{12}\text{H}_4\text{F}_9\text{O}_2$ [M^-]: calcd 351.0062, found 351.0070.



II.3.e
Chemical Formula: $\text{C}_{12}\text{H}_4\text{F}_9\text{O}_2$
Exact Mass: 352.01 g/mol
Yellow oil

(Z)-1,1,1-Trifluoro-4-hydroxy-4-(3-(trifluoromethyl)phenyl)but-3-en-2-one II.3.f

a) HMDS (1.5 equiv., 0.847 mL, 3.99 mmol); b) THF (5 mL); c) *n*-BuLi (1.5 equiv., 1.64 M, 2.43 mL, 3.99 mmol); d) 1-(3-(Trifluoromethyl)phenyl)ethan-1-one (1 equiv., 0.407 mL, 2.66 mmol); e) 2,2,2-trifluoroethyl 2,2,2-trifluoroacetate (1.5 equiv., 0.534 mL, 3.99 mmol); and f) (Z)-1,1,1-trifluoro-4-hydroxy-4-(3-(trifluoromethyl)phenyl)but-3-en-2-one **II.3.f** was obtained as colourless solid in 84% yield (634 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 14.91 (s, 1H, OH), 8.19 (s, 1H, C_6H), 8.13 (d, ${}^3J_{\text{H-H}}$ = 8.0 Hz, 1H, C_2H), 7.88 (d, ${}^3J_{\text{H-H}}$ = 7.8 Hz, 1H, C_4H), 7.67 (t, ${}^3J_{\text{H-H}}$ = 7.9 Hz, 1H, C_3H), 6.60 (s, 1H, C_8H) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -62.99 (s, C_3CF_3), -76.56 (s, CF_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 184.35 (s, C_7), 178.07 (q, ${}^2J_{\text{C-F}}$ = 36.7 Hz, C_9), 133.91 (s, C_1), 131.99 (q, ${}^2J_{\text{C-F}}$ = 33.2 Hz, C_5), 130.78 (s, C_2), 130.46 (q, ${}^3J_{\text{C-F}}$ = 3.6 Hz, C_4), 129.90 (s, C_3), 124.56 (q, ${}^3J_{\text{C-F}}$ = 3.8 Hz, C_6), 123.60 (q, ${}^1J_{\text{C-F}}$ = 273.7 Hz, C_5CF_3), 117.13 (q, ${}^1J_{\text{C-F}}$ = 283.4 Hz, CF_3), 92.85 (q, ${}^3J_{\text{C-F}}$ = 2.02 Hz, C_8) ppm. $\text{C}_{11}\text{H}_6\text{F}_6\text{O}_2$ (284): calcd (%) N 0, C 46.50, H 2.13, found N 0, C 46.52, H 2.16. MP: 40.3-41 °C.

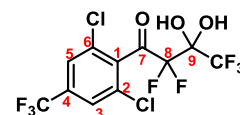


II.3.f
Chemical Formula: $\text{C}_{11}\text{H}_6\text{F}_6\text{O}_2$
Exact Mass: 284.03 g/mol
Colourless solid

1.4 Typical procedure C for the preparation of compounds from the difluorination reaction (II.4)

1-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one II.4.a

A solution of (Z)-4-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-1,1,1-trifluoro-4-hydroxybut-3-en-2-one **II.3.a** (1 equiv., 392 mg, 1.11 mmol) in MeCN (7.9 mL) was treated with Selectfluor® (2.5 equiv., 984 mg, 2.78 mmol) at room temperature for 24 h. The reaction mixture was then diluted with AcOEt and filtered through Celite. The residue was concentrated in *vacuo*, dissolved in DCM and washed with water. The aqueous layer was extracted with DCM. The combined organic layers were dried over with Na₂SO₄ and concentrated under vacuum to provide the desire 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.a** as a brown sluggy oil in 84% yield (381 mg). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 7.66 (s, 2H, C_{3,5}H), 4.72 (s, 2H, 2 * OH) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_{F} = -63.49 (s, C₄CF₃), -81.21 (t, ⁴J_{F-F} = 11.2 Hz, CF₃), -115.44 (q, ⁴J_{F-F} = 11.2 Hz, C₈CF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 193.00 (t, ²J_{C-F} = 33.6 Hz, C₇), 136.32 (s, C₁), 135.10 (q, ²J_{C-F} = 34.5 Hz, C₄), 133.94 (s, C₂, 6), 125.80 (q, ³J_{C-F} = 3.7 Hz, C₃, 5), 122.30 (qt, ¹J_{C-F} = 289.0, ³J_{C-F} = 1.9 Hz, CF₃), 122.09 (q, ¹J_{C-F} = 275.7 Hz, C₄CF₃), 109.81 (t, ¹J_{C-F} = 269.0 Hz, C₈), 95.37 - 90.08 (m, C₉) ppm. HRMS (ESI negative) for C₁₁H₃Cl₂F₈O₃ [M⁻]: calcd 404.9337, found 404.9361.



II.4.a

Chemical Formula: C₁₁H₄Cl₂F₈O₃

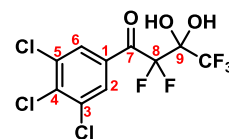
Exact Mass: 405,94 g/mol

Brown sluggy oil

The following experiments were carried out according to *Typical Procedure C*. Data are reported as: a) Compound (**II.3**); b) MeCN; c) Selectfluor®; d) yield and aspect. Individual analysis for each compound (**II.4**) is given below.

2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-(3,4,5-trichlorophenyl)butan-1-one II.4.b

a) (Z)-1,1,1-Trifluoro-4-hydroxy-4-(3,4,5-trichlorophenyl)but-3-en-2-one **II.3.b** (1 equiv., 409 mg, 1.28 mmol); b) MeCN (9 mL); c) Selectfluor® (2.5 equiv., 1135 mg, 3.21 mmol); d) 2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-(3,4,5-trichlorophenyl)butan-1-one **II.4.b** was obtained as a beige solid in 92% yield (440 mg). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 8.09 (s, 2H, C_{2,6}H), 4.40 (s, 2H, 2 * OH) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_{F} = -81.02 (t, ⁴J_{F-F} = 10.7 Hz, CF₃), -112.41 (q, ⁴J_{F-F} = 10.8 Hz, C₈CF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 188.29 (t, ²J_{C-F} = 29.1 Hz, C₇), 139.43 (s, C₄), 135.55 (s, C_{3,5}), 131.13 (s, C₁), 130.20 (t, ⁴J_{C-F} = 3.9 Hz, C_{2,6}), 120.89 (q, ¹J_{C-F} = 288.3 Hz, CF₃), 111.78 (t, ¹J_{C-F} = 268.3 Hz, C₈), 93.43 - 91.85 (m, C₉) ppm. IR ν (cm⁻¹): 3366 (OH); 1693 (C=O_{ketone}); 1578-1543 cm⁻¹ (C=C_{aro}). C₁₀H₄Cl₃F₅O₃ (372): calcd (%) N 0, C 32.16, H 1.08, found N 0, C 32.53, H 1.31. MP: 106.4-107 °C.



II.4.b

Chemical Formula: C₁₀H₄Cl₃F₅O₃

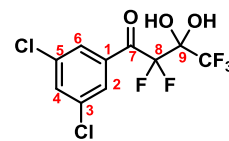
Exact Mass: 371,91 g/mol

Beige solid

1-(3,5-Dichlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one II.4.c

a) (Z)-4-(3,5-Dichlorophenyl)-1,1,1-trifluoro-4-hydroxybut-3-en-2-one **II.3.c** (1 equiv., 1 g, 3.51 mmol); b) MeCN (23.7 mL); c) Selectfluor® (2.5 equiv., 3.107 g, 8.77 mmol); d) 1-(3,5-Dichlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one

II.4.c was obtained as a beige solid in 95% yield (1.13 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.94$ (s, 2H, $\text{C}_2, 6\text{H}$), 7.68 (s, 1H, C_4H), 4.54 (s, 2H, 2 * OH) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -81.03$ (t, $^4J_{\text{F-F}} = 10.9$ Hz, CF_3), -112.40 (q, $^4J_{\text{F-F}} = 10.8$ Hz, C_8CF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 189.17$ (t, $^2J_{\text{C-F}} = 29.5$ Hz, C_7), 136.13 (s, $\text{C}_{3,5}$), 135.16 (s, C_4), 134.27 (t, $^3J_{\text{C-F}} = 2.3$ Hz, C_1), 128.80 (t, $^4J_{\text{C-F}} = 3.7$ Hz, $\text{C}_2, 6$), 120.91 (q, $^1J_{\text{C-F}} = 288.7$ Hz, CF_3), 111.63 (t, $^1J_{\text{C-F}} = 268.6$ Hz, C_8), 93.69 – 92.12 (m, C_9) ppm. HRMS (ESI negative) for $\text{C}_{10}\text{H}_4\text{F}_5\text{O}_3$ [M^-]: calcd 336.9463, found 336.9455. MP: 87.8–89 °C.

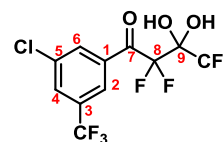
**II.4.c**

Chemical Formula: $\text{C}_{10}\text{H}_4\text{Cl}_2\text{F}_5\text{O}_3$
Exact Mass: 337.95 g/mol
Beige solid

1-(3-Chloro-5-(trifluoromethyl)phenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one II.4.d

a) (Z)-4-(3-Chloro-5-(trifluoromethyl)phenyl)-1,1,1-trifluoro-4-hydroxybut-3-en-2-one **II.3.d** (1 equiv., 630 mg, 1.98 mmol); b) MeCN (13.9 mL); c) Selectfluor® (2.5 equiv., 1.75 g, 4.94 mmol); d) 1-[3-chloro-5-(Trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.d** was obtained as a brown oil in 95% yield (697 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.23$ (s, 1H, C_2H), 8.22

(s, 1H, C_6H), 7.93 (s, 1H, C_4H), 4.44 (s, 2H, 2 * OH) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -63.11$ (s, C_3CF_3), -81.03 (t, $^4J_{\text{F-F}} = 10.8$ Hz, CF_3), -112.52 (q, $^4J_{\text{F-F}} = 10.7$ Hz, C_8CF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 188.90$ (t, $^2J_{\text{C-F}} = 29.6$ Hz, C_7), 136.25 (s, C_5), 134.12 (t, $^3J_{\text{C-F}} = 2.1$ Hz, C_1), 133.70 (t, $^4J_{\text{C-F}} = 3.4$ Hz, C_6), 133.28 (q, $^2J_{\text{C-F}} = 34.1$ Hz, C_3), 131.87 (q, $^3J_{\text{C-F}} = 3.5$ Hz, C_4), 125.51 (q, $^3J_{\text{C-F}} = 4.04$ Hz, C_2), 122.66 (q, $^1J_{\text{C-F}} = 273.3$ Hz, C_3CF_3), 120.90 (q, $^1J_{\text{C-F}} = 288.9$ Hz, CF_3), 111.85 (t, $^1J_{\text{C-F}} = 268.0$ Hz, C_8), 93.24 – 92.24 (m, C_9) ppm. HRMS (ESI negative) for $\text{C}_{11}\text{H}_4\text{ClF}_8\text{O}_3$ [M^-]: calcd 370.9727, found 370.9765.

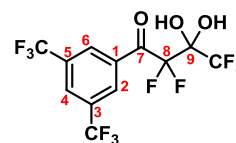
**II.4.d**

Chemical Formula: $\text{C}_{11}\text{H}_4\text{ClF}_8\text{O}_3$
Exact Mass: 371.98 g/mol
Brown oil

1-(3,5-Bis(trifluoromethyl)phenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one II.4.e

a) (Z)-4-(3,5-Bis(trifluoromethyl)phenyl)-1,1,1-trifluoro-4-hydroxybut-3-en-2-one **II.3.e** (1 equiv., 823 mg, 2.34 mmol); b) MeCN (15.8 mL); c) Selectfluor® (2.5 equiv., 2.07 g, 5.85 mmol); d) 1-[3,5-Bis(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-

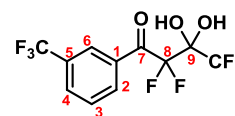
dihydroxybutan-1-one **II.4.e** was obtained as a clear oil in 95% yield (903 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.52$ (s, 2H, $\text{C}_2, 6\text{H}$), 8.19 (s, 1H, C_4H), 4.49 (s, 2H, 2 * OH) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = \delta - 63.18$ (s, $\text{C}_3, 5\text{CF}_3$), -81.07 (t, $^4J_{\text{F-F}} = 11.1$ Hz, CF_3), -112.74 (q, $^4J_{\text{F-F}} = 11.3$ Hz, C_8CF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 188.59$ (t, $^2J_{\text{C-F}} = 29.7$ Hz, C_7), 133.74 (s, C_1), 132.96 (q, $^2J_{\text{C-F}} = 34.5$ Hz, $\text{C}_3, 5$), 130.56 (q, $^3J_{\text{C-F}} = 3.3$ Hz, $\text{C}_2, 6$), 128.38 (m, C_4), 122.69 (q, $^1J_{\text{C-F}} = 274.4$ Hz, $\text{C}_3, 5\text{CF}_3$), 120.89 (q, $^1J_{\text{C-F}} = 289.5$ Hz, CF_3), 112.08 (t, $^1J_{\text{C-F}} = 267.8$ Hz, C_8), 93.51 – 91.68 (m, C_9) ppm. HRMS (ESI negative) for $\text{C}_{12}\text{H}_4\text{F}_{11}\text{O}_3$ [M^-]: calcd 404.9979, found 405.0023.

**II.4.e**

Chemical Formula: $\text{C}_{12}\text{H}_4\text{F}_{11}\text{O}_3$
Exact Mass: 406.01 g/mol
Clear oil

2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-(3-(trifluoromethyl)phenyl)butan-1-one
II.4.f

a) (Z)-1,1,1-Trifluoro-4-hydroxy-4-(3-(trifluoromethyl)phenyl)but-3-en-2-one **II.3.f** (1 equiv., 1.2 g, 4.22 mmol); b) MeCN (30 mL); c) Selectfluor® (2.5 equiv., 3.74 g, 10.6 mmol); d) 2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-[3-(trifluoromethyl)phenyl]butan-1-one **II.4.f** was obtained as a yellow oil in 90% yield (1.29 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.33$ (s, 1H, C_6H), 8.28 (d, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C_2H), 7.95 (d, $^3J_{\text{H-H}} = 7.8$ Hz, 1H, C_4H), 7.69 (t, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C_3H), 4.70 (s, 2H, 2 * OH) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = \delta -63.20$ (s, C_5CF_3), -81.13 (t, $^4J_{\text{F-F}} = 10.9$ Hz, CF_3), -112.39 (q, $^4J_{\text{F-F}} = 10.9$ Hz, C_8CF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 190.34$ (t, $^2J_{\text{C-F}} = 29.4$ Hz, C_7), 133.78 (t, $^4J_{\text{C-F}} = 3.3$ Hz, C_2), 132.56 (t, $^3J_{\text{C-F}} = 2.3$ Hz, C_1), 131.90 (q, $^3J_{\text{C-F}} = 3.5$ Hz, C_4), 131.89 (q, $^2J_{\text{C-F}} = 33.4$ Hz, C_5), 129.77 (s, C_3), 127.47 (q, $^3J_{\text{C-F}} = 7.2$ Hz, C_6), 123.44 (q, $^1J_{\text{C-F}} = 273.7$ Hz, C_5CF_3), 120.98 (q, $^1J_{\text{C-F}} = 288.5$ Hz, CF_3), 111.74 (t, $^1J_{\text{C-F}} = 268.2$ Hz, C_8), 93.67 – 92.14 (m, C_9) ppm. HRMS (ESI negative) for $\text{C}_{11}\text{H}_5\text{F}_8\text{O}_3$ [M]: calcd 337.0116, found 337.0101.

**II.4.f**

Chemical Formula: $\text{C}_{11}\text{H}_5\text{F}_8\text{O}_3$
Exact Mass: 338,02 g/mol
Yellow oil

2 KEY INTERMEDIATES 2**2.1 Synthesis of 4- or 5-formyl-2-(1H-1,2,4-triazol-1-yl)benzotrioles (II.5) and their intermediates****5-Formyl-2-(1H-1,2,4-triazol-1-yl)benzotriole II.5.a¹⁷⁷⁻¹⁷⁸**

To a stirring solution of 3-cyano-4-fluorobenzaldehyde (1 equiv., 2.02 g, 13.5 mmol) in MeCN (29.7 mL) was added potassium carbonate (K_2CO_3) (1.2 equiv., 2.25 g, 16.3 mmol) and 1,2,4-triazole (1.2 equiv., 1.12 g, 16.3 mmol). The suspension was stirred for 13 h under reflux. After completion of reaction, the reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to provide the desire 5-formyl-2-(1H-1,2,4-triazol-1-yl)benzotriole **II.5.a** as a brown solid in 51% yield (1.36 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 10.09$ (s, 1H, CHO), 8.98 (s, 1H, C_7H), 8.35 (s, 1H, C_8H), 8.28 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C_2), 8.24 (s, 1H, C_6), 8.07 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C_3) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 188.47$ (s, CO), 153.74 (s, C_7), 143.33 (s, C_8), 142.24 (s, C_4), 136.13 (s, C_1), 135.79 (s, C_6), 134.73 (s, C_3), 125.15 (s, C_2), 115.49 (s, CN), 106.30 (s, C_5) ppm.

**II.5.a**

Chemical Formula: $\text{C}_{10}\text{H}_6\text{N}_4\text{O}$
Exact Mass: 198,05 g/mol
Brown solid

2-Fluoro-4-formylbenzonitrile II.6¹⁷⁹

A solution of 4-bromo-2-fluorobenzonitrile (1 equiv., 2.07 g, 10.4 mmol) in dry THF (20.7 mL) at -10 °C under argon was treated with a solution of *i*PrMgCl.LiCl (1.1 equiv., 1.3 M, 8.77 mL, 11.4 mmol) dropwise before stirring at this temperature for 6 h. Then a solution of *N*-formylpiperidine (1.5 equiv., 1.73 mL, 15.5 mmol) in dry THF (6.22 mL) was added dropwise and the mixture allowed to warm up to room temperature. After 2 h, the resultant solution was treated with 4 M HCl and the organic layer was extracted with AcOEt, dried over Na₂SO₄ and concentrated under reduced pressure. The mixture was purified on column chromatography using a gradient of AcOEt in cyclohexane (5-15%) to provide the 2-fluoro-4-formylbenzonitrile **II.6** as a pale yellow solid in 64% yield (0.997 g). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 10.06 (d, ⁵*J*_{H-F} = 1.8 Hz, 1H, CHO), 7.87 – 7.77 (m, 2H, C_{2,3}H), 7.73 (dd, ³*J*_{H-H} = 8.5, ⁴*J*_{H-H} = 1.1 Hz, 1H, C₆H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_{F} = δ -104.00 – -104.10 (m, C₅F) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 189.28 (d, ⁴*J*_{C-F} = 1.9 Hz, CO), 163.60 (d, ¹*J*_{C-F} = 262.7 Hz, C₅), 141.32 (d, ³*J*_{C-F} = 6.3 Hz, C₁), 134.75 (s, C₃ + CN), 125.84 (d, ⁴*J*_{C-F} = 3.9 Hz, C₂), 116.42 (d, ²*J*_{C-F} = 20.3 Hz, C₆), 113.05 (s, C₄) ppm. GCMS: for C₈H₄FNO: *m/z* (%) 149 (73) [C₈H₄FNO], 148 (100) [C₈H₃FNO]⁺, 120 (56.3) [C₇H₃FN]⁺.

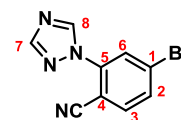


II.6

Chemical Formula: C₈H₄FNO
Exact Mass: 149,03 g/mol
Pale yellow solid

4-Bromo-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.7

To a stirring solution of 4-bromo-2-fluorobenzonitrile (1 equiv., 3.09 g, 15.5 mmol) in MeCN (30 mL) was added K₂CO₃ (1.2 equiv., 2.56 g, 18.5 mmol) and 1,2,4-triazole (1.2 equiv., 1.12 g, 16.3 mmol). The suspension was stirred for 13 h under reflux. After completion of reaction, the reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure to provide the desired 4-bromo-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.7** as a colourless solid in 94% yield (3.63 g). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 8.83 (s, 1H, C₈), 8.19 (s, 1H, C₇), 8.02 (t, ⁴*J*_{H-H} = 1.1 Hz, 1H, C₂H), 7.69 (d, ⁴*J*_{H-H} = 1.1 Hz, 2H, C_{3,6}H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 153.46 (s, C₇), 143.26 (s, C₈), 139.38 (s, C₅), 135.34 (s, C₃), 132.31 (s, C₂), 129.29 (s, C₆), 128.11 (s, C₁), 115.73 (s, CN), 104.64 (s, C₄) ppm. IR ν (cm⁻¹): 3126-3050 (Csp₂H), 2231 (CN). HRMS (ESI positive) for C₉H₆BrN₄ [M⁺]: calcd 248.9770, found 248.9770. MP: 170.6-171 °C.



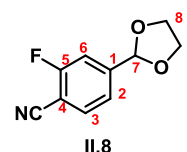
II.7

Chemical Formula: C₉H₅BrN₄
Exact Mass: 247,97 g/mol
Colourless solid

4-(1,3-Dioxolan-2-yl)-2-fluorobenzonitrile II.8

To a solution of 2-fluoro-4-formylbenzonitrile **II.6** (1 equiv., 1.5 g, 10.1 mmol) in toluene (37 mL) was added ethylene glycol (11.9 equiv., 6.68 mL, 119 mmol) and APTS.H₂O (0.05 equiv., 0.0957 g, 0.503 mmol). The solution was heated at 70 °C overnight. AcOEt was then added at room temperature and the solution was washed with a saturated solution of sodium bicarbonate (NaHCO₃), water and brine, dried over Na₂SO₄ and concentrated under vacuum to provide the desire 4-(1,3-dioxolan-2-yl)-2-fluorobenzonitrile **II.8** as a yellow oil in 94% yield (1.83 g).

¹H NMR (400 MHz, CDCl₃) δ_H = 7.63 (m, 1H, C₃H), 7.36 (m, 2H, C_{2,6}H), 5.83 (s, 1H, C₇H), 4.10 – 4.03 (m, 4H, C₈H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = δ -105.92 (m, C₅F) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 163.26 (d, ¹J_{C-F} = 259.7 Hz, C₅), 146.65 (d, ³J_{C-F} = 7.2 Hz, C₁), 133.69 (s, C₃ + CN), 122.92 (d, ⁴J_{C-F} = 3.6 Hz, C₂), 114.58 (d, ²J_{C-F} = 20.7 Hz, C₆), 113.87 (s, C₄), 101.77 (d, ⁴J_{C-F} = 1.7 Hz, C₇), 65.59 (s, C₈) ppm. IR ν (cm⁻¹): 2971-2900 (Csp₃H), 2239 (CN). HRMS (ESI positive) for C₁₀H₈FNO₂Na [M]: calcd 216.0431, found 216.0425.

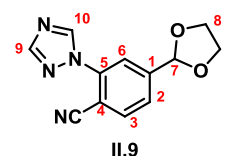


II.8
Chemical Formula: C₁₀H₈FNO₂
Exact Mass: 193,05 g/mol
Yellow oil

4-(1,3-Dioxolan-2-yl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.9

To a stirring solution of 4-(1,3-dioxolan-2-yl)-2-fluorobenzonitrile **II.8** (1 equiv., 1 g, 5.18 mmol) in MeCN (20 mL) was added K₂CO₃ (1.2 equiv., 0.859 g, 6.21 mmol) and 1,2,4-triazole (1.2 equiv., 0.429 g, 6.21 mmol). The suspension was stirred for 19 h under reflux. After completion of reaction, the reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were washed with water and brine, dried over Na₂SO₄ and concentrated under

reduced pressure to provide the desire 4-(1,3-dioxolan-2-yl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.9** as a colourless solid in 87% yield (1.10 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.77 (s, 1H, C₁₀H), 8.20 (s, 1H, C₉H), 7.89 (d, ⁴J_{H-H} = 1.5 Hz, 1H, C₆H), 7.85 (d, ³J_{H-H} = 8.0 Hz, 1H, C₃H), 7.66 (dd, ³J_{H-H} = 8.0, ⁴J_{H-H} = 1.2 Hz, 1H, C₂H), 5.91 (s, 1H, C₇H), 4.12 – 4.07 (m, 4H, C₈H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 153.24 (s, C₉), 145.76 (s, C₁), 143.23 (s, C₁₀), 138.79 (s, C₅), 134.74 (s, C₃), 127.06 (s, C₂), 122.87 (s, C₆), 115.97 (s, CN), 106.67 (s, C₄), 101.76 (s, C₇), 65.70 (s, C₈) ppm. IR ν (cm⁻¹): 3113 (Csp₂H), 2892 (Csp₃H), 2231 (CN), 1725 (C=N), 1511-1460 (C=C). HRMS (ESI positive) for C₁₂H₁₁N₄O₂ [M⁺]: calcd 243.0877, found 243.0881. MP: 116.6 - 117 °C.

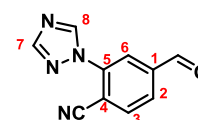


II.9
Chemical Formula: C₁₂H₁₀N₄O₂
Exact Mass: 242,08 g/mol
Colourless solid

4-Formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.5.b

4-(1,3-Dioxolan-2-yl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.9** (1 equiv., 0.996 g, 4.11 mmol) was dissolved in MeCN (100 mL) and HCl 2 M (34 equiv., 2 M, 69.7 mL, 139 mmol) was added dropwise, while the mixture was stirred at room temperature. After 4 h the solution was diluted with DCM. The organic phase was washed with aqueous NaHCO₃ solution and water, dried over Na₂SO₄ and concentrated under vacuum to provide the 4-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile

II.5.b as a pale yellow solid in 96% yield (0.782 g). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 10.15 (s, 1H, CHO), 8.89 (s, 1H, C₈H), 8.30 (s, 1H, C₆H), 8.24 (s, 1H, C₇H), 8.05 (s, 2H, C_{2,3}H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 189.25 (s, CO), 153.53 (s, C₇), 143.23 (s, C₈), 140.25 (s, C₁), 139.58 (s, C₅), 135.68 (s, C₃), 128.91 (s, C₂), 125.10 (s, C₆), 115.40 (s, CN), 110.62 (s, C₄) ppm. IR ν (cm⁻¹): 3124-3056 (Csp₂H), 2922-2739 (Csp₃H), 2229 (CN), 1706 (C=O_{aldehyde}), 1508-1439 (C=C). HRMS (ESI positive) for C₁₀H₇N₄O₁ [M⁺]: calcd 199.0614, found 199.0598. MP: 153.1-153.5 °C.

**II.5.b**Chemical Formula: C₁₀H₇N₄O

Exact Mass: 198,05 g/mol

Pale yellow solid

2.2 Synthesis of 2-chloro-N-cyclopropyl-4- or 5-formylbenzamides (II.11.a-b)

2.2.1 Typical procedure D for the halogen/metal exchange reaction

2-Chloro-5-formylbenzoic acid II.10.a

In a solution of 5-bromo-2-chlorobenzoic acid (1 equiv., 2 g, 8.49 mmol) of Et₂O:THF (2:1) (60 mL) under argon at -78 °C was added MeLi (1 equiv., 1.32 M, 6.43 mL, 8.49 mmol) dropwise. To the suspension was added dropwise *t*-BuLi (2 equiv., 1.76 M, 9.65 mL, 17 mmol). After 5 min of stirring, DMF (2 equiv., 1.31 mL, 17 mmol) was added at the same temperature and the temperature was raised to room temperature for 4 h. The reaction mixture was quenched with concentrated HCl. Organic layers were extracted with AcOEt, washed with water and dried over Na₂SO₄ before being concentrated under vacuum. The 2-chloro-5-formylbenzoic acid **II.10.a** was obtained as a beige solid in ca. 57% yield estimated (900mg) in mixture with impurities. The compound was directly used in the second step without further purification. ¹H NMR (400 MHz, CDCl₃) δ_{H} = 10.04 (s, 1H, CHO), 8.50 (d, ⁴J_{H-H} = 2.1 Hz, 1H, C₆H), 8.00 (dd, ³J_{H-H} = 8.2, ⁴J_{H-H} = 2.1 Hz, 1H, C₂H), 7.68 (d, ³J_{H-H} = 8.3 Hz, 1H, C₃H) ppm.

**II.10.a**Chemical Formula: C₈H₅ClO₃

Exact Mass: 183,99 g/mol

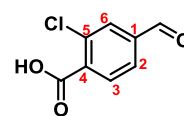
Beige solid

The following experiments were carried out according to *Typical Procedure D*. Data are reported as: a) Starting compound (commercially available bromo benzoic acid or **(II.12.a-b)**); b) Solvent; c) MeLi; d) *t*-BuLi; e) DMF; f) yield and aspect.

Individual analysis for each compound is given below.

2-Chloro-4-formylbenzoic acid II.10.b

a) 4-Bromo-2-chlorobenzoic acid (1 equiv., 1.96 g, 8.32 mmol); b) Et₂O:THF (2:1) (60 mL); c) MeLi (1 equiv., 1.32 M, 6.31 mL, 8.32 mmol); d) *t*-BuLi (2 equiv., 1.76 M, 9.46 mL, 16.6 mmol); e) DMF (2 equiv., 1.29 mL, 16.6 mmol); f) 2-chloro-4-formylbenzoic acid **II.10.b** was obtained as a colourless solid in 55% yield estimated (0.842 g). ¹H NMR (500 MHz, DMSO) δ_{H} = 10.03 (s, 1H, CHO), 8.02 (s, 1H, C₃H), 7.90 (s, 2H, C₂, ₆H) ppm. ¹³C NMR (126 MHz, DMSO) δ_{C} = 191.83 (s, CO₂H), 166.43 (s, CHO), 138.29 (s, C₁), 131.72 (s, C₄), 131.16 (s, C₃), 130.86 (s, C₅), 127.53 (s, C_{2,6}) ppm. HRMS (ESI negative) for C₈H₄ClO₃ [M⁻]: calcd 182.9854, found 182.9864

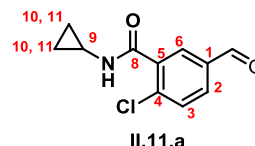


II.10.b

Chemical Formula: C₈H₅ClO₃
Exact Mass: 183,99 g/mol
Colourless solid

2-Chloro-N-cyclopropyl-5-formylbenzamide II.11.a

a) 5-Bromo-2-chloro-N-cyclopropylbenzamide **II.12.a** (1 equiv., 1.01 g, 3.67 mmol); b) Et₂O:THF (2:1) (16 mL); c) MeLi (1 equiv., 1.39 M, 2.65 mL, 3.67 mmol); d) *t*-BuLi (2 equiv., 1.76 M, 4.17 mL, 7.34 mmol); e) DMF (2 equiv., 0.567 mL, 7.34 mmol); f) 2-Chloro-N-cyclopropyl-5-formylbenzamide **II.11.a** was obtained as colourless solid in 59% yield (480 mg) after purification on column chromatography using a gradient of AcOEt in cyclohexane (40-60%). *Analysis: See procedure E.*

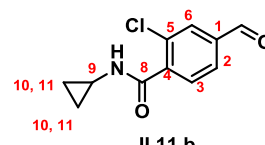


II.11.a

Chemical Formula: C₁₁H₁₀ClNO₂
Exact Mass: 223,04 g/mol
Colourless solid

2-Chloro-N-cyclopropyl-4-formylbenzamide II.11.b

a) 4-Bromo-2-chloro-N-cyclopropylbenzamide **II.12.b** (1 equiv., 1.01 g, 3.69 mmol); b) Et₂O:THF (2:1) (16 mL); c) MeLi (1 equiv., 1.39 M, 2.65 mL, 3.67 mmol); d) *t*-BuLi (2 equiv., 1.76 M, 4.17 mL, 7.34 mmol); e) DMF (2 equiv., 0.567 mL, 7.34 mmol); f) 2-chloro-N-cyclopropyl-4-formylbenzamide **II.11.b** was obtained as colourless solid in 42% yield (344 mg) after purification on column chromatography using a gradient of AcOEt in cyclohexane (40-60%). *Analysis: See procedure E.*



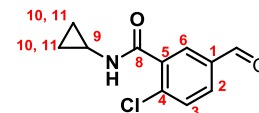
II.11.b

Chemical Formula: C₁₁H₁₀ClNO₂
Exact Mass: 223,04 g/mol
Colourless solid

2.2.2 Typical procedure E for the peptide coupling reaction

2-Chloro-N-cyclopropyl-5-formylbenzamide II.11.a

In a solution of 2-chloro-5-formylbenzoic acid **II.10.a** (1 equiv., 1.39 g, 3.78 mmol) in AcOEt (25.8 mL) was added DIPEA (3 equiv., 1.87 mL, 11.3 mmol), CPA (2 equiv., 0.523 mL, 7.55 mmol) and the coupling reagent T₃P 50wt.% in AcOEt (1.5 equiv., 3.37 mL, 5.66 mmol). The reaction mixture was stirred at room temperature for 4 h. It was then quenched with HCl 2 M and organic layer was extracted with AcOEt, dried over Na₂SO₄ and concentrated under vacuum. The desired 2-chloro-N-cyclopropyl-5-formylbenzamide **II.11.a** was obtained as colourless solid in 42% yield over two steps after purification on column chromatography using a gradient of AcOEt in cyclohexane (40-60%). ¹H NMR (400 MHz, CDCl₃) δ_H = 9.99 (s, 1H, CHO), 8.11 (d, ⁴J_{H-H} = 2.1 Hz, 1H, C₆H), 7.86 (dd, ³J_{H-H} = 8.3, ⁴J_{H-H} = 2.1 Hz, 1H, C₂H), 7.56 (d, ³J_{H-H} = 8.3 Hz, 1H, C₃H), 6.33 (s, 1H, NH), 2.99 – 2.90 (m, 1H, C₉H), 0.95 – 0.87 (m, 2H, C₁₀H), 0.71 – 0.62 (m, 2H, C₁₁H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 190.33 (s, CHO), 166.76 (s, C₈), 137.18 (s, C₁), 136.10 (s, C₄), 135.11 (s, C₅), 131.80 (s, C₆), 131.36 (s, C₃), 131.22 (s, C₂), 23.38 (s, C₉), 7.00 (s, C₁₀, ₁₁) ppm. MP: 169-170.8 °C.



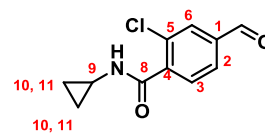
II.11.a

Chemical Formula: C₁₁H₁₀ClNO₂
Exact Mass: 223,04 g/mol
Colourless solid

The following experiments were carried out according to *Typical Procedure E*. Data are reported as: a) Starting compound (commercially available bromo benzoic acid or (**II.10.a-b**)); b) Solvent; c) DIPEA; d) CPA; e) T₃P; f) yield and aspect. Individual analysis for each compound is given below.

2-Chloro-N-cyclopropyl-4-formylbenzamide II.11.b

a) 2-Chloro-4-formylbenzoic acid **II.10.b** (1 equiv., 912 mg, 2.47 mmol); b) AcOEt (16.9 mL); c) DIPEA (3 equiv., 1.23 mL, 7.41 mmol); d) CPA (2 equiv., 0.343 mL, 4.94 mmol); e) T₃P (1.5 equiv., 2.21 mL, 3.71 mmol); f) 2-chloro-N-cyclopropyl-4-formylbenzamide **II.11.b** was obtained as colourless solid in 35% yield over two steps (501 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 9.95 (s, 1H, CHO), 7.82 (d, ⁴J_{H-H} = 1.4 Hz, 1H, C₆H), 7.75 (dd, ³J_{H-H} = 7.8, ⁴J_{H-H} = 1.5 Hz, 1H, C₂H), 7.69 (d, ³J_{H-H} = 7.8 Hz, 1H, C₃H), 6.46 (s, 1H, NH), 2.95 – 2.81 (m, 1H, C₉H), 0.92 – 0.82 (m, 2H, C₁₀H), 0.70 – 0.61 (m, 2H, C₁₁H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 190.26 (s, CHO), 167.03 (s, C₈), 140.35 (s, C₁), 138.20 (s, C₄), 131.95 (s, C₅), 130.86 (s, C₆), 130.59 (s, C₃), 128.10 (s, C₂), 23.29 (s, C₉), 6.86 (s, C₁₀, ₁₁) ppm. IR ν (cm⁻¹): 3675 (NH_{amide}), 3271 (Csp₂H), 2988-2901 (Csp₃H), 1707 (C=O_{aldehyde}), 1644 (C=O_{amide}). MP: 102.9-105.7 °C. C₁₁H₁₀ClNO₂ (223): calcd (%) N 6.26, C 59.07, H 4.51, found N 6.27, C 59.05, H 4.42.

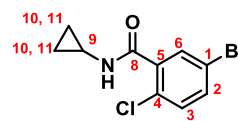


II.11.b

Chemical Formula: C₁₁H₁₀ClNO₂
Exact Mass: 223,04 g/mol
Colourless solid

5-Bromo-2-chloro-N-cyclopropylbenzamide II.12.a

a) 5-Bromo-2-chlorobenzoic acid (1 equiv., 1.05 g, 4.45 mmol); b) AcOEt (30 mL); c) DIPEA (3 equiv., 2.21 mL, 13.4 mmol); d) CPA (2 equiv., 0.617 mL, 8.9 mmol); e) T₃P (1.5 equiv., 3.97 mL, 6.68 mmol); f) 5-bromo-2-chloro-N-cyclopropylbenzamide **II.12.a** was obtained as colourless solid in 82% yield (1.01 g). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 7.76 (d, ⁴J_{H-H} = 2.3 Hz, 1H, C₆H), 7.46 (dd, ³J_{H-H} = 8.5, ⁴J_{H-H} = 2.5 Hz, 1H, C₂H), 7.24 (d, ³J_{H-H} = 8.4 Hz, 1H, C₃H), 6.30 (s, 1H, NH), 2.95 – 2.86 (m, 1H, C₉H), 0.93 – 0.85 (m, 2H, C₁₀H), 0.68 – 0.60 (m, 2H, C₁₁H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 166.44 (s, C₈), 136.62 (s, C₅), 134.35 (s, C₂), 133.09 (s, C₆), 131.75 (s, C₃), 129.74 (s, C₄), 121.01 (s, C₁), 23.33 (s, C₉), 6.97 (s, C_{10,11}) ppm. MP: 167.2-168.9 °C.

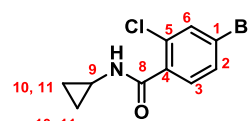


II.12.a

Chemical Formula: C₁₀H₉BrClNO
Exact Mass: 272,96 g/mol
Colourless solid

4-Bromo-2-chloro-N-cyclopropylbenzamide II.12.b

a) 4-Bromo-2-chlorobenzoic acid (1 equiv., 1.04 g, 4.4 mmol); b) AcOEt (30 mL); c) DIPEA (3 equiv., 2.18 mL, 13.2 mmol); d) CPA (2 equiv., 0.61 mL, 8.8 mmol); e) T₃P (1.5 equiv., 6.45 mL, 10.8 mmol); f) 4-bromo-2-chloro-N-cyclopropylbenzamide **II.12.b** was obtained as colourless solid in 95% yield (1.15 g). ¹H NMR (400 MHz, CDCl₃) δ_{H} = 7.52 (d, ⁴J_{H-H} = 1.8 Hz, 1H, C₆H), 7.46 (d, ³J_{H-H} = 8.3 Hz, 1H, C₃H), 7.40 (dd, ³J_{H-H} = 8.3, ⁴J_{H-H} = 1.8 Hz, 1H, C₂H), 6.48 (s, 1H, NH), 2.92 – 2.83 (m, 1H, C₉H), 0.89 – 0.81 (m, 2H, C₁₀H), 0.66 – 0.60 (m, 2H, C₁₁H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_{C} = 167.03 (s, C₈), 133.88 (s, C₁), 132.82 (s, C₆), 131.69 (s, C₅), 131.40 (s, C₃), 130.48 (s, C₂), 124.71 (s, C₄), 23.28 (s, C₉), 6.87 (s, C_{10,11}) ppm. IR ν (cm⁻¹): 3675 (NH_{amide}), 3274 (Csp₂H), 2988-2901 (Csp₃H), 1644 (C=O_{amide}). MP: 158.5-160.2 °C.



II.12.b

Chemical Formula: C₁₀H₉BrClNO
Exact Mass: 272,96 g/mol
Colourless solid

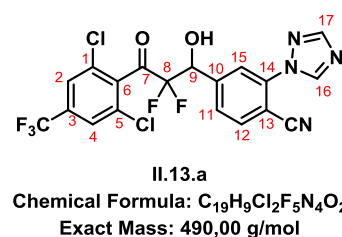
3 COUPLING REACTIONS BETWEEN 1 AND 2

All compounds were sent to Bayer Cropscience to be purified

3.1 Typical procedure F for the coupling reaction

4-{3-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-2,2-difluoro-1-hydroxy-3-oxopropyl}-2-(1H-1,2,4-triazol-1-yl)benzotrile **II.13.a**

To a solution of 4-formyl-2-(1H-1,2,4-triazol-1-yl)benzotrile **II.5.b** (1.04 equiv., 86 mg, 0.434 mmol), 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.a** (1 equiv., 195 mg, 0.418 mmol), and lithium bromine (LiBr) (3 equiv., 109 mg, 1.26 mmol) in THF (0.829 mL), was added NEt₃ (1 equiv., 0582 mL, 0.418 mmol) dropwise. After 6 h, the reaction was quenched with saturated aqueous ammonium chloride (NH₄Cl) and the resultant mixture was extracted with AcOEt. The organics were dried over Na₂SO₄ and concentrated under reduced pressure. 4-{3-[2,6-Dichloro-4-(trifluoromethyl)phenyl]-2,2-difluoro-1-hydroxy-3-oxopropyl}-2-(1H-1,2,4-triazol-1-yl)benzotrile **II.13.a** was obtained. ¹H NMR (602 MHz, DMF) δ_H = 9.31 (s, 1H, C₁₆H), 8.40 (s, 1H, C₁₇H), 8.21 (d, ³J_{H-H} = 8.1 Hz, 1H, C₁₂H), 8.19 (s, 2H, C_{2,4}H), 8.13 (s, 1H, C₁₅H), 7.97 (d, ³J_{H-H} = 8.1 Hz, 1H, C₁₁H), 7.35 (d, ³J_{H-OH} = 6.0 Hz, 1H, OH), 5.78 (dt, ³J_{H-F1} = 20.4, ³J_{H-F2} = 4.7 Hz, 1H, C₉H) ppm. ¹⁹F NMR (566 MHz, DMF) δ_F = -62.97 (s, C₃CF₃), -103.44 (dd, ²J_{F-F} = 272.1, ³J_{F2-H} = 3.6 Hz, F₂), -122.54 (dd, ²J_{F-F} = 272.1, ³J_{F1-H} = 20.2 Hz, F₁) ppm. HRMS (ESI positive) for C₁₉H₁₀Cl₂F₅N₄O₂ [M⁺]: calcd 491.0095, found 491.0082.

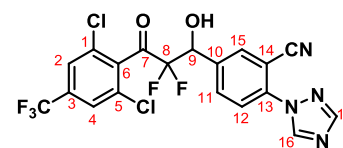


The following experiments were carried out according to *Typical Procedure F*. Data are reported as: a) Aldehyde (**II.5.a-b**, **II.11.a-b**); b) α,α -difluoro- β -dihydroxy ketones (**II.4.a-f**); c) LiBr; d) THF; e) NEt₃; f) yield and aspect.

Individual analysis for each compound is given below.

5-(3-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.13.b

a) 5-Formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.5.a** (1.01 equiv., 71.6 mg, 0.361 mmol); b) 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.a** (1 equiv., 145 mg, 0.356 mmol); c) LiBr (3 equiv., 92.9 mg, 1.07 mmol); d) THF (0.706 mL); e) NEt₃ (1 equiv., 0.0495 mL, 0.356 mmol); f) 5-(3-(2,6-Dichloro-4-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-

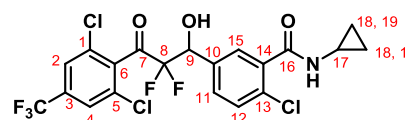
**II.13.b**

Chemical Formula: C₁₉H₉Cl₂F₅N₄O₂
Exact Mass: 490,00 g/mol

2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.13.b** was obtained. ¹H NMR (602 MHz, DMF) δ_{H} = 9.30 (s, 1H, C₁₆H), 8.41 (s, 1H, C₁₇H), 8.27 (s, 1H, C₁₅H), 8.20 (s, 2H, C_{2,4}H), 8.16 (d, ³J_{H-H} = 8.5 Hz, 1H, C₁₂H), 8.06 (d, ³J_{H-H} = 8.4 Hz, 1H, C₁₁H), 7.31 (d, ³J_{H-OH} = 3.6 Hz, 1H, OH), 5.76 (d, ³J_{H-F1} = 20.1 Hz, 1H, C₉H) ppm. ¹⁹F NMR (566 MHz, DMF) δ_{F} = -62.96 (s, C₃CF₃), -103.78 (dd, ²J_{F-F} = 271.9, ³J_{F2-H} = 3.5 Hz, F₂), -122.49 (dd, ²J_{F-F} = 271.9, ³J_{F1-H} = 20.1 Hz, F₁) ppm. HRMS (ESI positive) for C₁₉H₁₀Cl₂F₅N₄O₂ [M⁺]: calcd 491.0095, found 491.0112.

2-Chloro-N-cyclopropyl-5-(3-(2,6-dichloro-4-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide II.13.c

a) 2-Chloro-N-cyclopropyl-5-formylbenzamide **II.11.a** (1.05 equiv., 87.6 mg, 0.392 mmol); b) 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.a** (1 equiv., 151 mg, 0.373 mmol); c) LiBr (3 equiv., 97.2 mg, 1.12 mmol); d) THF (0.739 mL); e) NEt₃ (1 equiv., 0.0518 mL, 0.373 mmol); f) 2-Chloro-N-cyclopropyl-5-(3-(2,6-dichloro-4-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide **II.13.c** was obtained.

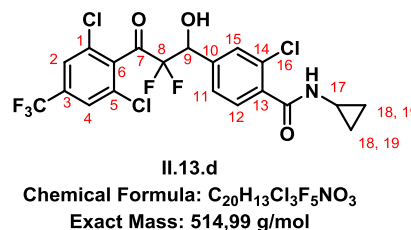
**II.13.c**

Chemical Formula: C₂₀H₁₃Cl₃F₅NO₃
Exact Mass: 514,99 g/mol

2-Chloro-N-cyclopropyl-5-(3-(2,6-dichloro-4-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide **II.13.c** was obtained. ¹H NMR (602 MHz, DMF) δ_{H} = 8.42 (d, ³J_{H-NH} = 3.7 Hz, 1H, NH), 8.17 (s, 2H, C_{2,4}H), 7.65 – 7.60 (m, 2H, C_{12,15}H), 7.56 – 7.52 (m, 1H, C₁₁H), 6.98 (d, ³J_{H-OH} = 3.6 Hz, 1H, OH), 5.53 (d, ³J_{H-F1} = 20.8 Hz, 1H, C₉H), 2.97 – 2.94 (m, 1H, C₁₇H), 0.79 – 0.74 (m, 2H, C₁₈H), 0.65 – 0.60 (m, 2H, C₁₉H) ppm. ¹⁹F NMR (566 MHz, DMF) δ_{F} = -62.96 (s, C₃CF₃), -103.25 (dd, ²J_{F-F} = 270.8, ³J_{F2-H} = 3.7 Hz, F₂), -123.86 (dd, ²J_{F-F} = 270.7, ³J_{F1-H} = 21.2 Hz, F₁) ppm. HRMS (ESI positive) for C₂₀H₁₄Cl₃F₅NO₃ [M⁺]: calcd 515.9954, found 515.9903.

2-Chloro-N-cyclopropyl-4-(3-(2,6-dichloro-4-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide II.13.d

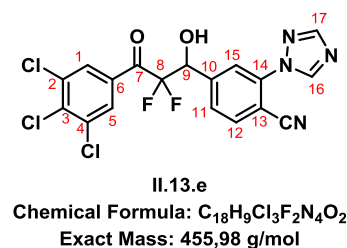
a) 2-Chloro-N-cyclopropyl-4-formylbenzamide **II.11.b** (1 equiv., 66.9 mg, 0.299 mmol); b) 1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.a** (1 equiv., 140 mg, 0.299 mmol); c) LiBr (3 equiv., 78 mg, 0.898 mmol); d) THF (0.593 mL); e) NEt₃ (1 equiv., 0.0416 mL, 0.299 mmol); f)



2-Chloro-N-cyclopropyl-4-(3-(2,6-dichloro-4-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide **II.13.d** was obtained. ¹H NMR (602 MHz, DMF) δ_H = 8.36 (d, ³J_{H-NH} = 4.0 Hz, 1H, NH), 8.18 (s, 2H, C_{2,4}H), 7.66 (s, 1H, C₁₅H), 7.58 (d, ³J_{H-H} = 7.9 Hz, 1H, C₁₂H), 7.50 (d, ³J_{H-H} = 7.9 Hz, 1H, C₁₁H), 7.04 (d, ³J_{H-OH} = 5.9 Hz, 1H, OH), 5.55 (dt, ³J_{H-F1} = 20.9, ³J_{H-F2} = 4.9 Hz, 1H, C₉H), 2.99 – 2.93 (m, 1H, C₁₇H), 0.83 – 0.74 (m, 2H, C₁₈H), 0.68 – 0.60 (m, 2H, C₁₉H) ppm. ¹⁹F NMR (566 MHz, DMF) δ_F = -63.13 (s, C₃CF₃), -103.61 (dd, ²J_{F-F} = 270.5, ³J_{F2-H} = 3.7 Hz, F₂), -123.47 (dd, ²J_{F-F} = 270.5, ³J_{F1-H} = 20.7 Hz, F₁) ppm. HRMS (ESI positive) for C₂₀H₁₄Cl₃F₅NO₃ [M⁺]: calcd 515.9954, found 515.9982.

4-[2,2-Difluoro-1-hydroxy-3-oxo-3-(3,4,5-trichlorophenyl)propyl]-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.13.e

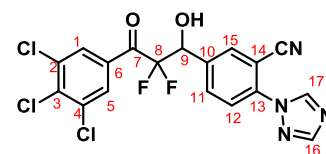
a) 4-Formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.5.b** (1 equiv., 122 mg, 0.616 mmol); b) 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(3,4,5-trichlorophenyl)butan-1-one **II.4.b** (1 equiv., 230 mg, 0.616 mmol); c) LiBr (3 equiv., 160 mg, 1.85 mmol); d) THF (1.22 mL); e) NEt₃ (1 equiv., 0.0856 mL, 0.616 mmol); f) 4-[2,2-Difluoro-1-hydroxy-3-oxo-3-(3,4,5-trichlorophenyl)propyl]-2-(1H-1,2,4-



4-[2,2-Difluoro-1-hydroxy-3-oxo-3-(3,4,5-trichlorophenyl)propyl]-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.13.e** was obtained. ¹H NMR (602 MHz, DMF) δ_H = 9.31 (s, 1H, C₁₆H), 8.41 (s, 1H, C₁₇H), 8.26 (s, 2H, C_{1,5}H), 8.22 (d, ³J_{H-H} = 8.1 Hz, 1H, C₁₂H), 8.16 (s, 1H, C₁₅H), 7.98 (d, ³J_{H-H} = 8.2 Hz, 1H, C₁₁H), 7.55 (d, ³J_{H-OH} = 5.7 Hz, 1H, OH), 5.76 (dt, ³J_{H-F1} = 19.1, ³J_{H-F2} = 5.5 Hz, 1H, C₉H) ppm. ¹⁹F NMR (566 MHz, DMF) δ_F = -103.93 (dd, ²J_{F-F} = 259.2, ³J_{F2-H} = 5.6 Hz, F₂), -117.09 (dd, ²J_{F-F} = 259.2, ³J_{F1-H} = 19.1 Hz, F₁) ppm. ¹³C NMR (151 MHz, DMF) δ_C = 189.07 (dd, ²J_{C-F1} = 30.7, ²J_{C-F2} = 26.7 Hz, C₇), 154.20 (s, C₁₇), 145.96 (s, C₁₆), 145.06 (s, C₁₀), 139.69 (s, C₁₄), 137.77 (s, C₃), 135.64 (s, C₁₂), 135.44 (s, C_{2,4}), 134.47 (s, C₆), 131.16 (dd, ⁴J_{C-F1} = 4.0, ⁴J_{C-F2} = 2.7 Hz, C_{1,5}), 130.06 (s, C₁₁), 125.88 (s, C₁₅), 118.19 (dd, ¹J_{C-F1} = 263.0, ¹J_{C-F2} = 255.4 Hz, C₈), 117.04 (s, CN), 108.32 (s, C₁₃), 72.97 (dd, ²J_{C-F1} = 29.4, ²J_{C-F2} = 23.6 Hz, C₉) ppm. HRMS (ESI positive) for C₁₈H₁₀Cl₃F₂N₄O₂ [M⁺]: calcd 456.9837, found 456.9837.

5-(2,2-Difluoro-1-hydroxy-3-oxo-3-(3,4,5-trichlorophenyl)propyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.13.f

a) 5-Formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.5.a** (1.01 equiv., 122 mg, 0.616 mmol); b) 12,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(3,4,5-trichlorophenyl)butan-1-one **II.4.b** (1 equiv., 230 mg, 0.616 mmol); c) LiBr (3 equiv., 160 mg, 1.85 mmol); d) THF (1.22 mL); e) NEt_3 (1 equiv., 0.0856 mL, 0.616 mmol); f) 5-(2,2-Difluoro-1-hydroxy-3-oxo-3-(3,4,5-trichlorophenyl)propyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.13.f** was obtained. ^1H NMR

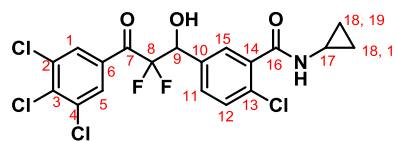


II.13.f
Chemical Formula: $\text{C}_{18}\text{H}_9\text{Cl}_3\text{F}_2\text{N}_4\text{O}_2$
Exact Mass: 455.98 g/mol

(602 MHz, DMF) $\delta_{\text{H}} = 9.31$ (s, 1H, C_{17}H), 8.41 (s, 1H, C_{16}H), 8.32 (d, $^3J_{\text{H-H}} = 1.5$ Hz, 1H, C_{15}H), 8.28 (s, 2H, C_{15}H), 8.19 (dd, $^3J_{\text{H-H}} = 8.4$, $^3J_{\text{H-H}} = 1.5$ Hz, 1H, C_{11}H), 8.07 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C_{12}H), 7.53 (s, 1H, OH), 5.74 (dd, $^3J_{\text{H-F1}} = 19.1$, $^3J_{\text{H-F2}} = 5.6$ Hz, 1H, C_9H) ppm. ^{19}F NMR (566 MHz, DMF) $\delta_{\text{F}} = -103.97$ (dd, $^2J_{\text{F-F}} = 259.2$, $^3J_{\text{F2-H}} = 5.5$ Hz, F_2), -117.35 (dd, $^2J_{\text{F-F}} = 259.2$, $^3J_{\text{F1-H}} = 19.2$ Hz, F_1) ppm. ^{13}C NMR (151 MHz, DMF) $\delta_{\text{C}} = 188.40$ (dd, $^2J_{\text{C-F1}} = 30.8$, $^2J_{\text{C-F2}} = 26.7$ Hz, C_7), 153.37 (s, C_{16}), 145.14 (s, C_{17}), 139.08 (s, C_{10}), 138.72 (s, C_{13}), 138.37 (s, C_6), 136.97 (s, C_3), 134.65 (s, $\text{C}_{2,4}$), 134.43 (s, C_{15}), 134.39 (s, C_{11}), 130.39 (dd, $^4J_{\text{C-F1}} = 3.9$, $^4J_{\text{C-F2}} = 2.7$ Hz, $\text{C}_{1,5}$), 125.46 (s, C_{12}), 117.41 (dd, $^1J_{\text{C-F1}} = 262.5$, $^1J_{\text{C-F2}} = 255$ Hz, C_8), 116.28 (s, CN), 107.12 (s, C_{14}), 71.82 (dd, $^2J_{\text{C-F1}} = 29.8$, $^2J_{\text{C-F2}} = 23.6$ Hz, C_9) ppm. HRMS (ESI positive) for $\text{C}_{18}\text{H}_9\text{Cl}_3\text{F}_2\text{N}_4\text{O}_2$ [M^+]: calcd 456.9832, found 456.9820.

2-Chloro-N-cyclopropyl-5-(2,2-difluoro-1-hydroxy-3-oxo-3-(3,4,5-trichlorophenyl)propyl)benzamide II.13.g

a) 2-Chloro-N-cyclopropyl-5-formylbenzamide **II.11.a** (0.871 equiv., 104 mg, 0.466 mmol); b) 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(3,4,5-trichlorophenyl)butan-1-one **II.4.b** (1 equiv., 199 mg, 0.535 mmol); c) LiBr (3 equiv., 139 mg, 1.6 mmol); d) THF (1.06 mL); e) NEt_3 (1 equiv., 0.0744 mL, 0.535 mmol); f) 2-Chloro-N-cyclopropyl-5-(2,2-difluoro-1-hydroxy-

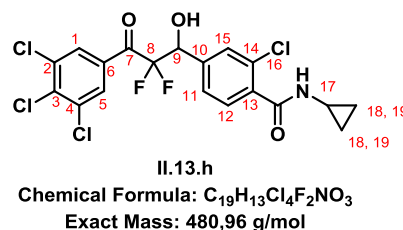


II.13.g
Chemical Formula: $\text{C}_{19}\text{H}_{13}\text{Cl}_4\text{F}_2\text{NO}_3$
Exact Mass: 480.96 g/mol

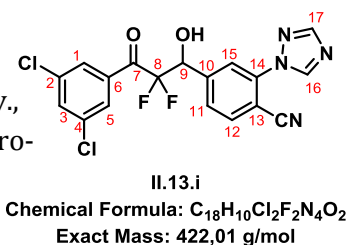
3-oxo-3-(3,4,5-trichlorophenyl)propyl)benzamide **II.13.g** was obtained. ^1H NMR (602 MHz, DMF) δ_{H} : **not interpretable, mixture between 3 products**. ^{19}F NMR (566 MHz, DMF) $\delta_{\text{F}} = -103.81$ (dd, $^2J_{\text{F-F}} = 257.7$, $^3J_{\text{F2-H}} = 5.5$ Hz, F_2), -117.86 (dd, $^2J_{\text{F-F}} = 257.7$, $^3J_{\text{F1-H}} = 19.9$ Hz, F_1) ppm. HRMS (ESI positive) for $\text{C}_{19}\text{H}_{14}\text{Cl}_4\text{F}_2\text{NO}_3$ [M^+]: calcd 481.9696, found 481.9697.

2-Chloro-N-cyclopropyl-4-(2,2-difluoro-1-hydroxy-3-oxo-3-(3,4,5-trichlorophenyl)propyl)benzamide II.13.h

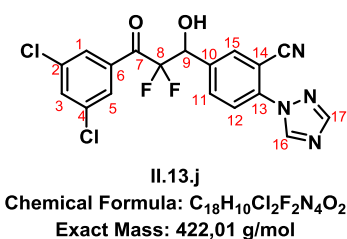
a) 2-Chloro-N-cyclopropyl-4-formylbenzamide **II.11.b** (1 equiv., 104 mg, 0.465 mmol); b) 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-(3,4,5-trichlorophenyl)butan-1-one **II.4.b** (1 equiv., 173 mg, 0.465 mmol); c) LiBr (3 equiv., 121 mg, 1.4 mmol); d) THF (0.922 mL); e) NEt_3 (1 equiv., 0.0647 mL, 0.465 mmol); f) 2-Chloro-N-cyclopropyl-4-(2,2-difluoro-1-hydroxy-3-oxo-3-(3,4,5-trichlorophenyl)propyl)benzamide **II.13.h** was obtained. ^1H NMR (602 MHz, DMF) δ_{H} : **not interpretable, mixture between 2 products**. ^{19}F NMR (566 MHz, DMF) δ_{F} = -103.93 (dd, $^2J_{\text{F-F}} = 257.7$, $^3J_{\text{F2-H}} = 5.3$ Hz, F_2), -117.73 (dd, $^2J_{\text{F-F}} = 257.7$, $^3J_{\text{F1-H}} = 19.7$ Hz, F_1) ppm. HRMS (ESI positive) for $\text{C}_{19}\text{H}_{14}\text{Cl}_4\text{F}_2\text{NO}_3$ [M^+]: calcd 481.9696, found 481.9698.

**4-(3-(3,5-Dichlorophenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzotrile II.13.i**

a) 4-Formyl-2-(1H-1,2,4-triazol-1-yl)benzotrile **II.5.b** (0.746 equiv., 78.7 mg, 0.397 mmol); b) 1-(3,5-dichlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.c** (1 equiv., 180 mg, 0.533 mmol); c) LiBr (3 equiv., 138 mg, 1.6 mmol); d) THF (1.06 mL); e) NEt_3 (1 equiv., 0.074 mL, 0.533 mmol); f) 4-(3-(3,5-Dichlorophenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzotrile **II.13.i** was obtained. ^1H NMR (602 MHz, DMF) δ_{H} = 9.32 (s, 1H, C_{16}H), 8.42 (s, 1H, C_{17}H), 8.22 (d, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, C_{12}H), 8.16 (s, 1H, C_{15}H), 8.08 (s, 2H, $\text{C}_{1,5}\text{H}$), 8.06 (d, $^4J_{\text{H-H}} = 1.8$ Hz, 1H, C_3H), 7.98 (d, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, C_{11}H), 7.55 (s, 1H, OH), 5.76 (dd, $^3J_{\text{H-F1}} = 19.3$, $^3J_{\text{H-F2}} = 5.2$ Hz, 1H, C_9H) ppm. ^{19}F NMR (566 MHz, DMF) δ_{F} = -103.60 (dd, $^2J_{\text{F-F}} = 259.6$, $^3J_{\text{F2-H}} = 5.3$ Hz, F_2), -117.15 (dd, $^2J_{\text{F-F}} = 259.6$, $^3J_{\text{F1-H}} = 19.3$ Hz, F_1) ppm. HRMS (ESI positive) for $\text{C}_{18}\text{H}_{11}\text{Cl}_2\text{F}_2\text{N}_4\text{O}_2$ [M^+]: calcd 423.0222, found 423.0221.

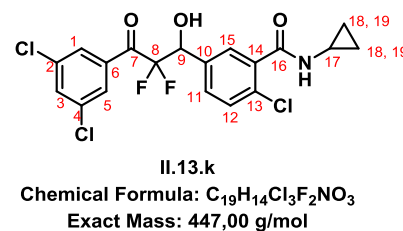
**5-(3-(3,5-Dichlorophenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzotrile II.13.j**

a) 5-Formyl-2-(1H-1,2,4-triazol-1-yl)benzotrile **II.5.a** (0.708 equiv., 124 mg, 0.629 mmol); b) 1-(3,5-dichlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.c** (1 equiv., 301 mg, 0.889 mmol); c) LiBr (3 equiv., 231 mg, 2.67 mmol); d) THF (1.76 mL); e) NEt_3 (1 equiv., 0.124 mL, 0.889 mmol); f) 5-(3-(3,5-Dichlorophenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzotrile **II.13.j** was obtained. ^1H NMR (602 MHz, DMF) δ_{H} = 9.31 (s, 1H, C_{16}H), 8.41 (s, 1H, C_{17}H), 8.31 (s, 1H, C_{15}H), 8.19 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C_{12}H), 8.10 (s, 2H, $\text{C}_{1,5}\text{H}$), 8.09 (d, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, C_{11}H), 8.07 (d, $^3J_{\text{H-H}} = 1.7$ Hz, 1H, C_3H), 7.49 (s, 1H, OH), 5.74 (dd, $^3J_{\text{H-F1}} = 19.3$, $^3J_{\text{H-F2}} = 4.2$ Hz, 1H, C_9H) ppm. ^{19}F NMR (566 MHz, DMF) δ_{F} = -103.85 (dd, $^2J_{\text{F-F}} = 259.5$, $^3J_{\text{F2-H}} = 5.5$ Hz, F_2), -117.57 (dd, $^2J_{\text{F-F}} = 259.5$, $^3J_{\text{F1-H}} = 19.3$ Hz, F_1) ppm. HRMS (ESI positive) for $\text{C}_{18}\text{H}_{11}\text{Cl}_2\text{F}_2\text{N}_4\text{O}_2$ [M^+]: calcd 423.0222, found 423.0212.

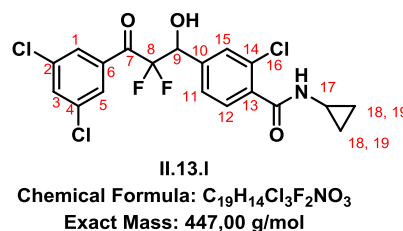


2-Chloro-N-cyclopropyl-5-(3-(3,5-dichlorophenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide II.13.k

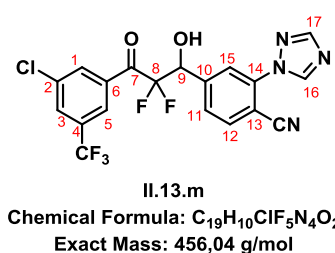
a) 2-Chloro-N-cyclopropyl-5-formylbenzamide **II.11.a** (1 equiv., 187 mg, 0.837 mmol); b) 1-(3,5-dichlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.c** (1 equiv., 283 mg, 0.837 mmol); c) LiBr (3 equiv., 218 mg, 2.51 mmol); d) THF (1.66 mL); e) NEt₃ (1 equiv., 0.116 mL, 0.837 mmol); f) 2-Chloro-N-cyclopropyl-5-(3-(3,5-dichlorophenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide **II.13.k** was obtained. ¹H NMR (602 MHz, DMF) δ_H : **not interpretable, mixture between 2 products**. ¹⁹F NMR (566 MHz, DMF) δ_F = -103.81 (dd, ²J_{F-F} = 258.1, ³J_{F2-H} = 5.3 Hz, F₂), -118.30 (dd, ²J_{F-F} = 258.1, ³J_{F1-H} = 20.1 Hz, F₁) ppm. HRMS (ESI positive) for C₁₉H₁₅Cl₃F₂NO₃ [M⁺]: calcd 448.0080, found 448.0076.

**2-Chloro-N-cyclopropyl-4-(3-(3,5-dichlorophenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide II.13.l**

a) 2-Chloro-N-cyclopropyl-4-formylbenzamide **II.11.b** (1 equiv., 198 mg, 0.888 mmol); b) 1-(3,5-dichlorophenyl)-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.c** (1 equiv., 301 mg, 0.888 mmol); c) LiBr (3 equiv., 231 mg, 2.66 mmol); d) THF (1.76 mL); e) NEt₃ (1 equiv., 0.123 mL, 0.888 mmol); f) 2-Chloro-N-cyclopropyl-4-(3-(3,5-dichlorophenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)benzamide **II.13.l** was obtained. ¹H NMR (602 MHz, DMF) δ_H : **not interpretable, mixture between 2 products**. ¹⁹F NMR (566 MHz, DMF) δ_F = -103.60 (dd, ²J_{F-F} = 258.1, ³J_{F2-H} = 5.1 Hz, F₂), -117.79 (dd, ²J_{F-F} = 258.1, ³J_{F1-H} = 19.9 Hz, F₁) ppm. HRMS (ESI positive) for C₁₉H₁₅Cl₃F₂NO₃ [M⁺]: calcd 448.0080, found 448.0084.

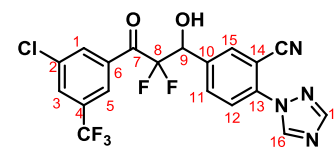
**4-(3-(3-Chloro-5-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzamide II.13.m**

a) 4-Formyl-2-(1H-1,2,4-triazol-1-yl)benzamide **II.5.b** (1 equiv., 186 mg, 0.939 mmol); b) 1-[3-Chloro-5-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.d** (1 equiv., 350 mg, 0.939 mmol); c) LiBr (3 equiv., 244 mg, 2.82 mmol); d) THF (1.86 mL); e) NEt₃ (1 equiv., 0.131 mL, 0.939 mmol); f) 4-(3-(3-Chloro-5-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzamide **II.13.m** was obtained. ¹H NMR (602 MHz, DMF) δ_H = δ 9.31 (s, 1H, C₁₆H), 8.41 (s, 1H, C₁₇H), 8.41 (s, 1H, C₆H), 8.34 (s, 1H, C₁H), 8.32 (s, 1H, C₃H), 8.22 (d, ³J_{H-H} = 8.1 Hz, 1H, C₁₂H), 8.15 (s, 1H, C₁₅H), 7.98 (d, ³J_{H-H} = 8.1 Hz, 1H, C₁₁H), 7.60 (d, ³J_{H-OH} = 5.7 Hz, 1H, OH), 5.76 (dt, ³J_{H-F1} = 18.8, ³J_{H-F2} = 5.7 Hz, 1H, C₉H) ppm. ¹⁹F NMR (566 MHz, DMF) δ_F = -62.87 (s, C₄CF₃), -104.00 (dd, ²J_{F-F} = 259.6, ³J_{F2-H} = 5.7 Hz, F₂), -117.10 (dd, ²J_{F-F} = 259.6, ³J_{F1-H} = 18.8 Hz, F₁) ppm. HRMS (ESI positive) for C₁₉H₁₁ClF₅N₄O₂ [M⁺]: calcd 457.0491, found 457.0494.



5-(3-(3-Chloro-5-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.13.n

a) 5-formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.5.a** (1 equiv., 186 mg, 0.939 mmol); b) 1-[3-Chloro-5-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.d** (1 equiv., 350 mg, 0.939 mmol); c) LiBr (3 equiv., 244 mg, 2.82 mmol); d) THF (1.86 mL); e) NEt₃ (1 equiv., 0.131 mL, 0.939 mmol); f) 5-(3-(3-Chloro-5-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.13.n** was



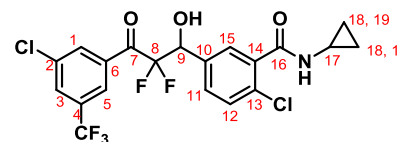
II.13.n

Chemical Formula: C₁₉H₁₀ClF₅N₄O₂
Exact Mass: 456,04

obtained. ¹H NMR (602 MHz, DMF) δ_H : **not interpretable, mixture between 2 products**. ¹⁹F NMR (566 MHz, DMF) δ_F = -62.70 (s, C₄CF₃), -103.89 (dd, ²J_{F-F} = 259.5, ³J_{F2-H} = 5.7 Hz, F₂), -117.21 (dd, ²J_{F-F} = 259.5, ³J_{F1-H} = 18.9 Hz, F₁) ppm. HRMS (ESI positive) for C₁₉H₁₁ClF₅N₄O₂ [M⁺]: calcd 457.0491, found 457.0492.

2-Chloro-5-(3-(3-chloro-5-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-N-cyclopropylbenzamide II.13.o

a) 2-Chloro-N-cyclopropyl-5-formylbenzamide **II.11.a** (1 equiv., 153 mg, 0.685 mmol); b) 1-[3-Chloro-5-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.d** (1 equiv., 255 mg, 0.685 mmol); c) LiBr (3 equiv., 178 mg, 2.05 mmol); d) THF (1.36 mL); e) NEt₃ (1 equiv., 0.0952 mL, 0.685 mmol); f) 2-Chloro-5-(3-(3-chloro-5-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-N-cyclopropylbenzamide **II.13.o** was obtained.



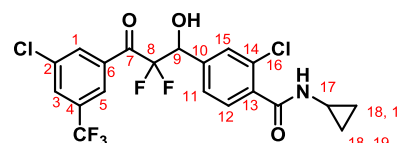
II.13.o

Chemical Formula: C₂₀H₁₄Cl₂F₅NO₃
Exact Mass: 481,03 g/mol

¹H NMR (602 MHz, DMF) δ_H : **not interpretable, mixture between 3 products**. ¹⁹F NMR (566 MHz, DMF) δ_F = -62.71 (s, C₄CF₃), -103.78 (dd, ²J_{F-F} = 258, ³J_{F2-H} = 5.3 Hz, F₂), -118.03 (dd, ²J_{F-F} = 258, ³J_{F1-H} = 19.8 Hz, F₁) ppm. HRMS (ESI positive) for C₂₀H₁₅Cl₂F₅NO₃ [M⁺]: calcd 482.0349, found 482.0353.

2-Chloro-4-(3-(3-chloro-5-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-N-cyclopropylbenzamide II.13.p

a) 2-Chloro-N-cyclopropyl-4-formylbenzamide **II.11.b** (1 equiv., 150 mg, 0.672 mmol); b) 1-[3-Chloro-5-(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.d** (1 equiv., 252 mg, 0.677 mmol); c) LiBr (3 equiv., 176 mg, 2.03 mmol); d) THF (1.34 mL); e) NEt₃ (1 equiv., 0.0941 mL, 0.677 mmol); f) 2-Chloro-4-(3-(3-chloro-5-(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-N-cyclopropylbenzamide **II.13.p** was obtained.



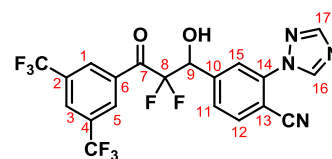
II.13.p

Chemical Formula: C₂₀H₁₄Cl₂F₅NO₃
Exact Mass: 481,03 g/mol

¹H NMR (602 MHz, DMF) δ_H : **not interpretable, mixture between 2 products**. ¹⁹F NMR (566 MHz, DMF) δ_F = -62.89 (s, C₄CF₃), -103.91 (dd, ²J_{F-F} = 258, ³J_{F2-H} = 5.4 Hz, F₂), -1187.86 (dd, ²J_{F-F} = 258.1, ³J_{F1-H} = 19.6 Hz, F₁) ppm. HRMS (ESI positive) for C₂₀H₁₅Cl₂F₅NO₃ [M⁺]: calcd 482.0349, found 482.0341.

4-(3-(3,5-Bis(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.13.q

a) 4-Formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.5.b** (1 equiv., 170 mg, 0.862 mmol); b) 1-[3,5-Bis(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.e** (1 equiv., 350 mg, 0.862 mmol); c) LiBr (3 equiv., 224 mg, 2.59 mmol); d) THF (1.71 mL); e) NEt_3 (1 equiv., 0.12 mL, 0.862 mmol); f) 4-(3-(3,5-Bis(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-



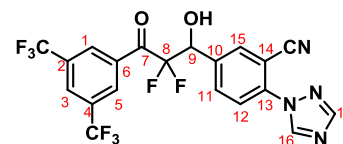
II.13.q

Chemical Formula: $\text{C}_{20}\text{H}_{10}\text{F}_8\text{N}_4\text{O}_2$
Exact Mass: 490,07 g/mol

oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.13.q** was obtained. ^1H NMR (602 MHz, DMF) δ_{H} : **not interpretable, mixture between 2 products.** ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -63.09 (s, $\text{C}_{2,4}\text{CF}_3$), -102.87 (dd, $^2J_{\text{F-F}} = 292.8$, $^3J_{\text{F}_2\text{-H}} = 4.3$ Hz, F_2), -117.13 (dd, $^2J_{\text{F-F}} = 292.8$, $^3J_{\text{F}_1\text{-H}} = 18.8$ Hz, F_1) ppm. HRMS (ESI positive) for $\text{C}_{20}\text{H}_{11}\text{F}_8\text{N}_4\text{O}_2$ [M^+]: calcd 491.0754, found 491.0754.

5-(3-(3,5-Bis(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.13.r

a) 5-Formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.5.a** (1 equiv., 170 mg, 0.862 mmol); b) 1-[3,5-Bis(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.e** (1 equiv., 350 mg, 0.862 mmol); c) LiBr (3 equiv., 224 mg, 2.59 mmol); d) THF (1.71 mL); e) NEt_3 (1 equiv., 0.12 mL, 0.862 mmol); f) 5-(3-(3,5-Bis(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.13.r** was obtained. ^1H NMR



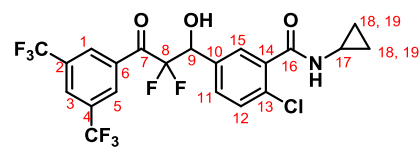
II.13.r

Chemical Formula: $\text{C}_{20}\text{H}_{10}\text{F}_8\text{N}_4\text{O}_2$
Exact Mass: 490,07 g/mol

(602 MHz, DMF) δ_{H} = δ 9.31 (s, 1H, C_{17}H), 8.70 (s, 2H, $\text{C}_{1,5}\text{H}$), 8.64 (s, 1H, C_3H), 8.41 (s, 1H, C_{16}H), 8.29 (d, $^4J_{\text{H-H}} = 1.4$ Hz, 1H, C_{15}H), 8.18 (dd, $^3J_{\text{H-H}} = 8.4$, $^4J_{\text{H-H}} = 1.4$ Hz, 1H, C_{12}H), 8.08 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C_{11}H), 7.64 (d, $^3J_{\text{H-OH}} = 5.6$ Hz, 1H, OH), 5.75 (dt, $^3J_{\text{H-F}_1} = 18.5$, $^3J_{\text{H-F}_2} = 5.7$ Hz, 1H, C_9H) ppm. ^{19}F NMR (566 MHz, DMF) δ_{F} = -62.86 (s, $\text{C}_{2,4}\text{CF}_3$), -104.29 (dd, $^2J_{\text{F-F}} = 259.3$, $^3J_{\text{F}_2\text{-H}} = 5.8$ Hz, F_2), -117.18 (dd, $^2J_{\text{F-F}} = 259.3$, $^3J_{\text{F}_1\text{-H}} = 18.5$ Hz, F_1) ppm. ^{13}C NMR (151 MHz, DMF) δ_{C} = 189.66 (dd, $^2J_{\text{C-F}_1} = 31.4$, $^2J_{\text{C-F}_2} = 26.7$ Hz, C_7), 153.37 (s, C_{16}), 145.13 (s, C_{17}), 139.11 (s, C_{10}), 138.65 (s, C_{13}), 135.97 (s, C_6), 134.39 (s, C_{15}), 134.4 (s, C_{12}), 131.81 (q, $^2J_{\text{C-F}} = 33.8$ Hz, $\text{C}_{2,4}$), 130.73 (s, $\text{C}_{1,5}$), 128.32 – 127.86 (m, C_3), 125.50 (s, C_{11}), 123.51 (q, $^1J_{\text{C-F}} = 272.8$ Hz, $\text{C}_{2,4}\text{CF}_3$), 117.51 (dd, $^1J_{\text{C-F}_1} = 262.4$, $^1J_{\text{C-F}_2} = 255.4$ Hz, C_8), 116.25 (s, CN), 107.15 (s, C_{14}), 71.88 (dd, $^2J_{\text{C-F}_1} = 29.9$, $^2J_{\text{C-F}_2} = 23.7$ Hz, C_9) ppm. HRMS (ESI positive) for $\text{C}_{20}\text{H}_{11}\text{F}_8\text{N}_4\text{O}_2$ [M^+]: calcd 491.0749, found 491.0710.

5-(3-(3,5-Bis(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-chloro-N-cyclopropylbenzamide II.13.s

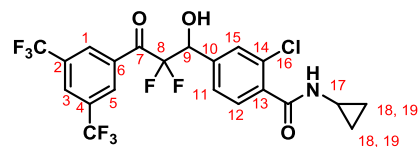
a) 2-Chloro-N-cyclopropyl-5-formylbenzamide **II.11.a** (1 equiv., 192 mg, 0.862 mmol); b) 1-[3,5-Bis(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.e** (1 equiv., 349 mg, 0.862 mmol); c) LiBr (3 equiv., 224 mg, 2.58 mmol); d) THF (1.71 mL); e) NEt_3 (1 equiv., 0.12 mL, 0.862 mmol); f) 5-(3-(3,5-Bis(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-chloro-N-cyclopropylbenzamide (**II.13.s**) was obtained. ^1H NMR (602 MHz, DMF) δ_{H} : **not interpretable, mixture between 2 products**. ^{19}F NMR (566 MHz, DMF) δ_{F} = -62.87 (s, $\text{C}_{2,4}\text{CF}_3$), -104.17 (dd, $^2J_{\text{F-F}} = 257.8$, $^3J_{\text{F2-H}} = 5.6$ Hz, F_2), -118.08 (dd, $^2J_{\text{F-F}} = 257.8$, $^3J_{\text{F1-H}} = 19.5$ Hz, F_1) ppm. HRMS (ESI positive) for $\text{C}_{21}\text{H}_{15}\text{ClF}_8\text{NO}_3$ [M^+]: calcd 516.0607, found 516.0614.



II.13.s
Chemical Formula: $\text{C}_{21}\text{H}_{14}\text{ClF}_8\text{NO}_3$
Exact Mass: 515,05 g/mol

4-(3-(3,5-Bis(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-chloro-N-cyclopropylbenzamide II.13.t

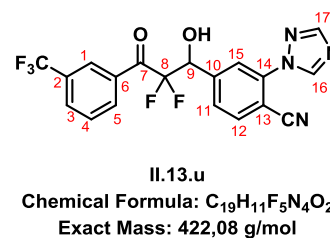
a) 2-Chloro-N-cyclopropyl-4-formylbenzamide **II.11.b** (1 equiv., 193 mg, 0.867 mmol); b) 1-[3,5-Bis(trifluoromethyl)phenyl]-2,2,4,4,4-pentafluoro-3,3-dihydroxybutan-1-one **II.4.e** (1 equiv., 352 mg, 0.867 mmol); c) LiBr (3 equiv., 225 mg, 2.6 mmol); d) THF (1.71 mL); e) NEt_3 (1 equiv., 0.12 mL, 0.867 mmol); f) 4-(3-(3,5-Bis(trifluoromethyl)phenyl)-2,2-difluoro-1-hydroxy-3-oxopropyl)-2-chloro-N-cyclopropylbenzamide **II.13.t** was obtained. ^1H NMR (602 MHz, DMF) δ_{H} : **not interpretable, mixture between 2 products**. ^{19}F NMR (566 MHz, DMF) δ_{F} = -62.72 (s, $\text{C}_{2,4}\text{CF}_3$), -103.95 (dd, $^2J_{\text{F-F}} = 257.9$, $^3J_{\text{F2-H}} = 5.5$ Hz, F_2), -117.56 (dd, $^2J_{\text{F-F}} = 257.8$, $^3J_{\text{F1-H}} = 19.3$ Hz, F_1) ppm. HRMS (ESI positive) for $\text{C}_{21}\text{H}_{15}\text{ClF}_8\text{NO}_3$ [M^+]: calcd 516.0607, found 516.0574.



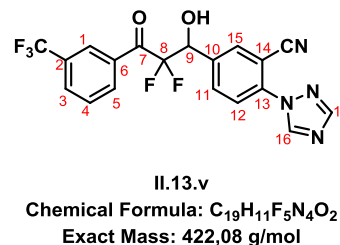
II.13.t
Chemical Formula: $\text{C}_{21}\text{H}_{14}\text{ClF}_8\text{NO}_3$
Exact Mass: 515,05 g/mol

4-(2,2-Difluoro-1-hydroxy-3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.13.u

4-Formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.5.b** (1 equiv., 175 mg, 0.887 mmol); b) 2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-[3-(trifluoromethyl)phenyl]butan-1-one **II.4.f** (1 equiv., 300 mg, 0.887 mmol); c) LiBr (3 equiv., 231 mg, 2.66 mmol); d) THF (1.76 mL); e) NEt_3 (1 equiv., 0.123 mL, 0.887 mmol); f) 4-(2,2-Difluoro-1-hydroxy-3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.13.u** was obtained. ^1H NMR (602 MHz, DMF) $\delta_{\text{H}} = \delta$ 9.31 (s, 1H, C₁₆H), 8.49 (d, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C₅H), 8.42 (s, 1H, C₁₇H), 8.38 (s, 1H, C₁H), 8.22 (d, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, C₁₂H), 8.20 (d, $^3J_{\text{H-H}} = 7.8$ Hz, 1H, C₃H), 8.16 (s, 1H, C₁₅H), 7.98 (d, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, C₁₁H), 7.95 (t, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C₄H), 7.49 (s, 1H, OH), 5.76 (dd, $^3J_{\text{H-F1}} = 19.4$, $^3J_{\text{H-F2}} = 5.3$ Hz, 1H, C₉H) ppm. ^{19}F NMR (566 MHz, DMF) $\delta_{\text{F}} = -62.83$ (s, C₂CF₃), -103.55 (dd, $^2J_{\text{F-F}} = 261.2$, $^3J_{\text{F2-H}} = 5.2$ Hz, F₂), -117.41 (dd, $^2J_{\text{F-F}} = 261.2$, $^3J_{\text{F1-H}} = 19.4$ Hz, F₁) ppm. ^{13}C NMR (151 MHz, DMF) $\delta_{\text{C}} = 190.02$ (dd, $^2J_{\text{C-F1}} = 30.6$, $^2J_{\text{C-F2}} = 26.2$ Hz, C₇), 153.40 (s, C₁₇), 145.15 (s, C₁₆), 144.48 (s, C₁₀), 138.88 (s, C₁₄), 134.82 (s, C₁₂), 134.42 (s, C₆), 134.24 (s, C₅), 131.19 (q, $^3J_{\text{C-F}} = 3.6$ Hz, C₃), 130.74 (s, C₄), 130.53 (q, $^2J_{\text{C-F}} = 32.6$ Hz, C₂), 129.26 (s, C₁₁), 126.77 – 126.23 (m, C₁), 125.11 (s, C₁₅), 124.27 (q, $^1J_{\text{C-F}} = 272.3$ Hz, C₂CF₃), 117.44 (dd, $^1J_{\text{C-F1}} = 263.2$, $^1J_{\text{C-F2}} = 255.2$ Hz, C₈), 116.25 (s, CN), 107.46 (s, C₁₃), 72.17 (dd, $^2J_{\text{C-F1}} = 29.5$, $^2J_{\text{C-F2}} = 23.5$ Hz) ppm. HRMS (ESI positive) for C₁₉H₁₂F₅N₄O₂ [M⁺]: calcd 423.0881, found 423.0880.

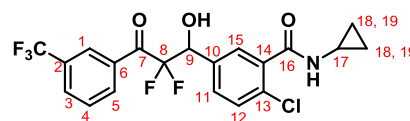
**5-(2,2-Difluoro-1-hydroxy-3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile II.13.v**

a) 5-Formyl-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.5.a** (1 equiv., 175 mg, 0.887 mmol); b) 2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-[3-(trifluoromethyl)phenyl]butan-1-one **II.4.f** (1 equiv., 300 mg, 0.887 mmol); c) LiBr (3 equiv., 231 mg, 2.66 mmol); d) THF (1.76 mL); e) NEt_3 (1 equiv., 0.123 mL, 0.887 mmol); f) 5-(2,2-Difluoro-1-hydroxy-3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)-2-(1H-1,2,4-triazol-1-yl)benzonitrile **II.13.v** was obtained. ^1H NMR (602 MHz, DMF) δ_{H} : **not interpretable, mixture between 2 products**. ^{19}F NMR (566 MHz, DMF) $\delta_{\text{F}} = -62.66$ (s, C₂CF₃), -103.51 (dd, $^2J_{\text{F-F}} = 261.1$, $^3J_{\text{F2-H}} = 5.3$ Hz, F₂), -117.45 (dd, $^2J_{\text{F-F}} = 261.1$, $^3J_{\text{F1-H}} = 19.4$ Hz, F₁) ppm. HRMS (ESI positive) for C₁₉H₁₂F₅N₄O₂ [M⁺]: calcd 423.0880, found 423.0882.



2-Chloro-N-cyclopropyl-5-(2,2-difluoro-1-hydroxy-3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)benzamide II.13.w

a) 2-Chloro-N-cyclopropyl-5-formylbenzamide **II.11.a** (1 equiv., 162 mg, 0.726 mmol); b) 2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-[3-(trifluoromethyl)phenyl]butan-1-one **II.4.f** (1 equiv., 256 mg, 0.758 mmol); c) LiBr (3 equiv., 197 mg, 2.27 mmol); d) THF (1.50 mL); e) NEt_3 (1 equiv., 0.105 mL, 0.758 mmol); f) 2-Chloro-N-cyclopropyl-5-(2,2-difluoro-1-hydroxy-



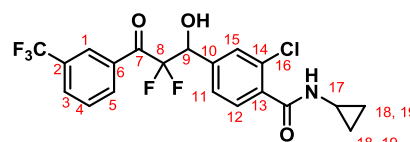
II.13.w

Chemical Formula: $\text{C}_{20}\text{H}_{15}\text{ClF}_5\text{NO}_3$
Exact Mass: 447,07 g/mol

3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)benzamide **II.13.w** was obtained. ^1H NMR (602 MHz, DMF) $\delta_{\text{H}} = \delta$ 8.47 (t, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C₅H), 8.43 (t, $^3J_{\text{H-NH}} = 6.0$ Hz, 1H, NH), 8.39 (s, 1H, C₁H), 8.19 (d, $^3J_{\text{H-H}} = 7.8$ Hz, 1H, C₃H), 7.95 (t, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C₄H), 7.67 (s, 1H, C₁₅H), 7.67 – 7.64 (m, 1H, C₁₁H), 7.56 (dd, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, C₁₂H), 7.14 (d, $^3J_{\text{H-OH}} = 5.6$ Hz, 1H, OH), 5.51 (dt, $^3J_{\text{H-F1}} = 20.3$, $^3J_{\text{H-F2}} = 5.2$ Hz, 1H, C₉H), 3.01 – 2.93 (m, 1H, C₁₇H), 0.81 – 0.75 (m, 2H, C₁₈H), 0.68 – 0.63 (m, 2H, C₁₉H) ppm. ^{19}F NMR (566 MHz, DMF) $\delta_{\text{F}} = -62.66$ (s, C₂CF₃), -103.45 (dd, $^2J_{\text{F-F}} = 259.5$, $^3J_{\text{F2-H}} = 4.9$ Hz, F₂), -118.28 (dd, $^2J_{\text{F-F}} = 259.5$, $^3J_{\text{F1-H}} = 20.3$ Hz, F₁) ppm. ^{13}C NMR (151 MHz, DMF) $\delta_{\text{C}} = 190.55$ (dd, $^2J_{\text{C-F1}} = 31.2$, $^2J_{\text{C-F1}} = 26.1$ Hz, C₇), 167.82 (s, C₁₆), 137.55 (s, C₁₄), 136.20 (s, C₁₀), 134.53 (s, C₆), 134.18 (s, C₅), 131.04 (q, $^3J_{\text{C-F}} = 3.6$ Hz, C₃), 130.89 (s, C₁₃), 130.68 (s, C₄), 130.48 (q, $^2J_{\text{C-F}} = 32.6$ Hz, C₂), 130.40 (s, C₁₁), 129.67 (s, C₁₂), 128.67 (s, C₁₅), 126.55 (s, C₁), 124.28 (q, $^1J_{\text{C-F}} = 272.2$ Hz, C₂CF₃), 117.59 (dd, $^1J_{\text{C-F1}} = 262.7$, $^1J_{\text{C-F2}} = 253.3$ Hz, C₈), 72.27 (dd, $^2J_{\text{C-F1}} = 29.9$, $^2J_{\text{C-F2}} = 23.3$ Hz, C₉), 23.15 (s, C₁₇), 5.74 (s, C_{18, 19}) ppm. HRMS (ESI positive) for $\text{C}_{20}\text{H}_{16}\text{F}_5\text{ClNO}_3$ [M^+]: calcd 448.0739, found 448.0732.

2-Chloro-N-cyclopropyl-4-(2,2-difluoro-1-hydroxy-3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)benzamide II.13.x

a) 2-Chloro-N-cyclopropyl-4-formylbenzamide **II.11.b** (1 equiv., 163 mg, 0.733 mmol); b) 2,2,4,4,4-Pentafluoro-3,3-dihydroxy-1-[3-(trifluoromethyl)phenyl]butan-1-one **II.4.f** (1 equiv., 251 mg, 0.745 mmol); c) LiBr (3 equiv., 194 mg, 2.23 mmol); d) THF (1.48 mL); e) NEt_3 (1 equiv., 0.104 mL, 0.745 mmol); f) 2-Chloro-N-cyclopropyl-4-(2,2-difluoro-1-hydroxy-3-oxo-3-(3-(trifluoromethyl)phenyl)propyl)benzamide



II.13.x

Chemical Formula: $\text{C}_{20}\text{H}_{15}\text{ClF}_5\text{NO}_3$
Exact Mass: 447,07 g/mol

II.13.x was obtained. ^1H NMR (602 MHz, DMF) δ_{H} : **not interpretable, mixture between 2 products**. ^{19}F NMR (566 MHz, DMF) $\delta_{\text{F}} = -62.67$ (s, C₂CF₃), -103.45 (dd, $^2J_{\text{F-F}} = 259.6$, $^3J_{\text{F2-H}} = 5.0$ Hz, F₂), -117.86 (dd, $^2J_{\text{F-F}} = 259.6$, $^3J_{\text{F1-H}} = 20.0$ Hz, F₁) ppm. HRMS (ESI positive) for $\text{C}_{20}\text{H}_{16}\text{ClF}_5\text{NO}_3$ [M^+]: calcd 448.0739, found 448.0743.

4 BIOLOGICAL ANALYSIS

All experimental protocols referred to biological analysis cannot be presented in this manuscript.

However, measures of the *in vivo* and *in vitro* activity of molecules **II.13.a-x** were inspired following the preparation protocol published by Gassel *et al.*⁴⁴⁷

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Chapter III: Synthesis of 2,4-bis(fluoroalkyl)- substituted quinolines

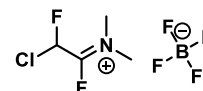
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1 FLUOROALKYL AMINO REAGENT (FAR) SYNTHESIS

N-(2-Chloro-1,2-difluoroethylidene)-*N*-methylmethanaminium tetrafluoroborate **D.2**

1-Chloro-1,2,2-trifluoroethene (1 equiv., 0.195 mL, 2.58 mmol) was liquefied in a Schlenk apparatus under argon at -78 °C. Dimethylamine 2 M in THF (1 equiv., 2 M, 1.29 mL, 2.58 mmol) was added slowly via syringe at -78 °C. After 5 min, cold bath was replaced by water bath and the mixture was stirred for 15 min. Boron trifluoride diethyl etherate (BF₃•Et₂O) (1 equiv., 0.328 mL, 2.59 mmol) was added via syringe and the reaction mixture was stirred for 30 min. Anhydrous DCM was then added to precipitate the salts. (In case of polymerization addition of anhydrous acetonitrile (MeCN) solubilizes the mixture). Yield of (**D.2**) was estimated at 99% (589 mg) according to ¹H NMR analysis. ¹H NMR (400 MHz, DMSO) δ_H = 7.16 (d, ²J_{H-F} = 48.8 Hz, 1H, CHFCl), 2.97 and 2.87 (2 * s, 6H, N(CH₃)₂⁺) ppm. ¹⁹F NMR (376 MHz, DMSO) δ_F = -144.34 (d, ²J_{F-H} = 48.8 Hz, CHFCl), -148.03 (s, CF), -148.08 (s, BF₄⁻) ppm.

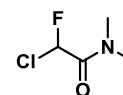


D.2

Chemical Formula: C₄H₇BClF₆N
Exact Mass: 229,03 g/mol

¹³C NMR analysis of the corresponding amide after hydrolysis.

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

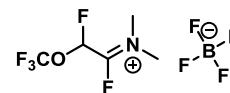


D.3

Chemical Formula: C₄H₇ClFNO
Exact Mass: 139,02 g/mol

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

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



E.2

Chemical Formula: C₅H₇BF₉NO
Exact Mass: 279,05 g/mol

2 IMINES AND ENAMINES SYNTHESIS

2.1 From fluorinated ketone

2.1.1 Typical procedure A for the synthesis of ketimines derivatives (III.1)

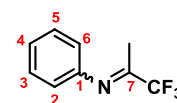
Under argon atmosphere, an excess of cold perfluoroacetone (2 equiv.) was added to aniline derivatives (1 equiv.) in anhydrous DCM (2 mL/1 mmol) in presence of desiccant (*e.g.* (4 Å MS) or MgSO₄). Then the reaction mixture was stirred for the indicated time at room temperature. The desiccant was then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

The following experiments were carried out according to **Typical Procedure A**. Data are reported as: a) Commercially available perfluoroacetone; b) aniline derivatives; c) desiccant and time; and d) yield and aspect.

Individual analysis for each compound **III.1** is given below.

N-(1,1,1-Trifluoropropan-2-ylidene)aniline **III.1.a**³⁸⁹

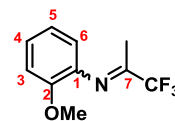
a) 1,1,1-Trifluoroacetone (2 equiv., 1.92 mL, 21.4 mmol); b) Aniline (1 equiv., 0.98 mL, 10.7 mmol); c) 4 Å MS, for 3 h; and d) *N*-(1,1,1-Trifluoropropan-2-ylidene)aniline **III.1.a** was obtained as a brown oil in 87% yield, estimated (1.74 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.38 (t, ³J_{H-H} = 7.9 Hz, 2H, C_{3,5}H), 7.18 (t, ³J_{H-H} = 7.5 Hz, 1H, C₄H), 6.82 – 6.74 (m, 2H, C_{2,6}H), 2.02 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -74.68 (s, C₇CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 157.41 (q, ²J_{C-F} = 33.9 Hz, C₇), 147.72 (s, C₁), 129.33 (s, C_{3,5}), 125.29 (s, C₄), 119.87 (q, ¹J_{C-F} = 278.4 Hz, C₇CF₃) 118.87 (s, C_{2,6}), 14.50 (s, C₇CH₃) ppm.



III.1.a
Chemical Formula: C₉H₈F₃N
Exact Mass: 187.06 g/mol
Brown oil

N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.b**

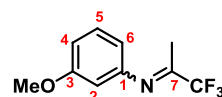
a) 1,1,1-Trifluoroacetone (2 equiv., 1.46 mL, 16.2 mmol); b) 2-Methoxyaniline (1 equiv., 0.92 mL, 8.12 mmol); c) 4 Å MS, for 21 h; and d) 2-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.b** was obtained as a brown oil in 90% yield (1.59 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.16 - 7.12 (m, 1H, C₄H), 7.00 - 6.90 (m, 2H, C_{5,6}H), 6.78 - 6.75 (m, 1H, C₃H), 3.78 (s, 3H, C₂OCH₃), 1.95 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -74.33 – -74.42 (m, C₇CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 158.86 (q, ²J_{C-F} = 33.7 Hz, C₇), 148.19 (s, C₂), 136.43 (s, C₁), 126.15 (s, C₄), 120.90 (s, C₅), 120.14 (s, C₃), 119.77 (q, ¹J_{C-F} = 278.4 Hz, C₇CF₃), 111.78 (s, C₆), 55.51 (s, C₂OCH₃), 14.90 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₁₁F₃NO [M⁺]: calcd 218.0787, found 218.0773.



III.1.b
Chemical Formula: C₁₀H₁₀F₃NO
Exact Mass: 217.07 g/mol
Brown oil

3-Methoxy-N-(1,1,1-trifluoropropan-2-ylidene)aniline III.1.c

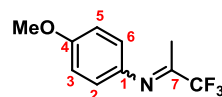
a) 1,1,1-Trifluoroacetone (2 equiv., 1.47 mL, 16.4 mmol); b) 3-Methoxyaniline (1 equiv., 0.91 mL, 8.12 mmol); c) 4 Å MS, for 24 h; and d) 3-Methoxy-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.c** was obtained as a brown oil in 92% yield, estimated (1.62 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.35 – 7.22 (m, 1H, C₅H), 6.79 – 6.70 (m, 1H, C₄H), 6.44 – 6.32 (m, 2H, C_{2,6}H), 3.79 (s, 3H, C₃OCH₃), 2.05 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -74.81 and -74.91 (s, C₇CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 160.50 (s, C₃), 157.56 (q, ²J_{C-F} = 33.9 Hz, C₇), 148.95 (s, C₁), 130.08 (s, C₅), 119.78 (q, ¹J_{C-F} = 278.2 Hz, C₇CF₃), 110.60 (s, C_{4,6}), 104.49 (s, C₂), 54.91 (s, C₃OCH₃), 14.01 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₁₁F₃NO [M⁺]: calcd 218.0787, found 218.0818.



III.1.c
 Chemical Formula: C₁₀H₁₀F₃NO
 Exact Mass: 217,07 g/mol
 Brown oil

4-Methoxy-N-(1,1,1-trifluoropropan-2-ylidene)aniline III.1.d

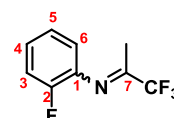
a) 1,1,1-Trifluoroacetone (2 equiv., 1.47 mL, 16.4 mmol); b) 4-Methoxyaniline (1 equiv., 1.01 g, 8.2 mmol); c) 4 Å MS, for 20 h; and d) 4-Methoxy-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.d** was obtained as a brown oil in 93% yield (1.65 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 6.86 (m, 2H, AA', C_{2,6}H), 6.73 (m, 2H, BB', C_{3,5}H), 3.75 – 3.71 (m, 3H, C₄OCH₃), 2.03 – 2.00 (m, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -74.58 – -74.63 (m, C₇CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 157.51 (s, C₄), 156.53 (q, ²J_{C-F} = 33.5 Hz, C₇), 140.36 (s, C₁), 120.85 (s, C_{3,5}), 119.96 (q, ¹J_{C-F} = 278.1 Hz, C₇CF₃), 114.31 (s, C_{2,6}), 55.09 (s, C₄OCH₃), 13.99 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₁₁F₃NO [M⁺]: calcd 218.0787, found 218.0815.



III.1.d
 Chemical Formula: C₁₀H₁₀F₃NO
 Exact Mass: 217,07 g/mol
 Brown oil

2-Fluoro-N-(1,1,1-trifluoropropan-2-ylidene)aniline III.1.e

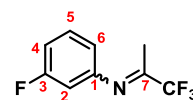
a) 1,1,1-Trifluoroacetone (2 equiv., 3.23 mL, 36 mmol); b) 2-Fluoroaniline (1 equiv., 1.74 mL, 18 mmol); c) 4 Å MS, for 16 h; and d) 2-Fluoro-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.e** was obtained as a brown oil in 70% yield (2.58 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.21 – 7.07 (m, 3H, C_{4,5,6}H), 6.93 – 6.86 (m, 1H, C₃H), 2.02 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -74.65 (s, C₇CF₃), -126.51 – -126.58 (m, C₂F) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 160.40 (qd, ²J_{C-F} = 34.1, ⁴J_{C-F} = 0.5 Hz, C₇), 151.01 (d, ¹J_{C-F} = 246.3 Hz, C₂), 134.91 (d, ²J_{C-F} = 12.8 Hz, C₁), 126.57 (d, ³J_{C-F} = 7.3 Hz, C₄), 124.59 (d, ⁴J_{C-F} = 3.8 Hz, C₅), 121.68 (d, ³J_{C-F} = 1.1 Hz, C₆), 119.53 (q, ¹J_{C-F} = 278.2 Hz, C₇CF₃), 116.18 (d, ²J_{C-F} = 19.7 Hz, C₃), 15.01 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₉H₈F₄N [M⁺]: calcd 206.0587, found 206.0590.



III.1.e
 Chemical Formula: C₉H₇F₄N
 Exact Mass: 205,05 g/mol
 Brown oil

3-Fluoro-N-(1,1,1-trifluoropropan-2-ylidene)aniline III.1.f

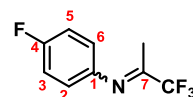
a) 1,1,1-Trifluoroacetone (2 equiv., 1.61 mL, 18 mmol); b) 3-Fluoroaniline (1 equiv., 0.87 mL, 9 mmol); c) 4 Å MS, for 48 h; and d) 3-Fluoro-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.f** was obtained as a brown oil in 62% yield (1.14 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.36 – 7.28 (m, 1H, C₅H), 6.90 – 6.82 (m, 1H, C₄H), 6.57 – 6.49 (m, 2H, C_{2,6}H), 2.02 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -73.12 – -77.79 (m, C₇CF₃), -109.19 – -115.09 (m, C₃F) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 163.44 (d, ¹J_{C-F} = 247.2 Hz, C₃), 158.64 (q, ²J_{C-F} = 34.3 Hz, C₇), 149.33 (d, ³J_{C-F} = 9.1 Hz, C₁), 130.70 (d, ³J_{C-F} = 9.2 Hz, C₅), 119.56 (q, ¹J_{C-F} = 278.3 Hz, C₇CF₃), 114.45 (d, ⁴J_{C-F} = 2.9 Hz, C₆), 112 (d, ²J_{C-F} = 21.3 Hz, C₄), 106.38 (d, ²J_{C-F} = 24.1 Hz, C₂), 14.36 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₉H₈F₄N [M⁺]: calcd 206.0587, found 206.0572.



III.1.f
Chemical Formula: C₉H₇F₄N
Exact Mass: 205,05 g/mol
Brown oil

4-Fluoro-N-(1,1,1-trifluoropropan-2-ylidene)aniline III.1.g

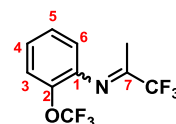
a) 1,1,1-Trifluoroacetone (2 equiv., 1.87 mL, 20.8 mmol); b) 4-Fluoroaniline (1 equiv., 1 mL, 10.4 mmol); c) 4 Å MS, for 13 h; and d) 4-Fluoro-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.g** was obtained as a brown oil in 93% yield (1.97 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.10 – 7.03 (m, 2H, C_{3,5}H), 6.79 – 6.73 (m, 2H, C_{2,6}H), 2.03 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -74.77 – -74.79 (m, C₇CF₃), -117.79 – -118.66 (m, C₄F) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 160.39 (d, ¹J_{C-F} = 244.1 Hz, C₄), 158.01 (qd, ²J_{C-F} = 33.9, ⁶J_{C-F} = 1.1 Hz, C₇), 143.59 (d, ⁴J_{C-F} = 2.7 Hz, C₁), 120.68 (d, ³J_{C-F} = 8.2 Hz, C_{2,6}), 119.68 (q, ¹J_{C-F} = 278.2 Hz, C₇CF₃), 115.98 (d, ²J_{C-F} = 22.8 Hz, C_{3,5}), 14.38 (s, C₇CH₃) ppm. LCMS (ESI negative) for C₉H₆F₄N [M⁻] m/z 223 (M⁺ H₂O, 100%), 153 (15%).



III.1.g
Chemical Formula: C₉H₇F₄N
Exact Mass: 205,05 g/mol
Brown oil

N-2-(Trifluoromethoxy)-N-(1,1,1-trifluoropropan-2-ylidene)aniline III.1.h

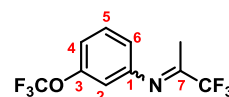
a) 1,1,1-Trifluoroacetone (3 equiv., 3.03 mL, 33.9 mmol); b) 2-(Trifluoromethoxy)aniline (1 equiv., 1.54 mL, 11.3 mmol); c) 4 Å MS, for 48 h; and d) N-2-(Trifluoromethoxy)-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.h** was obtained as a brown oil in 15% yield, estimated (448 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.35 – 7.30 (m, 2H, C_{4,6}H), 7.24 – 7.20 (m, 1H, C₅H), 6.86 (dd, ³J_{H-H} = 8.1, ⁴J_{H-H} = 1.5 Hz, 1H, C₃H), 2.02 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -58.19 (s, C₂OCF₃), -87.18 (s, C₇CF₃) ppm. HRMS (ESI positive) for C₁₀H₈F₆NO [M⁺]: calcd 272.0505, found 272.0493.



III.1.h
Chemical Formula: C₁₀H₇F₆NO
Exact Mass: 271,04 g/mol
Brown oil

3-(Trifluoromethoxy)-N-(1,1,1-trifluoropropan-2-ylidene)aniline III.1.i

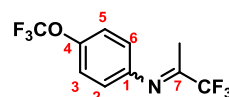
a) 1,1,1-Trifluoroacetone (2 equiv., 1.01 mL, 11.3 mmol); b) 3-(Trifluoromethoxy)aniline (1 equiv., 0.76 mL, 5.65 mmol); c) 4 Å MS, for 48 h; and d) 3-(Trifluoromethoxy)-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.i** was obtained as a brown oil in 82% yield (1.25 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.40 (t, ³J_{H-H} = 8.1 Hz, 1H, C₅H), 7.04 (d, ³J_{H-H} = 8.3 Hz, 1H, C₄H), 6.71 (d, ³J_{H-H} = 7.9 Hz, 1H, C₆H), 6.68 (s, 1H, C₂H), 2.03 (s, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -58.08 (s, C₃OCF₃), -74.91 (s, C₇CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 158.85 (q, ²J_{C-F} = 34.3 Hz, C₇), 150.05 (q, ³J_{C-F} = 2.02 Hz, C₃), 149.12 (s, C₁), 130.75 (s, C₅), 120.41 (q, ¹J_{C-F} = 258.2 Hz, C₃OCF₃), 119.49 (q, ¹J_{C-F} = 278.3 Hz, C₇CF₃), 117.27 (s, C₄), 116.96 (s, C₆), 111.58 (s, C₂), 14.52 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₈F₆NO [M⁺]: calcd 272.0505, found 272.0488.



III.1.i
Chemical Formula: C₁₀H₇F₆NO
Exact Mass: 271,04 g/mol
Brown oil

4-(Trifluoromethoxy)-N-(1,1,1-trifluoropropan-2-ylidene)aniline III.1.j

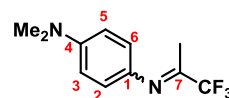
a) 1,1,1-Trifluoroacetone (2 equiv., 2.02 mL, 22.6 mmol); b) 4-(Trifluoromethoxy)aniline (1 equiv., 1.53 mL, 11.3 mmol); c) 4 Å MS, for 48 h; and d) 4-(Trifluoromethoxy)-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.j** was obtained as a brown oil in 93% yield (2.85 g). Presence of isomer (Z/E-E/Z) ratio 87:13. ¹H NMR (400 MHz, CDCl₃) δ_H = 7.17 (d, ³J_{H-H} = 8.8 Hz, 2H, C_{2,6}H), 6.95 (d, ³J_{H-H} = 8.8 Hz, 2H, C_{2,6}H), 6.73 (d, ³J_{H-H} = 8.8 Hz, 2H, C_{3,5}H), 6.61 (d, ³J_{H-H} = 8.8 Hz, 2H, C_{3,5}H), 1.96 (s, 3H, C₇CH₃), 1.96 (s, 3H, C₇CH₃') ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -58.40 – -58.67 (m, C₄OCF₃), -74.89 – -75.12 (m, C₇CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 158.94 (q, ²J_{C-F} = 34.3 Hz, C₇), 146.84 (q, ³J_{C-F} = 2.02 Hz, C₄), 146.15 (s, C₁), 122.26 (s, C_{2,6}), 120.31 (s, C_{3,5}), 120.76 (q, ¹J_{C-F} = 256.8 Hz, C₄OCF₃), 119.79 (q, ¹J_{C-F} = 278.2 Hz, C₇CF₃), 14.46 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₈F₆NO [M⁺]: calcd 272.0505, found 272.0496.



III.1.j
Chemical Formula: C₁₀H₇F₆NO
Exact Mass: 271,04 g/mol
Brown oil

1-N,N-Dimethyl-4-N-(1,1,1-trifluoropropan-2-ylidene)benzene-1,4-diamine III.1.k

a) 1,1,1-Trifluoroacetone (2 equiv., 1.32 mL, 14.8 mmol); b) N,N-Dimethyl-1,4-benzenediamine (1 equiv., 0.92 mL, 7.39 mmol); c) 4 Å MS, for 24 h; and d) 1-N,N-Dimethyl-4-N-(1,1,1-trifluoropropan-2-ylidene)benzene-1,4-diamine **III.1.k** was obtained as a brown oil in 80% yield (1.36 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 6.83 (m, 2H, AA', C_{2,6}H), 6.74 (m, 2H, BB', C_{3,5}H), 2.96 (s, 6H, C₄N(CH₃)₂), 2.11 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -74.19 (s, C₇CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 154.86 (q, ²J_{C-F} = 33.3 Hz, C₇), 148.94 (s, C₄), 136.65 (s, C₁), 121.94 (s, C_{2,6}), 120.15 (q, ¹J_{C-F} = 278.0 Hz, C₇CF₃), 112.86 (s, C_{3,5}), 40.84 (s, C₄N(CH₃)₂), 14.67 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₁H₁₄F₃N₂ [M⁺]: calcd 231.1104, found 231.1125.



III.1.k
Chemical Formula: C₁₁H₁₃F₃N₂
Exact Mass: 230,10 g/mol
Brown oil

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

a) 1,1,1-Trifluoroacetone (2 equiv., 2.87 mL, 32 mmol); b) 3-Fluoro-2-methylaniline (1 equiv., 1.82 mL, 16 mmol); c) 4 Å MS, for 26 h; and d) 3-Fluoro-2-methyl-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.l** was obtained as a brown oil in 57% yield, estimated (2.01 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.17$ (dd, $^3J_{\text{H-F}} = 14.3$, $^3J_{\text{H-H}} = 7.8$ Hz, 1H, C₄H), 6.97 (dd, $^4J_{\text{H-F}} = 14.8$, $^3J_{\text{H-H}} = 7.8$ Hz, 1H, C₅H), 6.43 (d, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C₆H), 2.01 (s, 3H, C₂CH₃), 1.99 (s, 3H, C₇CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -74.56$ (s, C₇CF₃), -115.94 (s, C₃F) ppm. HRMS (ESI positive) for C₁₀H₁₀F₄N [M⁺]: calcd 220.0744, found 220.0746.

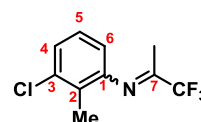


III.1.l

Chemical Formula: C₁₀H₉F₄N
Exact Mass: 219,07 g/mol
Brown oil

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

a) 1,1,1-Trifluoroacetone (2 equiv., 2.53 mL, 28.2 mmol); b) 3-Chloro-2-methylaniline (1 equiv. 1.71 mL, 14.1 mmol); c) 4 Å MS, for 26 h; and d) 3-Chloro-2-methyl-N-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.m** was obtained as a brown oil in 50% yield, estimated (1.67 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.22$ (dd, $^3J_{\text{H-H}} = 8.0$, $^4J_{\text{H-H}} = 1.0$ Hz, 1H, C₄H), 7.14 (t, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C₅H), 6.53 (dd, $^3J_{\text{H-H}} = 7.8$, $^4J_{\text{H-H}} = 0.8$ Hz, 1H, C₆H), 2.14 (s, 3H, C₂CH₃), 1.98 (s, 3H, C₇CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -74.51$ (s, C₇CF₃) ppm. HRMS (ESI positive) for C₁₀H₁₀F₃NCl [M⁺]: calcd 236.0448, found 236.0462.

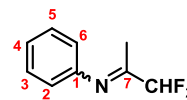


III.1.m

Chemical Formula: C₁₀H₉ClF₃N
Exact Mass: 235,04 g/mol
Brown oil

N-(1,1-Difluoropropan-2-ylidene)aniline III.1.aa

a) 1,1-Difluoroacetone (1.07 equiv., 5 mL, 58.2 mmol); b) Aniline (1 equiv., 5 mL, 54.6 mmol); c) 4 Å MS, for 3 h; and d) N-(1,1-Difluoropropan-2-ylidene)aniline **III.1.aa** was obtained as a brown oil in 96% yield (8.57 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.37$ (t, $^3J_{\text{H-H}} = 7.8$ Hz, 2H, C_{3,5}H), 7.16 (t, $^3J_{\text{H-H}} = 7.2$ Hz, 1H, C₄H), 6.78 (d, $^3J_{\text{H-H}} = 7.4$ Hz, 2H, C_{2,6}H), 6.07 (t, $^2J_{\text{H-F}} = 55.6$ Hz, 1H, C₇CHF₂), 1.95 (s, 3H, C₇CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -121.27$ (d, $^2J_{\text{F-H}} = 55.5$ Hz, C₇CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 163.54$ (t, $^2J_{\text{C-F}} = 28.8$ Hz, C₇), 148.47 (s, C₁), 129.12 (s, C_{3,5}), 124.86 (s, C₄), 119.01 (s, C_{2,6}), 114.96 (t, $^1J_{\text{C-F}} = 243.0$ Hz, C₇CHF₂), 12.65 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₉H₁₀F₂N [M⁺]: calcd 170.0774, found 170.0776.

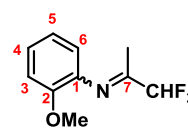


III.1.aa

Chemical Formula: C₉H₉F₂N
Exact Mass: 169,07 g/mol
Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-2-methoxyaniline III.1.bb**

a) 1,1-Difluoroacetone (2 equiv., 1.32 mL, 16.2 mmol); b) 2-Methoxyaniline (1 equiv., 0.92 mL, 8.12 mmol); c) 4 Å MS, for 5 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-2-methoxyaniline **III.1.bb** was obtained as a brown oil in 98% yield (1.59 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.14 (td, ³J_{H-H} = 7.8, ⁴J_{H-H} = 1.6 Hz, 1H, C₄H), 6.99 – 6.92 (m, 2H, C_{5, 6}H), 6.74 (dd, ³J_{H-H} = 7.6, ⁴J_{H-H} = 1.6 Hz, 1H, C₃H), 6.12 (t, ²J_{H-F} = 55.6 Hz, 1H, C₇CHF₂), 3.80 (s, 3H, C₂OCH₃), 1.89 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -120.86 (d, ²J_{F-H} = 55.5 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.88 (t, ²J_{C-F} = 28.6 Hz, C₇), 148.64 (s, C₂), 137.30 (s, C₁), 125.75 (s, C₄), 120.87 (s, C₅), 120.17 (s, C₃), 114.83 (t, ¹J_{C-F} = 242.8 Hz, C₇CHF₂), 111.65 (s, C₆), 55.56 (s, C₂OCH₃), 13.11 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₁₂F₂NO [M⁺]: calcd 200.0881, found 200.0875.

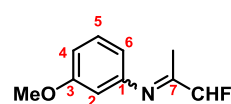


III.1.bb

Chemical Formula: C₁₀H₁₁F₂NO
Exact Mass: 199,08 g/mol
Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-3-methoxyaniline III.1.cc**

a) 1,1-Difluoroacetone (2 equiv., 1.32 mL, 16.2 mmol); b) 3-Methoxyaniline (1 equiv., 0.91 mL, 8.12 mmol); c) 4 Å MS, for 4 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-3-methoxyaniline **III.1.cc** was obtained as a brown oil in 98% yield (1.58 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.30 – 7.26 (m, 1H, C₅H), 6.75 – 6.73 (m, 1H, C₄H), 6.39 – 6.38 (m, 2H, C_{2, 6}H), 6.10 (t, ²J_{H-F} = 55.6 Hz, 1H, C₇CHF₂), 3.83 - 3.80 (m, 3H, C₃OCH₃), 1.99 – 1.97 (m, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.26 – -121.44 (m, ²J_{F-H} = 55.6 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 163.41 (t, ²J_{C-F} = 28.7 Hz, C₇), 160.41 (s, C₃), 149.81 (s, C₁), 129.95 (s, C₅), 114.89 (t, ¹J_{C-F} = 242.9 Hz, C₇CHF₂), 110.92 (s, C₆), 110.25 (s, C₄), 104.65 (s, C₂), 55.01 (s, C₃OCH₃), 12.35 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₁₂F₂NO [M⁺]: calcd 200.0881, found 200.0884.

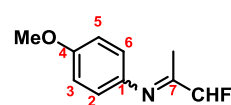


III.1.cc

Chemical Formula: C₁₀H₁₁F₂NO
Exact Mass: 199,08 g/mol
Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-4-methoxyaniline III.1.dd**

a) 1,1-Difluoroacetone (2 equiv., 1.44 mL, 17.8 mmol); b) 4-Methoxyaniline (1 equiv., 1.1 g, 8.91 mmol); c) 4 Å MS, for 5 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-4-methoxyaniline **III.1.dd** was obtained as a brown oil in 98% yield, estimated (1.74 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 6.87 (m, 2H, **AA'**, C_{2, 6}H), 6.73 (m, 2H, **BB'**, C_{3, 5}H), 6.02 (t, ²J_{H-F} = 55.7 Hz, 1H, C₇CHF₂), 3.77 – 3.69 (m, 3H, C₄OCH₃), 1.94 - 1.93 (m, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.11 (dd, ²J_{F-H} = 55.8, ⁴J_{F-H} = 4.0 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 162.77 (t, ²J_{C-F} = 29.4 Hz, C₇), 157.11 (s, C₄), 141.22 (s, C₁), 120.80 (s, C_{3, 5}), 115.23 (t, ¹J_{C-F} = 242.7 Hz, C₇CHF₂), 114.21 (s, C_{2, 6}), 55.11 (s, C₄OCH₃), 12.26 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₁₂F₂NO [M⁺]: calcd 200.0881, found 200.0893.

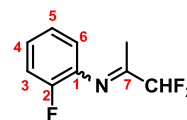


III.1.dd

Chemical Formula: C₁₀H₁₁F₂NO
Exact Mass: 199,08 g/mol
Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-2-fluoroaniline III.1.ee**

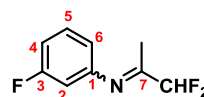
a) 1,1-Difluoroacetone (2 equiv., 2.92 mL, 36 mmol); b) 2-Fluoroaniline (1 equiv., 1.74 mL, 18 mmol); c) 4 Å MS, for 4 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-2-fluoroaniline **III.1.ee** was obtained as a brown oil in 78% yield, estimated (2.62 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.19 – 7.08 (m, 3H, C_{4,5,6}H), 6.90 – 6.82 (m, 1H, C₃H), 6.10 (t, ²J_{H-F} = 55.5 Hz, 1H, C₇CHF₂), 1.99 – 1.91 (m, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.24 (d, ²J_{F-H} = 55.5 Hz, C₇CHF₂), -126.63 (s, C₂F) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 166.37 (t, ²J_{C-F} = 28.9 Hz, C₇), 151.51 (d, ¹J_{C-F} = 245.8 Hz, C₂), 135.82 (d, ²J_{C-F} = 13.0 Hz, C₁), 126.07 (d, ³J_{C-F} = 7.3 Hz, C₄), 124.48 (d, ⁴J_{C-F} = 3.8 Hz, C₅), 121.72 (s, C₆), 116.11 (d, ²J_{C-F} = 19.8 Hz, C₃), 114.49 (t, ¹J_{C-F} = 243.0 Hz, C₇CHF₂), 13.14 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₉H₉F₃N [M⁺]: calcd 188.0682, found 188.0687.



III.1.ee
 Chemical Formula: C₉H₈F₃N
 Exact Mass: 187,06 g/mol
 Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-3-fluoroaniline III.1.ff**

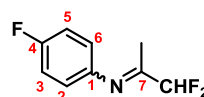
a) 1,1-Difluoroacetone (2 equiv., 1.46 mL, 18 mmol); b) 3-Fluoroaniline (1 equiv., 0.87 mL, 9 mmol); c) 4 Å MS, for 5 h; and d) *N*-(1,1-difluoropropan-2-ylidene)-3-fluoroaniline **III.1.ff** was obtained as a brown oil in 91% yield (1.53 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.33 – 7.28 (m, 1H, C₅H), 6.84 (td, ³J_{H-H} = 8.5, ⁴J_{H-H} = 2.5 Hz, 1H, C₄H), 6.55 – 6.49 (m, 2H, C_{2,6}H), 6.03 (t, ²J_{H-F} = 55.5 Hz, 1H, C₇CHF₂), 1.94 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -111.96 – -112.07 (m, C₃F), -121.51 (d, ²J_{F-H} = 55.4 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.38 (t, ²J_{C-F} = 28.9 Hz, C₇), 163.35 (d, ¹J_{C-F} = 247.45 Hz, C₃), 150.28 (d, ³J_{C-F} = 9.2 Hz, C₁), 130.63 (d, ³J_{C-F} = 9.2 Hz, C₅), 114.57 (t, ¹J_{C-F} = 242.4 Hz, C₇CHF₂), 114.48 (d, ⁴J_{C-F} = 2.9 Hz, C₆), 111.38 (d, ²J_{C-F} = 21.3 Hz, C₄), 106.36 (d, ²J_{C-F} = 23.7 Hz, C₂), 12.65 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₉H₉F₃N [M⁺]: calcd 188.0682, found 188.0672.



III.1.ff
 Chemical Formula: C₉H₈F₃N
 Exact Mass: 187,06 g/mol
 Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-4-fluoroaniline III.1.gg**

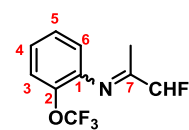
a) 1,1-Difluoroacetone (2 equiv., 1.35 mL, 16.7 mmol); b) 4-Fluoroaniline (1 equiv., 0.8 mL, 8.33 mmol); c) 4 Å MS, for 3 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-4-fluoroaniline **III.1.gg** was obtained as a brown oil in 83% yield (1.29 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.04 (t, ³J_{H-H} = 8.7 Hz, 2H, C_{2,6}H), 6.75 – 6.72 (m, 2H, C_{3,5}H), 6.02 (t, ²J_{H-F} = 55.6 Hz, 1H, C₇CHF₂), 1.94 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -118.69 – -119.06 (m, C₄F), -121.38 (dd, ²J_{F-H} = 55.6, ⁴J_{F-H} = 2.6 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.10 (t, ²J_{C-F} = 28.2 Hz, C₇), 160.27 (d, ¹J_{C-F} = 243.3 Hz, C₄), 144.44 (d, ⁴J_{C-F} = 1.2 Hz, C₁), 120.60 (d, ³J_{C-F} = 8.1 Hz, C_{2,6}), 115.86 (d, ²J_{C-F} = 22.6 Hz, C_{3,5}), 114.82 (t, ¹J_{C-F} = 243.0 Hz, C₇CHF₂), 12.57 (s, C₇CH₃) ppm. HRMS (ESI negative) for C₉H₇F₃N [M⁻]: calcd 186.0525, found 186.0544.



III.1.gg
 Chemical Formula: C₉H₈F₃N
 Exact Mass: 187,06 g/mol
 Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethoxy)aniline III.1.hh**

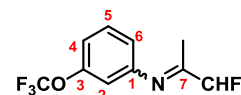
a) 1,1-Difluoroacetone (2 equiv., 1.83 mL, 22.6 mmol); b) 2-(Trifluoromethoxy)aniline (1 equiv., 1.54 mL, 11.3 mmol); c) 4 Å MS, for 5 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethoxy)aniline **III.1.hh** was obtained as a brown oil in 75% yield (2.13 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.27 - 7.18$ (m, 2H, C₄, ₆H), 7.12 - 7.06 (m, 1H, C₅H), 6.78 - 6.73 (m, 1H, C₃H), 6.03 (t, $^2J_{\text{H-F}} = 55.5$ Hz, 1H, C₇CHF₂), 1.85 (s, 3H, C₇CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -58.46$ (s, C₂OCF₃), -121.95 (d, $^2J_{\text{F-H}} = 55.4$ Hz, C₇CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 166.44$ (t, $^2J_{\text{C-F}} = 29.1$ Hz, C₇), 141.52 (s, C₂), 138.31 (s, C₁), 127.75 (s, C₄), 125.82 (s, C₅), 122.38 (s, C₆), 122.14 (q, $^1J_{\text{C-F}} = 234.3$ Hz, C₂OCF₃), 120.96 (s, C₃), 114.62 (t, $^1J_{\text{C-F}} = 242.9$ Hz, C₇CHF₂), 12.96 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₉F₅NO [M^+]: calcd 254.0599, found 254.0622.



III.1.hh
 Chemical Formula: C₁₀H₈F₅NO
 Exact Mass: 253.05 g/mol
 Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethoxy)aniline III.1.ii**

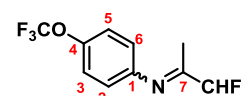
a) 1,1-Difluoroacetone (2 equiv., 0.92 mL, 11.3 mmol); b) 3-(Trifluoromethoxy)aniline (1 equiv., 0.76 mL, 5.65 mmol); c) 4 Å MS, for 7 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethoxy)aniline **III.1.ii** was obtained as a brown oil in 93% yield (1.32 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.37$ (t, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, C₅H), 7.04 - 6.99 (m, 1H, C₄H), 6.69 (d, 1H, $^3J_{\text{H-H}} = 7.9$ Hz, C₆H), 6.66 (s, 1H, C₂H), 6.03 (t, $^2J_{\text{H-F}} = 55.5$ Hz, 1H, C₇CHF₂), 1.94 (s, 3H, C₇CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -58.10$ (s, C₃OCF₃), -121.65 (d, $^2J_{\text{F-H}} = 55.6$ Hz, C₇CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 164.80$ (t, $^2J_{\text{C-F}} = 29.0$ Hz, C₇), 150.07 - 150.02 (m, C_{1,3}), 130.57 (s, C₅), 121.72 (q, $^1J_{\text{C-F}} = 258.6$ Hz, C₃OCF₃), 117.37 (s, C₄), 117.00 (s, C₆), 114.68 (t, $^1J_{\text{C-F}} = 243.2$ Hz, C₇CHF₂), 111.92 (s, C₂), 12.74 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₉F₅NO [M^+]: calcd 254.0599, found 254.0583.



III.1.ii
 Chemical Formula: C₁₀H₈F₅NO
 Exact Mass: 253.05 g/mol
 Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethoxy)aniline III.1.jj**

a) 1,1-Difluoroacetone (2 equiv., 1.83 mL, 22.6 mmol); b) 4-(Trifluoromethoxy)aniline (1 equiv., 1.53 mL, 11.3 mmol); c) 4 Å MS, for 3 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethoxy)aniline **III.1.jj** was obtained as a brown oil in 91% yield (2.59 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.22$ (d, $^3J_{\text{H-H}} = 8.6$ Hz, 2H, C₂, ₆H), 6.78 (d, $^3J_{\text{H-H}} = 8.8$ Hz, 2H, C₃, ₅H), 6.03 (t, $^2J_{\text{H-F}} = 55.6$ Hz, 1H, C₇CHF₂), 1.94 (s, 3H, C₇CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -58.44$ (s, C₄OCF₃), -121.67 (dd, $^2J_{\text{F-H}} = 55.6$, $^4J_{\text{F-H}} = 2$ Hz, C₇CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 164.54$ (t, $^2J_{\text{C-F}} = 28.9$ Hz, C₇), 147.21 (s, C₁), 146.39 (q, $^3J_{\text{C-F}} = 2$ Hz, C₄), 122.10 (s, C₂, ₆), 120.76 (q, $^1J_{\text{C-F}} = 256.7$ Hz, C₄OCF₃), 120.34 (s, C₃, ₅), 114.84 (t, $^1J_{\text{C-F}} = 244.4$ Hz, C₇CHF₂), 12.38 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₉F₅NO [M^+]: calcd 254.0599, found 254.0622.



III.1.jj
 Chemical Formula: C₁₀H₈F₅NO
 Exact Mass: 253.05 g/mol
 Brown oil

3-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,3-diamine
III.1.kk

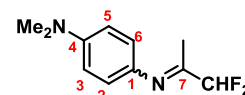
a) 1,1-Difluoroacetone (2 equiv., 0.83 mL, 10.2 mmol); b) 1-*N,N*-Dimethyl-1,3-phenylenediamine dihydrochloride (1 equiv., 695 mg, 5.1 mmol) and sodium hydride (2.1 equiv., 257.2 mg, 10.72 mmol); c) 4 Å MS, for 24 h; and d) 3-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,3-diamine **III.1.kk** was obtained as a black paste (1.26 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.21 (t, ³J_{H-H} = 8.2 Hz, 1H, C₅H), 6.56 – 6.51 (m, 1H, C₄H), 6.13 – 6.08 (m, 2H, C_{2,6}H), 6.06 (t, ²J_{H-F} = 55.5 Hz, 1H, C₇CHF₂), 2.95 (s, 6H, C₃N(CH₃)₂), 1.96 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.31 (d, ²J_{F-H} = 55.5 Hz, C₇CHF₂) ppm. HRMS (ESI positive) for C₁₁H₁₅F₂N₂ [M⁺]: calcd 213.1198, found 213.1209.



III.1.kk
 Chemical Formula: C₁₁H₁₄F₂N₂
 Exact Mass: 212,11 g/mol
 Black paste

4-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,4-diamine III.1.ii

a) 1,1-Difluoroacetone (2 equiv., 1.19 mL, 14.7 mmol); b) *N,N*-Dimethyl-1,4-benzenediamine (1 equiv., 0.92 mL, 7.35 mmol); c) 4 Å MS, for 20 h; and d) 4-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,4-diamine **III.1.ii** was obtained as a yellow solid in 94% yield (1.46 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 6.77 (A₂B₂, ³J_{H-H} = 8.9 Hz, Δν = 27.76 Hz, 4H, C_{2,6} / 3, 5H), 6.05 (t, ²J_{H-F} = 55.9 Hz, 1H, C₇CHF₂), 2.96 (s, 6H, C₄N(CH₃)₂), 2.03 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -120.62 (d, ²J_{F-H} = 55.9 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 161.26 (t, ²J_{C-F} = 28.4 Hz, C₇), 148.61 (s, C₄), 137.60 (s, C₁), 121.72 (s, C_{2,6}), 115.70 (t, ¹J_{C-F} = 242.6 Hz, C₇CHF₂), 112.84 (s, C_{3,5}), 40.83 (s, C₄N(CH₃)₂), 12.74 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₁H₁₅F₂N₂ [M⁺]: 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.



III.1.ii
 Chemical Formula: C₁₁H₁₄F₂N₂
 Exact Mass: 212,11 g/mol
 Yellow solid

***N*-(1,1-Difluoropropan-2-ylidene)-3-fluoro-2-methylaniline III.1.mm**

a) 1,1-Difluoroacetone (2 equiv., 2.59 mL, 32 mmol); b) 3-Fluoro-2-methylaniline (1 equiv., 1.82 mL, 16 mmol); c) 4 Å MS, for 18 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-3-fluoro-2-methylaniline **III.1.mm** was obtained as a brown oil in 90% yield, estimated (2.88 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.16 – 7.13 (m, 1H, C₄H), 6.83 (t, ³J_{H-H} = 8.8 Hz, 1H, C₅H), 6.41 (d, ³J_{H-H} = 7.9 Hz, 1H, C₆H), 6.10 (t, ²J_{H-F} = 55.5 Hz, 1H, C₇CHF₂), 1.99 (d, ⁴J_{H-F} = 2.0 Hz, 3H, C₂CH₃), 1.89 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -116.18 - -116.24 (m, C₃F), -121.21 (dd, ²J_{F-H} = 55.5, ⁴J_{F-H} = 2.4 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.50 (t, ²J_{C-F} = 29.0 Hz, C₇), 161.79 (d, ¹J_{C-F} = 244.3 Hz, C₃), 148.91 (d, ³J_{C-F} = 7.8 Hz, C₁), 126.98 (d, ³J_{C-F} = 9.8 Hz, C₅), 114.68 (s, C₂), 114.55 (t, ¹J_{C-F} = 243.0 Hz, C₇CHF₂), 113.50 (d, ⁴J_{C-F} = 3.1 Hz, C₆), 111.17 (d, ²J_{C-F} = 23.0 Hz, C₄), 12.83 (s, C₇CH₃), 9.02 (d, ³J_{C-F} = 4.8 Hz, C₂CH₃) ppm. HRMS (ESI positive) for C₁₀H₁₁F₃N [M⁺]: calcd 202.0838, found 202.0866.



III.1.mm
 Chemical Formula: C₁₀H₁₀F₃N
 Exact Mass: 201,08 g/mol
 Brown oil

3-Chloro-N-(1,1-difluoropropan-2-ylidene)-2-methylaniline III.1.nn

a) 1,1-Difluoroacetone (2 equiv., 2.29 mL, 28.2 mmol); b) 3-Chloro-2-methylaniline (1 equiv., 1.71 mL, 14.1 mmol); c) 4 Å MS, for 18 h; and d) 3-Chloro-N-(1,1-difluoropropan-2-ylidene)-2-methylaniline

III.1.nn was obtained as a brown oil in 91% yield, estimated (2.79 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.17 (dd, ³J_{H-H} = 8.0, ⁴J_{H-H} = 1.1 Hz, 1H, C₄H), 7.10 (t, ³J_{H-H} = 7.7 Hz, 1H, C₅H), 6.52 (dd, ³J_{H-H} = 7.7, ⁴J_{H-H} = 0.9 Hz, 1H, C₆H), 6.11 (t, ²J_{H-F} = 55.5 Hz, 1H, C₇CHF₂), 2.12 (s, 3H, C₂CH₃), 1.88

(s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.15 (d, ²J_{F-H} = 55.5 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.43 (t, ²J_{C-F} = 28.9 Hz, C₇), 148.44 (s, C₁), 135.57 (s, C₃), 127.06 (s, C₅), 125.48 (s, C₄), 116.39 (s, C₆), 114.63 (t, ¹J_{C-F} = 243.1 Hz, C₇CHF₂), 113.56 (s, C₂), 14.26 (s, C₂CH₃), 12.89 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₁₁F₂NCl [M⁺]: calcd 218.0543, found 218.0557.



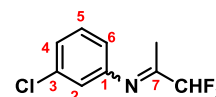
III.1.nn

Chemical Formula: C₁₀H₁₀ClF₂N
Exact Mass: 217,05 g/mol
Brown oil

3-Chloro-N-(1,1-difluoropropan-2-ylidene)aniline III.1.oo

a) 1,1-Difluoroacetone (2 equiv., 5.08 mL, 62.7 mmol); b) 3-Chloroaniline (1 equiv., 3.33 mL, 31.4 mmol); c) 4 Å MS, for 18 h; and d) 3-Chloro-N-(1,1-difluoropropan-2-ylidene)-aniline

III.1.oo was obtained as a brown oil (9.68 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.31 (t, ³J_{H-H} = 8.0 Hz, 1H, C₅H), 7.16 (d, ³J_{H-H} = 8.1 Hz, 1H, C₄H), 6.81 (t, ⁴J_{H-H} = 1.9 Hz, 1H, C₂H), 6.68 (d, ³J_{H-H} = 7.9 Hz, 1H, C₆H), 6.06 (t, ²J_{H-F} = 55.4 Hz, 1H, C₇CHF₂), 1.97 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.46 (d, ²J_{F-H} = 55.4 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.76 (t, ²J_{C-F} = 29.0 Hz, C₇), 149.64 (s, C₁), 134.99 (s, C₃), 130.44 (s, C₅), 124.96 (s, C₄), 119.18 (s, C₂), 117.24 (s, C₆), 114.55 (t, ¹J_{C-F} = 243.2 Hz, C₇CHF₂), 12.87 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₉H₉F₂NCl [M⁺]: calcd 204.0386, found 204.0367.



III.1.oo

Chemical Formula: C₉H₈ClF₂N
Exact Mass: 203,03 g/mol
Brown oil

N-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethyl)aniline III.1.pp

a) 1,1-Difluoroacetone (2 equiv., 0.503 mL, 6.21 mmol); b) 2-(Trifluoromethyl)aniline (1 equiv., 0.386 mL, 3.1 mmol); c) Anhydrous MgSO₄, for 16 h; and d) N-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethyl)aniline

III.1.pp was obtained as a brown oil in 40% yield, estimated (215 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.67 (d, ³J_{H-H} = 7.9 Hz, 1H, C₃H), 7.52 (t, ³J_{H-H} = 7.7 Hz, 1H, C₅H), 7.23 (t, ³J_{H-H} = 7.7 Hz, 1H, C₄H), 6.72 (d, ³J_{H-H} = 7.9 Hz, 1H, C₆H), 6.08 (t, ²J_{H-F} = 55.4 Hz, 1H, C₇CHF₂), 1.90 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -61.85 (s, C₂CF₃), -121.82 (d, ²J_{F-H} = 55.4 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 165.58 (t, ²J_{C-F} = 29.4 Hz, C₇), 146.98 (q, ³J_{C-F} = 2.02 Hz, C₁), 132.87 (s, C₅), 126.77 (q, ³J_{C-F} = 5.05 Hz, C₃), 124.50 (s, C₄), 123.67 (q, ¹J_{C-F} = 273.0 Hz, C₂CF₃), 119.65 (q, ²J_{C-F} = 31.3 Hz, C₂), 119.18 (s, C₆), 114.27 (t, ¹J_{C-F} = 243.3 Hz, C₇CHF₂), 13.42 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₉F₅N [M⁺]: calcd 238.0650, found 238.0654.

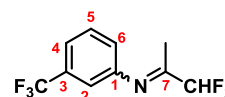


III.1.pp

Chemical Formula: C₁₀H₈F₅N
Exact Mass: 237,06 g/mol
Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethyl)aniline III.1.qq**

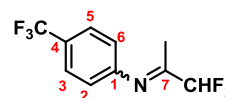
a) 1,1-Difluoroacetone (2 equiv., 1.01 mL, 12.4 mmol); b) 3-(Trifluoromethyl)aniline (1 equiv., 0.767 mL, 6.21 mmol); c) 4 Å MS, for 5 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethyl)aniline **III.1.qq** was obtained as a brown oil in 93% yield, estimated (1.47 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.49 (t, ³J_{H-H} = 7.8 Hz, 1H, C₅H), 7.42 (d, ³J_{H-H} = 7.8 Hz, 1H, C₄H), 7.03 (s, 1H, C₂H), 6.94 (d, ³J_{H-H} = 7.2 Hz, 1H, C₆H), 6.05 (t, ²J_{H-F} = 55.5 Hz, 1H, C₇CHF₂), 1.95 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -62.80 (s, C₃CF₃), -121.44 (d, ²J_{F-H} = 55.4 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 165.21 (t, ²J_{C-F} = 28.9 Hz, C₇), 148.91 (s, C₁), 131.84 (q, ²J_{C-F} = 32.5 Hz, C₃), 129.96 (s, C₅), 124.03 (q, ¹J_{C-F} = 272.3 Hz, C₃CF₃), 122.38 (s, C₆), 121.68 (q, ³J_{C-F} = 3.8 Hz, C₄), 116.01 (q, ³J_{C-F} = 4.0 Hz, C₂), 114.53 (t, ¹J_{C-F} = 243.2 Hz, C₇CHF₂), 12.78 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₉F₅N [M⁺]: calcd 238.0650, found 238.0660.



III.1.qq
 Chemical Formula: C₁₀H₈F₅N
 Exact Mass: 237,06 g/mol
 Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethyl)aniline III.1.rr**

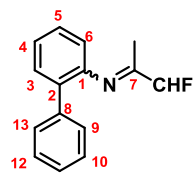
a) 1,1-Difluoroacetone (2 equiv., 0.503 mL, 6.21 mmol); b) 4-(Trifluoromethyl)aniline (1 equiv., 0.386 mL, 3.1 mmol); c) Anhydrous MgSO₄, for 16 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethyl)aniline **III.1.rr** was obtained as a brown oil in 29% yield, estimated (212 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.63 (d, ³J_{H-H} = 8.3 Hz, 2H, C_{3,5}H), 6.85 (d, ³J_{H-H} = 8.2 Hz, 2H, C_{2,6}H), 6.05 (t, ²J_{H-F} = 55.4 Hz, 1H, C₇CHF₂), 1.93 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -62.13 (s, C₄CF₃), -121.34 – -121.59 (2m, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.59 (t, ²J_{C-F} = 29.0 Hz, C₇), 151.64 (s, C₁), 126.64 (q, ³J_{C-F} = 3.8 Hz, C_{3,5}), 124.30 (q, ¹J_{C-F} = 271.6 Hz, C₄CF₃), 120.30 (q, ²J_{C-F} = 32.6 Hz, C₄), 119.03 (s, C_{2,6}), 114.49 (t, ¹J_{C-F} = 243.3 Hz, C₇CHF₂), 12.97 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₀H₉F₅N [M⁺]: calcd 238.0650, found 238.0658.



III.1.rr
 Chemical Formula: C₁₀H₈F₅N
 Exact Mass: 237,06 g/mol
 Brown oil

***N*-(1,1-Difluoropropan-2-ylidene)-2-phenylaniline III.1.ss**

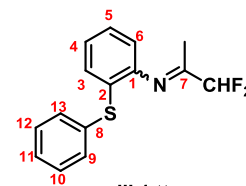
a) 1,1-Difluoroacetone (2 equiv., 0.485 mL, 5.98 mmol); b) 2-Aminodiphenyl (1 equiv., 505 mg, 2.99 mmol); c) Anhydrous MgSO₄, for 14 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-2-phenylaniline **III.1.ss** was obtained as a brown oil (953.7 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.42 – 7.23 (m, 8H, C_{3,4,5,9,10,11,12,13}H), 6.71 (dd, ³J_{H-H} = 7.8, ⁴J_{H-H} = 1.0 Hz, 1H, C₆H), 5.88 (t, ²J_{H-F} = 55.6 Hz, 1H, C₇CHF₂), 1.64 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.61 (d, ²J_{F-H} = 55.5 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 163.53 (t, ²J_{C-F} = 28.8 Hz, C₇), 146.07 (s, C₁), 139.00 (s, C₈), 132.02 (s, C₂), 131.44 – 123.83 (m, C_{3,4,5,9,10,11,12,13}), 119.16 (s, C₆), 114.67 (t, ¹J_{C-F} = 243.2 Hz, C₇CHF₂), 13.40 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₅H₁₄F₂N [M⁺]: calcd 246.1089, found 246.1112.



III.1.ss
 Chemical Formula: C₁₅H₁₃F₂N
 Exact Mass: 245,10 g/mol
 Brown oil

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

a) 1,1-Difluoroacetone (2 equiv., 0.422 mL, 5.2 mmol); b) 2-(Phenylsulfanyl)aniline (1 equiv., 523 mg, 2.6 mmol); c) Anhydrous MgSO₄, for 12 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)-2-(phenylsulfanyl)aniline **III.1.tt** was obtained as a brown oil (796.1 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.34 – 7.20 (m, 6H, C₃, 9, 10, 11, 12, 13H), 7.09 (td, ³J_{H-H} = 7.65, ⁴J_{H-H} = 1.3 Hz, 2H, C₄, 5H), 6.69 (dd, ³J_{H-H} = 7.8, ⁴J_{H-H} = 1.1 Hz, 1H, C₆H), 6.01 (t, ²J_{H-F} = 55.5 Hz, 1H, C₇CHF₂), 1.78 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.06 (d, ²J_{F-H} = 55.4 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.78 (t, ²J_{C-F} = 28.9 Hz, C₇), 148.85 (s, C₁), 136.88 (s, C₈), 134.64 (s, C₂), 132.37 - 127.42 (m, C₃, 9, 10, 11, 12, 13), 126.57 (s, C₅), 125.43 (s, C₄), 118.87 (s, C₆), 114.45 (t, ¹J_{C-F} = 243.3 Hz, C₇CHF₂), 13.04 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₅H₁₄F₂NS [M⁺]: calcd 278.0810, found 278.0781.



III.1.tt

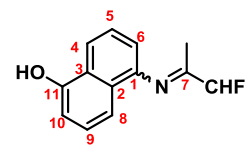
Chemical Formula: C₁₅H₁₃F₂NS

Exact Mass: 277,07 g/mol

Brown oil

***5*-[1,1-Difluoropropan-2-ylideneamino]-1-naphthol III.1.uu**

a) 1,1-Difluoroacetone (2 equiv., 0.509 mL, 6.28 mmol); b) 5-Amino-1-naphthol (1 equiv., 500 mg, 3.14 mmol); c) Anhydrous MgSO₄, for 14 h; and d) 5-[[1,1-Difluoropropan-2-ylideneamino]-1-naphthol **III.1.uu** was obtained as a purple solid in 91% yield, estimated (690 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.01 (d, ³J_{H-H} = 8.5 Hz, 1H, C₄H), 7.45 (t, ³J_{H-H} = 8.0 Hz, 1H, C₅H), 7.35 – 7.17 (m, 2H, C₈, 9H), 6.84 (d, ³J_{H-H} = 7.3 Hz, 1H, C₁₀H), 6.78 (d, ³J_{H-H} = 7.2 Hz, 1H, C₆H), 6.24 (t, ²J_{H-F} = 55.6 Hz, 1H, C₇CHF₂), 5.45 (br s, 1H, OH), 1.91 (s, 3H, C₇CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -120.84 (d, ²J_{F-H} = 55.5 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 165.18 (t, ²J_{C-F} = 28.9 Hz, C₇), 151.81 (s, C₁₁), 144.46 (s, C₁), 126.46 (s, C₂), 126.24 (s, C₉), 125.23 (s, C₃), 125.00 (s, C₅), 118.80 (s, C₄), 115.48 (s, C₈), 114.83 (t, ¹J_{C-F} = 243.3 Hz, C₇CHF₂), 114.07 (s, C₆), 109.46 (s, C₁₀), 13.18 (s, C₇CH₃) ppm. HRMS (ESI positive) for C₁₃H₁₂F₂NO [M⁺]: calcd 236.0881, found 236.0909.



III.1.uu

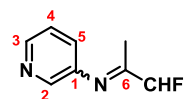
Chemical Formula: C₁₃H₁₁F₂NO

Exact Mass: 235,08 g/mol

Purple solid

***N*-(1,1-Difluoropropan-2-ylidene)pyridin-3-amine III.1.vv**

a) 1,1-Difluoroacetone (2 equiv., 1.72 mL, 21.3 mmol); b) 3-Pyridinamine (1 equiv., 1 g, 10.6 mmol); c) 4 Å MS, for 16 h; and d) *N*-(1,1-Difluoropropan-2-ylidene)pyridin-3-amine **III.1.vv** was obtained as a brown oil in 79% yield, estimated (1.42 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.43 (dd, ³J_{H-H} = 4.8, ⁴J_{H-H} = 1.5 Hz, 1H, C₃H), 8.12 (d, ⁴J_{H-H} = 2.3 Hz, 1H, C₂H), 7.31 (dd, ³J_{H-H} = 8.1, ³J_{H-H} = 4.8 Hz, 1H, C₅H), 7.13 (ddd, ³J_{H-H} = 8.1, ⁴J_{H-H} = 2.5, ⁴J_{H-H} = 1.6 Hz, 1H, C₄H), 6.05 (t, ²J_{H-F} = 55.4 Hz, 1H, C₆CHF₂), 1.97 (s, 3H, C₆CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -121.33 (d, ²J_{F-H} = 55.4 Hz, C₆CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 165.50 (t, ²J_{C-F} = 29.1 Hz, C₆), 145.98 (s, C₃), 144.36 (s, C₁), 140.05 (s, C₂), 126.86 (s, C₄), 123.83 (s, C₅), 114.30 (t, ¹J_{C-F} = 243.5 Hz, C₆CHF₂), 12.91 (s, C₆CH₃) ppm. HRMS (ESI positive) for C₈H₉F₂N₂ [M⁺]: calcd 171.0728, found 171.0726.



III.1.vv

Chemical Formula: C₈H₈F₂N₂

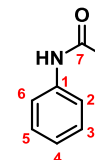
Exact Mass: 170,07 g/mol

Brown oil

2.2 From carboxylic anhydrides and oxalate derivatives

N-Phenylacetamide III.5

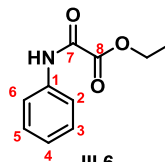
In a solution of *N*-(1,1-difluoropropan-2-ylidene)aniline **III.1.aa** (1 equiv., 210 mg, 1.25 mmol) in anhydrous MeCN (3.16 mL) at room temperature was added Ac₂O (1 equiv., 0.117 mL, 1.25 mmol). The reaction mixture was stirred for 2 h and then quenched with water. Organic layer was extracted with AcOEt, dried over Na₂SO₄ and concentrated under vacuum. *N*-phenylacetamide was obtained as a colourless solid in 91% yield (154 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.49 (d, ³J_{H-H} = 8.0 Hz, 2H, C_{2,6}H), 7.32 (t, ³J_{H-H} = 7.8 Hz, 2H, C_{3,5}H), 7.16 (s, 1H, NH), 7.11 (t, ³J_{H-H} = 7.4 Hz, 1H, C₄H), 2.18 (s, 3H, C₇CH₃) ppm.



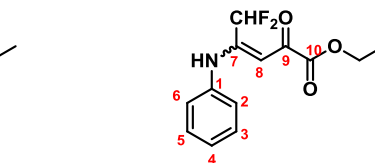
III.5
Chemical Formula: C₈H₉NO
Exact Mass: 135,07 g/mol
Colourless solid

Ethyl 2-oxo-2-(phenylamino)acetate III.6

A solution of ethyl oxalyl monochloride (1.1 equiv., 0.148 mL, 1.32 mmol) in MeCN (3.05 mL) was added to pyridine (1.5 equiv., 0.146 mL, 1.8 mmol) at room temperature. After 5 min of stirring, *N*-(1,1-difluoropropan-2-ylidene)aniline **III.1.aa** (1 equiv., 203 mg, 1.2 mmol) was



III.6
Chemical Formula: C₁₀H₁₁NO₃
Exact Mass: 193,07 g/mol
Brown solid

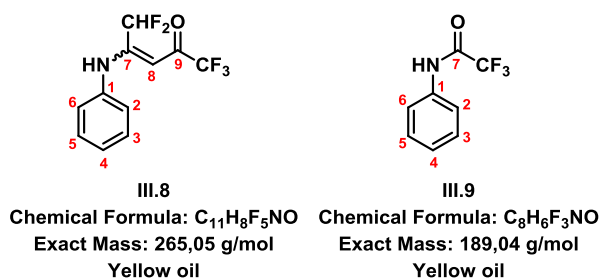


III.7
Chemical Formula: C₁₃H₁₃F₂NO₃
Exact Mass: 269,09 g/mol

added dropwise. The reaction mixture was stirred for 1.5 h and quenched with water. Organic layer was extracted with AcOEt, dried over Na₂SO₄ and concentrated under vacuum. After purification on flash chromatography using a gradient of AcOEt in cyclohexane, desired ethyl 5,5-difluoro-2-oxo-4-(phenylamino)pent-3-enoate **III.7** was obtained as minor fraction in mixture with unknown side product (26.3 mg) and ethyl 2-oxo-2-(phenylamino)acetate **III.6** was obtained as major fraction as brown solid in 65% yield (152 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.88 (s, 1H, NH), 7.79 – 7.55 (m, 2H, C_{2,6}H), 7.50 – 7.31 (m, 2H, C_{3,5}H), 7.21 – 7.08 (m, 1H, C₄H), 4.42 (q, ³J_{H-H} = 7.2 Hz, 2H, C₈OCH₂CH₃), 1.43 (t, ³J_{H-H} = 7.2 Hz, 3H, C₈OCH₂CH₃) ppm.

1,1,1,5,5-Pentafluoro-4-(phenylamino)pent-3-en-2-one III.8

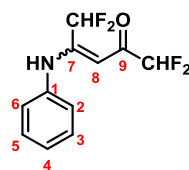
A solution of *N*-(1,1-difluoropropan-2-ylidene)aniline **III.1.aa** (1 equiv., 706 mg, 4.18 mmol) in dry MeCN (9.09 mL) was slowly added onto a solution of TFAA (2 equiv., 1.16 mL, 8.35 mmol) in MeCN (9.09 mL) via a syringe under argon at room temperature. The reaction mixture was stirred at 50 °C for 19 h, and then MeCN was removed under reduced pressure. The mixture was purified by flash chromatography using a gradient of AcOEt in pentane (0-5%). Two compounds were isolated, the:



- 2,2,2-Trifluoro-*N*-phenylacetamide **III.9** as a yellow oil in 15% yield (120 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.92 (s, 1H, NH), 7.64 – 7.51 (m, 2H, C_{2,6}H), 7.46 – 7.32 (m, 2H, C_{3,5}H), 7.29 – 7.20 (m, 1H, C₄H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -75.74 (s, C₇CF₃) ppm.
- 1,1,1,5,5-Pentafluoro-4-(phenylamino)pent-3-en-2-one **III.8** as a yellow oil in 49% yield (548 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 12.03 (s, 1H, NH), 7.49 – 7.43 (m, 2H, C_{3,5}H), 7.42 – 7.35 (m, 1H, C₄H), 7.26 – 7.21 (m, 2H, C_{2,6}H), 6.24 (t, ²J_{H-F} = 52.7 Hz, 1H, C₇CHF₂), 6.01 (s, 1H, C₈H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -77.23 (s, C₉CF₃), -118.34 (d, ²J_{F-H} = 52.7 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 180.42 (q, ²J_{C-F} = 34.9 Hz, C₉), 157.95 (t, ²J_{C-F} = 25.1 Hz, C₇), 135.44 (s, C₁), 130.05 (s, C_{3,5}), 128.57 (s, C₄), 125.59 (s, C_{2,6}), 116.82 (q, ¹J_{C-F} = 288.3 Hz, C₉CF₃), 108.02 (t, ¹J_{C-F} = 243.0 Hz, C₇CHF₂), 86.95 (td, ³J_{C-F1} = 5.5, ³J_{C-F2} = 1.0 Hz, C₈) ppm. IR ν (cm⁻¹): 3675 (NH), 2988-2901 (CH_{sp2}H), 1638-1581 (C=C, C=O_{ketone}). C₁₁H₈F₅NO (265): calcd: N 5.28, C 49.82, H 3.04, found: N 5.18, C 49.49, H 3.07. HRMS (ESI positive) for C₁₁H₈F₅NO [M⁺]: calcd 266.0599, found 266.0595.

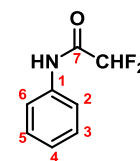
1,1,5,5-Tetrafluoro-4-(phenylamino)pent-3-en-2-one III.10

A solution of 2,2-difluoroacetyl 2,2-difluoroacetate (1 equiv., 0.151 mL, 1.21 mmol) and pyridine (1.5 equiv., 0.147 mL, 1.82 mmol) was added dropwise at room temperature in a solution of *N*-(1,1-difluoropropan-2-ylidene)aniline **III.1.a** (1 equiv., 205 mg, 1.21 mmol) in MeCN (3.08 mL). The reaction mixture was stirred for 1.5 h. The mixture was then quenched with water and organic layer was extracted with AcOEt, dried over Na₂SO₄ and evaporated under vacuum. It was purified on flash chromatography using a gradient of AcOEt in cyclohexane (0-10%). Two compounds were isolated, the:



III.10

Chemical Formula: C₁₁H₉F₄NO
Exact Mass: 247,06 g/mol
Brown oil



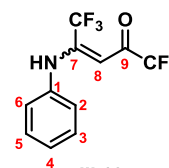
III.11

Chemical Formula: C₈H₇F₂NO
Exact Mass: 171,05 g/mol
beige solid

- ➔ 1,1,5,5-Tetrafluoro-4-(phenylamino)pent-3-en-2-one **III.10** as a brown oil in 29% yield (87.6 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 12.05 (s, 1H, NH), 7.47 – 7.40 (m, 2H, C_{3,5}H), 7.38 – 7.32 (m, 1H, C₄H), 7.23 (d, ³J_{H-H} = 7.7 Hz, 2H, C_{2,6}H), 6.24 (t, ²J_{H-F} = 52.9 Hz, 1H, C₇CHF₂), 6.02 (s, 1H, C₈H), 5.86 (t, ²J_{H-F} = 54.7 Hz, 1H, C₉CHF₂) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -118.07 (dd, ²J_{F-H} = 52.9, ⁴J_{F-H} = 2.0 Hz, C₇CHF₂), -125.69 (d, ²J_{F-H} = 54.8 Hz, C₉CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 188.18 (t, ²J_{C-F} = 24.6 Hz, C₉), 156.56 (t, ²J_{C-F} = 24.9 Hz, C₇), 135.93 (s, C₁), 129.94 (s, C_{3,5}), 128.12 (s, C₄), 125.54 (s, C_{2,6}), 110.29 (t, ¹J_{C-F} = 251.4 Hz, C₉CHF₂), 108.37 (t, ¹J_{C-F} = 243.4 Hz, C₇CHF₂), 87.67 (t, ³J_{C-F} = 5.6 Hz, C₈) ppm. IR ν (cm⁻¹): 2989-2869 (CH_{sp2}H), 1636-1578 (C=C, C=O_{ketone}). HRMS (ESI positive) for C₁₁H₁₀F₄NO [M⁺]: calcd 248.0693, found 248.0666.
- ➔ 2,2-Difluoro-*N*-phenylacetamide **III.11** as a beige solid in 64% yield (133 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.90 (s, 1H, NH), 7.62 – 7.53 (m, 2H, C_{2,6}H), 7.43 – 7.34 (m, 2H, C_{3,5}H), 7.24 – 7.17 (m, 1H, C₄H), 6.02 (t, ²J_{H-F} = 54.4 Hz, 1H, C₇CHF₂) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -125.51 (dd, ²J_{F-H} = 54.4, 2.4 Hz, C₇CHF₂) ppm.

1,1,1,5,5,5-Hexafluoro-4-(phenylamino)pent-3-en-2-one III.12

A solution of *N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.a** (1 equiv., 500 mg, 2.68 mmol) in dry MeCN (5 mL) was slowly added onto a solution of TFAA (2 equiv., 0.745 mL, 5.35 mmol) in MeCN (5 mL) via a syringe under argon at room temperature. The reaction mixture was stirred at 50 °C for 19 h, and then MeCN was removed under reduced pressure. The mixture was purified by flash chromatography using a gradient of AcOEt in pentane (0-5%). 1,1,1,5,5,5-hexafluoro-4-(phenylamino)pent-3-en-2-one **III.12** was obtained as a yellow solid, which become liquid around 37 °C, in 65% yield (0.496 g). ¹H NMR (400 MHz, CDCl₃) δ_H = 11.91 (s, 1H, NH), 7.55 – 7.32 (m, 3H, C_{3,4,5}H), 7.35 – 7.13 (m, 2H, C_{2,6}H), 6.04 (s, 1H, C₈) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -63.62 (s, C₇CF₃), -77.32 (s, C₉CF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 180.67 (q, ²J_{C-F} = 35.5 Hz, C₉), 153.25 (q, ²J_{C-F} = 32.8 Hz, C₇), 136.13 (s, C₁), 129.47 (s, C_{2,6}), 128.73 (s, C_{3,5}), 126.31 (s, C₄), 119.15 (q, ¹J_{C-F} = 279.0 Hz, C₇CF₃), 116.62 (q, ¹J_{C-F} = 289.9 Hz, C₉CF₃), 88.18 – 87.86 (m, C₈) ppm. HRMS (ESI positive) for C₁₁H₆F₆NO [M⁺]: calcd 282.0359, found 282.0369.

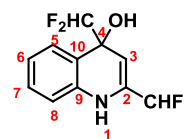


III.12

Chemical Formula: C₁₁H₇F₆NO
Exact Mass: 283,04 g/mol
Yellow solid

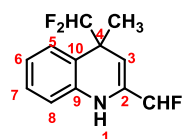
Analysis of unexpected side products:

- Traces of 2,4-bis(difluoromethyl)-1,4-dihydroquinolin-4-ol **III.13** were observed. ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.24$ (dd, $^3J_{\text{H-H}} = 7.8$, $^4J_{\text{H-H}} = 1.5$ Hz, 1H, C₅H), 7.09 (td, $^3J_{\text{H-H}} = 7.8$, $^4J_{\text{H-H}} = 1.4$ Hz, 1H, C₆H), 6.70 (td, $^3J_{\text{H-H}} = 8.0$, $^4J_{\text{H-H}} = 1.2$ Hz, 1H, C₇H), 6.54 (dd, $^3J_{\text{H-H}} = 8.0$, $^4J_{\text{H-H}} = 1.2$ Hz, 1H, C₈H), 6.40 (td, $^2J_{\text{H-F}} = 54.7$, $^4J_{\text{H-F}} = 0.6$ Hz, 1H, C₂CHF₂), 5.76 (dd, $^2J_{\text{H-F1}} = 57.4$, $^2J_{\text{H-F2}} = 56.2$ Hz, 1H, C₄CHF₂), 5.74 (s, 1H, C₃H), 3.93 (s, 1H, NH), 1.55 (s, 1H, OH) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -116.52$ (dd, $^2J_{\text{F-H}} = 54.7$, $^4J_{\text{F-H}} = 8.2$ Hz, C₂CHF₂), -131.75 - -135.76 (m, C₄CHF₂) ppm.



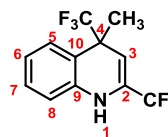
III.13
Chemical Formula: C₁₁H₉F₄NO
Exact Mass: 247,06 g/mol

- Traces of 2,4-bis(difluoromethyl)-4-methyl-1,4-dihydroquinoline **III.14** were observed. ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.25$ (dd, $^3J_{\text{H-H}} = 7.8$, $^4J_{\text{H-H}} = 1.5$ Hz, 1H, C₅H), 7.09 (td, $^3J_{\text{H-H}} = 8.0$, $^4J_{\text{H-H}} = 1.3$ Hz, 1H, C₇H), 6.71 (td, $^3J_{\text{H-H}} = 7.7$, $^4J_{\text{H-H}} = 1.1$ Hz, 1H, C₆H), 6.54 (dd, $^3J_{\text{H-H}} = 8.0$, $^4J_{\text{H-H}} = 0.8$ Hz, 1H, C₈H), 6.40 (t, $^2J_{\text{H-F}} = 54.7$ Hz, 1H, C₂CHF₂), 5.77 (dd, $^2J_{\text{H-F1}} = 57.4$, $^2J_{\text{H-F2}} = 56.2$ Hz, 1H, C₄CHF₂), 5.74 (s, 1H, C₃H), 3.93 (s, 1H, NH), 1.42 (t, $^4J_{\text{H-F}} = 1.2$ Hz, 3H, C₄CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -116.49$ (dd, $^2J_{\text{F-H}} = 54.7$, $^4J_{\text{F-H}} = 8.7$ Hz, C₂CHF₂), -132.03 - -135.36 (m, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 142.23$ (s, C₉), 131.79 (t, $^2J_{\text{C-F}} = 20.5$ Hz, C₂), 130.51 (s, C₇), 129.94 (s, C₁₀), 124.68 (t, $^4J_{\text{C-F}} = 1.7$ Hz, C₅), 123.10 (tdd, $^4J_{\text{C-F1}} = 9.9$, $^4J_{\text{C-F2}} = 4.3$, $^4J_{\text{C-F}} = 1.4$ Hz, C₃), 118.64 (s, C₆), 118.27 - 112.26 (m, C₄CHF₂), 114.14 (t, $^1J_{\text{C-F}} = 240.4$ Hz, C₂CHF₂), 113.88 (s, C₈), 57.14 - 56.45 (m, C₄), 20.96 (d, $^3J_{\text{C-F}} = 1.5$ Hz, C₄CH₃) ppm. HRMS (ESI positive) for C₁₂H₁₁F₄N [M⁺]: calcd 246.0900, found 246.0898.



III.14
Chemical Formula: C₁₂H₁₁F₄N
Exact Mass: 245,08 g/mol

- Traces of 4-methyl-2,4-bis(trifluoromethyl)-1,4-dihydroquinoline **III.15** were observed. ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.25$ (d, $^3J_{\text{H-H}} = 8.1$ Hz, 1H, C₅H), 7.09 (t, $^3J_{\text{H-H}} = 7.7$ Hz, 1H, C₇H), 6.70 (t, $^3J_{\text{H-H}} = 7.6$ Hz, 1H, C₆H), 6.52 (d, $^3J_{\text{H-H}} = 8.0$ Hz, 1H, C₈H), 5.96 (s, 1H, C₃H), 4.01 (s, 1H, NH), 1.53 (s, 3H, C₄CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -64.80$ (s, C₂CF₃), -83.21 (s, C₄CF₃) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 141.88$ (s, C₉), 131.00 (s, C₇), 130.09 (q, $^2J_{\text{C-F}} = 31.3$ Hz, C₂), 129.36 (s, C₁₀), 125.40 (q, $^4J_{\text{C-F}} = 2.3$ Hz, C₅), 125.33 (q, $^1J_{\text{C-F}} = 288.9$ Hz, C₄CF₃), 122.72 (q, $^1J_{\text{C-F}} = 275.7$ Hz, C₂CF₃), 121.32 (q, $^3J_{\text{C-F}} = 6.0$ Hz, C₃), 118.98 (s, C₆), 113.72 (s, C₈), 58.06 (q, $^2J_{\text{C-F}} = 28.9$ Hz, C₄), 23.80 (s, C₄CH₃) ppm. HRMS (ESI positive) for C₁₂H₁₀F₆N [M⁺]: calcd 282.0712, found 282.0727.



III.15
Chemical Formula: C₁₂H₉F₆N
Exact Mass: 281,06 g/mol

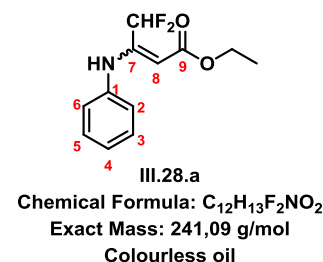
2.3 From fluorinated acetoacetate

The following experiments were carried out according to *Typical Procedure A*. Data are reported as: a) Commercially available perfluoroacetone; b) aniline derivatives; c) desiccant and time; and d) yield and aspect.

Individual analysis for each compound (**III.28**) is given below.

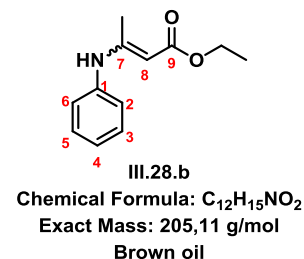
Ethyl-4,4-difluoro-3-(phenylamino)but-2-enoate III.28.a

a) Ethyl-4,4-difluoroacetoacetate (1 equiv., 8.43 mL, 64.4 mmol); b) Aniline (1 equiv., 5.87 mL, 64.4 mmol); c) 4 Å MS, for 4 h; and d) Ethyl-4,4-difluoro-3-(phenylamino)but-2-enoate **III.28.a** was obtained in 36% yield (5.63 g) as colourless oil after purification by column chromatography using a gradient of AcOEt in pentane (2-98%) and aspect. Compound can be used directly without any further purification to avoid its degradation on silica gel column. ¹H NMR (400 MHz, CDCl₃) δ_H = 9.93 (s, 1H, NH), 7.36 (t, ³J_{H-H} = 7.8 Hz, 2H, C_{3,5}H), 7.22 (t, ³J_{H-H} = 7.4 Hz, 1H, C₄H), 7.15 (d, ³J_{H-H} = 7.6 Hz, 2H, C_{2,6}H), 6.21 (t, ²J_{H-F} = 53.3 Hz, 1H, C₇CHF₂), 5.26 (s, 1H, C₈H), 4.20 (q, ³J_{H-H} = 7.1 Hz, 2H, C₉OCH₂CH₃), 1.31 (t, ³J_{H-H} = 7.1 Hz, 3H, C₉OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -117.33 (dd, ²J_{F-H} = 53.3, ⁴J_{F-H} = 1.8 Hz, C₇CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 170.31 (s, C₉), 151.37 (t, ²J_{C-F} = 23.2 Hz, C₇), 138.00 (s, C₁), 129.61 (s, C_{3,5}), 126.19 (s, C₄), 124.83 (s, C_{2,6}), 109.51 (t, ¹J_{C-F} = 241.5 Hz, C₇CHF₂), 86.73 (t, ³J_{C-F} = 7.0 Hz, C₈), 59.88 (s, C₉OCH₂CH₃), 14.49 (s, C₉OCH₂CH₃). HRMS (ESI positive) for C₁₂H₁₄F₂NO₂ [M⁺]: calcd 242.0987, found 242.0972.



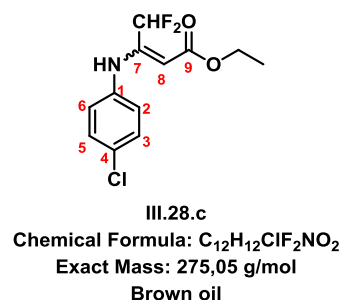
Ethyl-3-(phenylamino)but-2-enoate III.28.b

a) Ethyl-3-oxobutanoate (1 equiv., 8.14 mL, 64.4 mmol); b) aniline (1 equiv., 5.87 mL, 64.4 mmol); c) 4 Å MS, for 24 h; and d) Ethyl-3-(phenylamino)but-2-enoate **III.28.b** was obtained in 95% yield (12.6 g) as a brown oil. ¹H NMR (400 MHz, CDCl₃) δ_H = 10.38 (s, 1H, NH), 7.36 – 7.28 (m, 2H, C_{3,5}H), 7.19 – 7.12 (m, 1H, C₄H), 7.11 – 7.06 (m, 2H, C_{2,6}H), 4.69 (m, 1H, C₈H), 4.15 (q, ³J_{H-H} = 7.1 Hz, 2H, C₉OCH₂CH₃), 2.00 (m, 3H, C₇CH₃), 1.29 (t, ³J_{H-H} = 7.1 Hz, 3H, C₉OCH₂CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 170.35 (s, C₉), 158.85 and 158.83 (d, iso¹ - iso², C₇), 139.34 (s, C₁), 129.03 (s, C_{3,5}), 124.86 (s, C₄), 124.34 and 124.32 (d, iso¹ - iso², C_{2,6}), 86.10 (s, C₈), 58.69 (s, C₉OCH₂CH₃), 20.25 and 20.24 (d, iso¹ - iso², C₇CH₃), 14.57 (s, C₉OCH₂CH₃) ppm.

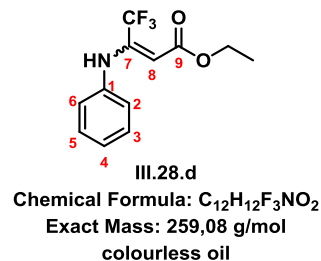


Ethyl-3-[(4-chlorophenyl)amino]-4,4-difluorobut-2-enoate III.28.c

a) Ethyl-4,4-difluoroacetoacetate (2 equiv., 10.4 g, 8.16 mL, 62.3 mmol); b) *p*-Chloroaniline (1 equiv., 3.98 g, 31.2 mmol); c) 4 Å MS, for 21 h; and d) Ethyl-3-[(4-chlorophenyl)amino]-4,4-difluorobut-2-enoate **III.28.c** was obtained in 90% yield (7.76 g) as a brown oil with an estimated purity around 75%. ^1H NMR (400 MHz, CDCl_3) δ_{H} = 9.85 (s, 1H, NH), 7.31 (d, $^3J_{\text{H-H}} = 8.7$ Hz, 2H, C_{3,5}H), 7.09 (d, $^3J_{\text{H-H}} = 8.6$ Hz, 2H, C_{2,6}H), 6.15 (t, $^2J_{\text{H-F}} = 53.3$ Hz, 1H, C₇CHF₂), 5.25 (s, 1H, C₈H), 4.20 (q, $^3J_{\text{H-H}} = 7.1$ Hz, 2H, C₉OCH₂CH₃), 1.31 (t, $^3J_{\text{H-H}} = 7.1$ Hz, 3H, C₉OCH₂CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -116.93 (dd, $^2J_{\text{F-H}} = 53.3$, $^4J_{\text{F-H}} = 1.2$ Hz, C₇CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 170.22 (s, C₉), 150.88 (t, $^2J_{\text{C-F}} = 22.9$ Hz, C₇), 136.71 (s, C₄), 131.80 (s, C₁), 129.70 (s, C_{3,5}), 126.15 (s, C_{2,6}), 109.81 (t, $^1J_{\text{C-F}} = 242.0$ Hz, C₇CHF₂), 87.87 (t, $^3J_{\text{C-F}} = 7.2$ Hz, C₈), 60.06 (s, C₉OCH₂CH₃), 14.47 (s, C₉OCH₂CH₃) ppm. HRMS (ESI positive) for C₁₂H₁₃ClF₂NO₂ [M⁺]: calcd 276.0597, found 276.0605.

**Ethyl-4,4,4-trifluoro-3-(phenylamino)but-2-enoate III.28.d⁴²³**

A mixture of ethyl 4,4,4-trifluoroacetoacetate (1 equiv., 1.58 mL, 10.7 mmol) and aniline (1 equiv., 0.98 mL, 10.7 mmol) were put under reflux in acetic acid (1 equiv., 0.615 mL, 10.7 mmol) for 3 h. The reaction mixture was quenched by addition of saturated solution of sodium bicarbonate (NaHCO_3), extracted with ether, dried over Na_2SO_4 , and concentrated in vacuum. The mixture was purified by column chromatography, using a mixture of AcOEt in pentane (2-98%) to provide the ethyl-4,4,4-trifluoro-3-(phenylamino)but-2-enoate **III.28.d** as colourless oil in 19% yield (530 mg). Both form imine-enamine were observed by NMR analysis, however the imine form was not stable and rapidly degraded into the enamine form. **ENAMINE form** ^1H NMR (400 MHz, CDCl_3) δ_{H} = 9.84 (s, 1H, NH), 7.37 – 7.30 (m, 2H, C_{3,5}H), 7.28 – 7.22 (m, 1H, C₄H), 7.21 – 7.17 (m, 2H, C_{2,6}H), 5.35 (s, 1H, C₈H), 4.22 (q, $^3J_{\text{H-H}} = 7.1$ Hz, 2H, C₉OCH₂CH₃), 1.32 (t, $^3J_{\text{H-H}} = 7.1$ Hz, 3H, C₉OCH₂CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -63.33 (s, C₇CF₃) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 169.81 (s, C₉), 147.29 (q, $^2J_{\text{C-F}} = 31.4$ Hz, C₇), 138.50 (s, C₁), 129.08 (s, C_{3,5}), 126.76 (s, C₄), 126.13 (q, $^5J_{\text{C-F}} = 1.5$ Hz, C_{2,6}), 120.37 (q, $^1J_{\text{C-F}} = 277.4$ Hz, C₇CF₃), 88.67 (q, $^3J_{\text{C-F}} = 5.4$ Hz, C₈), 60.26 (s, C₉OCH₂CH₃), 14.44 (s, C₉OCH₂CH₃) ppm. **IMINE form** ^1H NMR (400 MHz, CDCl_3) δ_{H} = 7.40 – 7.32 (m, 2H, C_{3,5}H), 7.20 – 7.14 (m, 1H, C₄H), 6.88 – 6.82 (m, 2H, C_{2,6}H), 4.15 (q, $^3J_{\text{H-H}} = 7.0$ Hz, 2H, C₉OCH₂CH₃), 3.41 (s, 2H, C₈H), 1.24 (t, $^3J_{\text{H-H}} = 7.1$ Hz, 3H, C₉OCH₂CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -72.64 (s, C₇CF₃) ppm.



3 QUINOLINE DERIVATIVES SYNTHESIS

3.1 Typical procedure B for the synthesis of quinoline derivatives (III.2)

Under argon atmosphere, a solution of the desired FAR (1,1,2,2-tetrafluoro-*N,N*-dimethylethan-1-amine (**A.1**; TFEDMA), 2-chloro-*N,N*-diethyl-1,1,2-trifluoroethan-1-amine (**B.1**; Yarovenko reagent), and *N,N*-diethyl-1,1,2,3,3,3-hexafluoropropan-1-amine (**C.1**; Ishikawa reagent) (1.2 equiv.) was activated by adding boron trifluoride diethyl etherate (BF₃•Et₂O) (1.2 equiv.) in dry MeCN (3.6 mmol/5 mL) and stirred for 15 min. Then a solution of the desired imine derivative (**III.1**) (1 equiv.) in dry MeCN (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. MeCN was removed under reduced pressure and the reaction mixture was purified by flash chromatography using a gradient of AcOEt in pentane to provide the final compound (**III.2**).

The following experiments were carried out according to *Typical Procedure B*. Data are reported as: a) FAR; b) BF₃•Et₂O; c) Imine (**III.1**); and d) yield and aspect.

Individual analysis for each compound (**III.2**) is given below.

3.1.1 From fluorinated ketone (III.2.a-m)

4-(Difluoromethyl)-2-(trifluoromethyl)quinoline III.2.aA

a) TFEDMA **A.1** (1.2 equiv., 0.42 mL, 3.61 mmol); b) BF₃•Et₂O (1.2 equiv., 0.46 mL, 3.61 mmol); c) *N*-(1,1,1-Trifluoropropan-2-ylidene)aniline **III.1.a** (1 equiv., 562 mg, 3.01 mmol); and d) 4-(Difluoromethyl)-2-(trifluoromethyl)quinoline **III.2.aA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 62% yield (458 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.33

(d, ³J_{H-H} = 8.5 Hz, 1H, C₈H), 8.16 (d, ³J_{H-H} = 8.5 Hz, 1H, C₅H), 7.93 (s, 1H, C₃H), 7.92 – 7.87 (m, 1H, C₇H), 7.80 (t, ³J_{H-H} = 7.7 Hz, 1H, C₆H), 7.22 (t, ²J_{H-F} = 54.2 Hz, 1H, C₄CHF₂) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -67.66 (s, C₂CF₃), -115.53 (d, ²J_{F-H} = 54.1 Hz, C₄CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 147.94 (q, ²J_{C-F} = 35.3 Hz, C₂), 147.87 (t, C₉), 140.33 (t, ²J_{C-F} = 22.3 Hz, C₄), 131.39 (s, C₇), 131.29 (s, C₈), 130.06 (s, C₆), 125.09 (s, C₁₀), 123.44 (s, C₅), 121.33 (q, ¹J_{C-F} = 275.73 Hz, C₂CF₃), 114.14 (td, ³J_{C-F} = 7.9, ³J_{C-F} = 2.1 Hz, C₃), 112.74 (t, ¹J_{C-F} = 241.5 Hz, C₄CHF₂) ppm. HRMS (ESI positive) for C₁₁H₇F₅N [M⁺]: 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.



III.2.aA

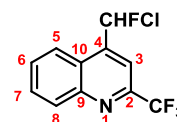
Chemical Formula: C₁₁H₆F₅N

Exact Mass: 247,04 g/mol

Yellow solid

4-[Chloro(fluoro)methyl]-2-(trifluoromethyl)quinoline III.2.aB

a) Yarovenko's reagent **B.1** (1.2 equiv., 0.73 mL, 3.21 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.41 mL, 3.21 mmol); c) *N*-(1,1,1-Trifluoropropan-2-ylidene)aniline **III.1.a** (1 equiv., 500 mg, 2.67 mmol); and d) 4-[Chloro(fluoro)methyl]-2-(trifluoromethyl)quinoline **III.2.aB** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a light yellow solid in 57% yield (402 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.32$ (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C₈H), 8.13 (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, C₅H), 7.95 (s, 1H, C₃H), 7.92 – 7.88 (m, 1H, C₇H), 7.81 – 7.77 (m, 1H, C₆H), 7.66 (d, $^2J_{\text{H-F}} = 48.9$ Hz, 1H, C₄CHFCl) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -67.65$ (s, C₂CF₃), -138.75 (d, $^2J_{\text{F-H}} = 48.9$ Hz, C₄CHFCl) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 148.02$ (q, $^2J_{\text{C-F}} = 35.4$ Hz, C₂), 147.88 (s, C₉), 143.82 (d, $^2J_{\text{C-F}} = 21.1$ Hz, C₄), 131.40 (s, C₇), 131.31 (s, C₈), 129.82 (s, C₆), 124.03 (d, $^3J_{\text{C-F}} = 3.6$ Hz, C₁₀), 123.08 (s, C₅), 121.34 (q, $^1J_{\text{C-F}} = 275.4$ Hz, C₂CF₃), 113.04 (dq, $^3J_{\text{C-F}} = 9.9$, $^3J_{\text{C-F}} = 2.0$ Hz, C₃), 96.75 (d, $^1J_{\text{C-F}} = 244.6$ Hz, C₄CHFCl) ppm. HRMS (ESI positive) for C₁₁H₇F₄NCl [M⁺]: calcd 264.0198, found 264.0231. C₁₁H₆F₄NCl (263): calcd (%) N 5.31, C 50.07, H 2.27, found N 5.11, C 50.19, H 2.65. MP: 49.4 – 50.4 °C.

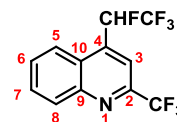
**III.2.aB**Chemical Formula: C₁₁H₆ClF₄N

Exact Mass: 263,01 g/mol

Light yellow solid

4-(1,2,2,2-Tetrafluoroethyl)-2-(trifluoromethyl)quinoline III.2.aC

a) Ishikawa's reagent **C.1** (1.2 equiv., 0.95 mL, 3.26 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.41 mL, 3.26 mmol); c) *N*-(1,1,1-Trifluoropropan-2-ylidene)aniline **III.1.a** (1 equiv., 508 mg, 2.71 mmol); and d) 4-(1,2,2,2-Tetrafluoroethyl)-2-(trifluoromethyl)quinoline **III.2.aC** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a light brown solid in 14% yield, estimated (112 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.32$ (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C₈H), 7.99 – 7.97 (m, 2H, C₃, 5H), 7.89 (t, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C₇H), 7.78 (t, $^3J_{\text{H-H}} = 8.3$ Hz, 1H, C₆H), 6.46 (dq, $^2J_{\text{H-F}} = 43.9$, $^3J_{\text{H-F}} = 5.5$ Hz, C₄CHF₂CF₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -67.72$ (s, C₂CF₃), -77.25 (dd, $^3J_{\text{F-F}} = 13.1$, $^3J_{\text{F-H}} = 5.8$ Hz, C₄CHF₂CF₃), -198.87 (dq, $^2J_{\text{F-H}} = 44.3$, $^3J_{\text{F-F}} = 12.8$ Hz, C₄CHF₂CF₃) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 147.72$ (q, $^2J_{\text{C-F}} = 35.4$ Hz, C₂), 147.51 (s, C₉), 137.94 (d, $^2J_{\text{C-F}} = 19.1$ Hz, C₄), 131.34 (s, C₇), 131.16 (s, C₈), 130.06 (s, C₆), 125.89 (d, $^3J_{\text{C-F}} = 3.7$ Hz, C₁₀), 122.72 (s, C₅), 121.91 (q, $^1J_{\text{C-F}} = 282.6$ Hz, C₄CHF₂CF₃), 121.68 (q, $^1J_{\text{C-F}} = 282.6$ Hz, C₂CF₃), 115.77 (d, $^3J_{\text{C-F}} = 10.4$ Hz, C₃), 85.41 (dq, $^1J_{\text{C-F}} = 189.9$, $^2J_{\text{C-F}} = 36.1$ Hz, C₄CHF₂CF₃) ppm. HRMS (ESI positive) for C₁₁H₇F₇N [M⁺]: calcd 298.0461, found 298.0462. C₁₂H₆F₇N (297): calcd (%) N 4.71, C 48.45, H 2.02, found N 4.71, C 48.80, H 2.32. MP: 58 – 58.8 °C.

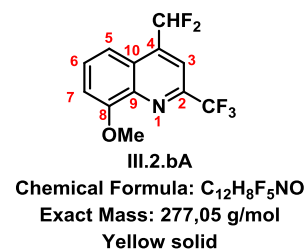
**III.2.aC**Chemical Formula: C₁₂H₆F₇N

Exact Mass: 297,04 g/mol

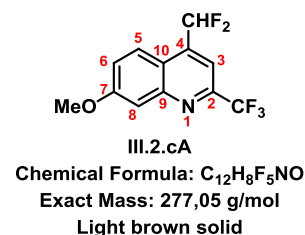
Light brown solid

4-(Difluoromethyl)-8-methoxy-2-(trifluoromethyl)quinoline III.2.bA

a) TFEDMA **A.1** (1.2 equiv., 0.33 mL, 2.82 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.357 mL, 2.82 mmol); c) 2-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.b** (1 equiv., 510 mg, 2.35 mmol); and d) 4-(Difluoromethyl)-8-methoxy-2-(trifluoromethyl)quinoline **III.2.bA** was obtained after purification using a gradient of AcOEt in pentane (10-25%) as a yellow solid in 88% yield (575 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.97$ (s, 1H, C_5H), 7.74 – 7.63 (m, 2H, $\text{C}_6, \text{C}_7\text{H}$), 7.21 (d, $^4J_{\text{H-F}} = 7.8$ Hz, 1H, C_3H), 7.20 (t, $^2J_{\text{H-F}} = 54.3$ Hz, 1H, C_4CHF_2), 4.12 (s, 3H, C_8OCH_3) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -67.16$ (s, C_2CF_3), -116.17 (d, $^2J_{\text{F-H}} = 54.4$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 156.58$ (s, C_8), 146.50 (q, $^2J_{\text{C-F}} = 35.7$ Hz, C_2), 140.11 (t, $^2J_{\text{C-F}} = 22.2$ Hz, C_4), 139.95 (s, C_9), 130.74 (s, C_6), 126.43 (s, C_{10}), 121.40 (q, $^1J_{\text{C-F}} = 275.2$ Hz, C_2CF_3), 114.70 – 114.16 (m, C_5, C_7), 112.55 (t, $^1J_{\text{C-F}} = 241.5$ Hz, C_4CHF_2), 109.56 (s, C_3), 56.58 (s, C_8OCH_3) ppm. $\text{C}_{12}\text{H}_8\text{F}_5\text{NO}$ (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.

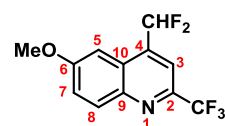
**4-(Difluoromethyl)-7-methoxy-2-(trifluoromethyl)quinoline III.2.cA**

a) TFEDMA **A.1** (1.2 equiv., 0.324 mL, 2.77 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.35 mL, 2.77 mmol); c) 3-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.c** (1 equiv., 500 mg, 2.3 mmol); and d) 4-(Difluoromethyl)-7-methoxy-2-(trifluoromethyl)quinoline **III.2.cA** was obtained after purification using a gradient of AcOEt in pentane (10-25%) as a light brown solid in 64% yield (407 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.00$ (d, $^3J_{\text{H-H}} = 9.3$ Hz, 1H, C_5H), 7.76 (s, 1H, C_3H), 7.57 (d, $^4J_{\text{H-H}} = 2.6$ Hz, 1H, C_8H), 7.39 (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-H}} = 2.6$ Hz, 1H, C_6H), 7.14 (t, $^2J_{\text{H-F}} = 54.3$ Hz, 1H, C_4CHF_2), 3.97 (s, 3H, C_7OCH_3) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -67.74$ (s, C_2CF_3), -115.04 (d, $^2J_{\text{F-H}} = 54.4$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 161.92$ (s, C_7), 150.09 (s, C_9), 148.04 (q, $^2J_{\text{C-F}} = 35.2$ Hz, C_2), 140.01 (t, $^2J_{\text{C-F}} = 22.4$ Hz, C_4), 124.36 (s, C_5), 123.61 (s, C_6), 121.26 (q, $^1J_{\text{C-F}} = 275.2$ Hz, C_2CF_3), 120.32 (t, $^3J_{\text{C-F}} = 2.8$ Hz, C_{10}), 112.86 (t, $^1J_{\text{C-F}} = 241.4$ Hz, C_4CHF_2), 111.81 (td, $^3J_{\text{C-F}} = 8.0$, $^3J_{\text{C-F}} = 2.3$ Hz, C_3), 108.56 (s, C_8), 55.91 (s, C_7OCH_3) ppm. $\text{C}_{12}\text{H}_8\text{F}_5\text{NO}$ (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 III.2.dA

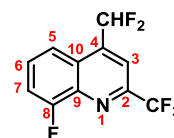
a) TFEDMA **A.1** (1.2 equiv., 0.325 mL, 2.78 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.352 mL, 2.78 mmol); c) 4-Methoxy-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.d** (1 equiv., 502 mg, 2.31 mmol); and d) 4-(Difluoromethyl)-6-methoxy-2-(trifluoromethyl)quinoline **III.2.dA** was obtained after purification using a gradient of AcOEt in pentane (10-25%) as a brown solid in 85% yield (543 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.16 (d, $^3J_{\text{H-H}} = 9.3$ Hz, 1H, C₈H), 7.85 (s, 1H, C₃H), 7.50 (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-H}} = 2.6$ Hz, 1H, C₇H), 7.29 (s, 1H, C₅H), 7.11 (t, $^2J_{\text{H-F}} = 54.3$ Hz, 1H, C₄CHF₂), 3.97 (s, 3H, C₆OCH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -67.30 (s, C₂CF₃), -115.95 (d, $^2J_{\text{F-H}} = 54.4$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 160.35 (s, C₆), 144.95 (q, $^2J_{\text{C-F}} = 35.4$ Hz, C₂), 144.11 (s, C₉), 138.21 (t, $^2J_{\text{C-F}} = 22.1$ Hz, C₄), 132.56 (s, C₈), 126.63 (s, C₁₀), 124.40 (s, C₇), 121.43 (q, $^1J_{\text{C-F}} = 274.7$ Hz, C₂CF₃), 114.59 (td, $^3J_{\text{C-F}} = 8.1$, $^3J_{\text{C-F}} = 2.3$ Hz, C₃), 113.17 (t, $^1J_{\text{C-F}} = 241.1$ Hz, C₄CHF₂), 101.06 (s, C₅), 55.88 (s, C₆OCH₃) 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.



III.2.dA
 Chemical Formula: C₁₂H₈F₅NO
 Exact Mass: 277,05 g/mol
 Brown solid

4-(Difluoromethyl)-8-fluoro-2-(trifluoromethyl)quinoline III.2.eA

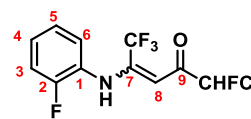
TFEDMA **A.1** (1.2 equiv., 0.347 mL, 2.97 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.376 mL, 2.97 mmol); c) 2-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.e** (1 equiv., 507 mg, 2.47 mmol); and d) 4-(Difluoromethyl)-8-fluoro-2-(trifluoromethyl)quinoline **III.2.eA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as an orange solid in 70% yield (466 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 7.99 (s, 1H, C₃H), 7.94 (d, $^3J_{\text{H-H}} = 8.6$ Hz, 1H, C₅H), 7.76 (td, $^3J_{\text{H-H}} = 8.2$, $^4J_{\text{H-F}} = 5.0$ Hz, 1H, C₆H), 7.63 – 7.55 (m, 1H, C₇H), 7.20 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C₄CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -67.64 (s, C₂CF₃), -115.74 (d, $^2J_{\text{F-H}} = 54.2$ Hz, C₄CHF₂), -119.97 (dd, $^3J_{\text{F-H}} = 10.5$, $^4J_{\text{F-H}} = 5.4$ Hz, C₈F) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 158.51 (d, $^1J_{\text{C-F}} = 261.9$ Hz, C₈), 147.96 (qd, $^2J_{\text{C-F}} = 34.4$ Hz, $^4J_{\text{C-F}} = 1.7$ Hz, C₂), 140.33 (td, $^2J_{\text{C-F}} = 22.6$, $^4J_{\text{C-F}} = 2.9$ Hz, C₄), 138.40 (d, $^2J_{\text{C-F}} = 12.2$ Hz, C₉), 130.35 (d, $^3J_{\text{C-F}} = 8.1$ Hz, C₆), 126.50 (s, C₁₀), 120.95 (q, $^1J_{\text{C-F}} = 275.5$ Hz, C₂CF₃), 119.25 (d, $^4J_{\text{C-F}} = 5.3$ Hz, C₅), 115.90 (d, $^2J_{\text{C-F}} = 18.6$ Hz, C₇), 115.20 (t, $^3J_{\text{C-F}} = 7.5$ Hz, C₃), 112.48 (t, $^1J_{\text{C-F}} = 241.9$ Hz, C₄CHF₂) 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.



III.2.eA
 Chemical Formula: C₁₁H₅F₆N
 Exact Mass: 265,03 g/mol
 Orange solid

1-Chloro-1,5,5,5-tetrafluoro-4-((2-fluorophenyl)amino)pent-3-en-2-one
III.3'.eB

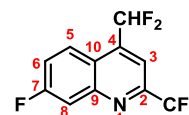
Yarovenko's reagent **B.1** (1.2 equiv., 0.669 mL, 2.94 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.372 mL, 2.94 mmol); c) 2-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.e** (1 equiv., 502 mg, 2.45 mmol); and d) 1-Chloro-1,5,5,5-tetrafluoro-4-((2-fluorophenyl)amino)pent-3-en-2-one **III.3'.eB** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a brown oil in mixture with traces of desired **III.2.eB** in 50% yield (367 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 11.34 (s, 1H, NH), 7.35 (m, 2H, $\text{C}_{3,6}\text{H}$), 7.17 (m, 2H, $\text{C}_{4,5}\text{H}$), 6.30 (d, $^2J_{\text{H-F}} = 50.9$ Hz, 1H, C_9CHFCl), 6.12 (d, $^4J_{\text{H-F}} = 2.5$ Hz, 1H, C_8H) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -65.25 (d, $^6J_{\text{F-F}} = 4.1$ Hz, C_7CF_3), -120.12 – -121.86 (m, C_2F), -145.47 (dt, $^2J_{\text{F-H}} = 51.1$, $^4J_{\text{F-H}} = 2.6$ Hz, C_9CHFCl) ppm.



III.3'.eB
 Chemical Formula: $\text{C}_{11}\text{H}_7\text{ClF}_5\text{NO}$
 Exact Mass: 299.01 g/mol
 Brown oil

4-(Difluoromethyl)-7-fluoro-2-(trifluoromethyl)quinoline III.2.fA

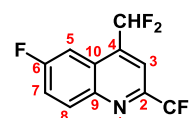
a) TFEDMA **A.1** (1.2 equiv., 0.349 mL, 2.98 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.378 mL, 2.98 mmol); c) 3-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.f** (1 equiv., 509 mg, 2.48 mmol); and d) 4-(Difluoromethyl)-7-fluoro-2-(trifluoromethyl)quinoline **III.2.fA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 62% yield (405 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.19 (dd, $^3J_{\text{H-H}} = 9.2$, $^4J_{\text{H-F}} = 5.7$ Hz, 1H, C_5H), 7.93 (dd, $^3J_{\text{H-F}} = 9.3$, $^4J_{\text{H-H}} = 2.3$ Hz, 1H, C_8H), 7.88 (s, 1H, C_3H), 7.61 – 7.54 (m, 1H, C_6H), 7.17 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C_4CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -67.89 (s, C_2CF_3), -105.57 – -105.66 (m, C_7F), -114.89 (d, $^2J_{\text{F-H}} = 54.0$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 163.84 (d, $^1J_{\text{C-F}} = 254.8$ Hz, C_7), 149.36 (d, $^3J_{\text{C-F}} = 13.1$ Hz, C_9), 149.09 (q, $^2J_{\text{C-F}} = 35.6$ Hz, C_2), 140.60 (td, $^2J_{\text{C-F}} = 22.5$, $^5J_{\text{C-F}} = 1.4$ Hz, C_4), 125.92 (d, $^3J_{\text{C-F}} = 9.8$ Hz, C_5), 122.08 (s, C_{10}), 121.04 (q, $^1J_{\text{C-F}} = 275.4$ Hz, C_2CF_3), 120.77 (d, $^2J_{\text{C-F}} = 25.6$ Hz, C_6), 114.89 (d, $^2J_{\text{C-F}} = 20.7$ Hz, C_8), 113.92 – 113.16 (m, C_3), 112.81 (t, $^1J_{\text{C-F}} = 241.8$ Hz, C_4CHF_2) ppm. $\text{C}_{11}\text{H}_5\text{F}_6\text{N}$ (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.



III.2.fA
 Chemical Formula: $\text{C}_{11}\text{H}_5\text{F}_6\text{N}$
 Exact Mass: 265.03 g/mol
 Yellow solid

4-(Difluoromethyl)-6-fluoro-2-(trifluoromethyl)quinoline III.2.gA

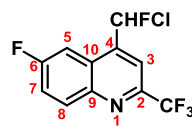
a) TFEDMA **A.1** (1.2 equiv., 0.346 mL, 2.96 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.374 mL, 2.96 mmol); c) 4-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.g** (1 equiv., 505 mg, 2.46 mmol); and d) 4-(Difluoromethyl)-6-fluoro-2-(trifluoromethyl)quinoline **III.2.gA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 67% yield (434 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.32 (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-F}} = 5.5$ Hz, 1H, C_8H), 7.93 (s, 1H, C_3H), 7.81 – 7.73 (m, 1H, C_5H), 7.67 – 7.66 (m, 1H, C_7H), 7.12 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C_4CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -67.69 (s, C_2CF_3), -105.84 – -105.77 (m, C_6F), -115.61 (d, $^2J_{\text{F-H}} = 54.1$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 162.40 (d, $^1J_{\text{C-F}} = 254.3$ Hz, C_6), 147.31 (qd, $^2J_{\text{C-F}} = 35.7$, $^6J_{\text{C-F}} = 3.2$ Hz, C_2), 145.05 (s, C_9), 139.92 (td, $^2J_{\text{C-F}} = 22.5$, $^4J_{\text{C-F}} = 6.2$ Hz, C_4), 133.96 (d, $^3J_{\text{C-F}} = 9.8$ Hz, C_8), 126.06 (d, $^3J_{\text{C-F}} = 10.7$ Hz, C_{10}), 122.01 (d, $^2J_{\text{C-F}} = 26.0$ Hz, C_7), 121.24 (q, $^1J_{\text{C-F}} = 275.1$ Hz, C_2CF_3), 115.17 – 115.02 (m, C_3), 112.74 (t, $^1J_{\text{C-F}} = 237.4$ Hz, C_4CHF_2), 107.68 (d, $^2J_{\text{C-F}} = 24.1$ Hz, C_5) ppm. HRMS (ESI positive) for $\text{C}_{11}\text{H}_6\text{F}_6\text{N}$ [M^+]: calcd 266.0399, found 266.0387. MP: 68.2 – 69.8 °C.



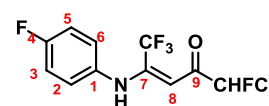
III.2.gA
 Chemical Formula: $\text{C}_{11}\text{H}_5\text{F}_6\text{N}$
 Exact Mass: 265.03 g/mol
 Yellow solid

4-[Chloro(fluoro)methyl]-6-fluoro-2-(trifluoromethyl)quinoline III.2.gB

a) Yarovenko's reagent **B.1** (1.2 equiv., 0.675 mL, 2.97 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.2 equiv., 0.376 mL, 2.97 mmol); c) 4-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.g** (1 equiv., 507 mg, 2.47 mmol); and d) 4-



III.2.gB
Chemical Formula: $\text{C}_{11}\text{H}_5\text{ClF}_5\text{N}$
Exact Mass: 281,00 g/mol



III.3'.gB
Chemical Formula: $\text{C}_{11}\text{H}_7\text{ClF}_5\text{NO}$
Exact Mass: 299,01 g/mol

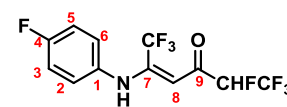
[Chloro(fluoro)methyl]-6-fluoro-2-(trifluoromethyl)quinoline **III.2.gB** was obtained after purification using a gradient of AcOEt in pentane (0-5%) in mixture with the non-cyclized compound, 1-chloro-1,5,5,5-tetrafluoro-4-((4-fluorophenyl)amino)pent-3-en-2-one **III.3'.gB'** with a ratio of 7:1 in 35% yield determined by ^{19}F NMR. ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.32$ (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-F}} = 5.5$ Hz, 1H, C_8H), 7.94 (s, 1H, C_3H), 7.75 (dd, $^3J_{\text{H-F}} = 9.4$, $^4J_{\text{H-H}} = 2.7$ Hz, 1H, C_5H), 7.65 (ddd, $^3J_{\text{H-F}} = 9.4$, $^4J_{\text{H-F}} = 7.9$, $^4J_{\text{H-H}} = 2.7$ Hz, 1H, C_7H), 7.54 (d, $^2J_{\text{H-F}} = 48.7$ Hz, 1H, C_4CHFCl) ppm.

6-Fluoro-4-(1,2,2,2-tetrafluoroethyl)-2-(trifluoromethyl)quinoline III.2.gC

a) Ishikawa's reagent **C.1** (1.2 equiv., 0.854 mL, 2.92 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.21 equiv., 0.372 mL, 2.93 mmol); c) 4-Fluoro-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.g** (1 equiv., 498 mg, 2.43 mmol); and d) 6-Fluoro-4-(1,2,2,2-



III.2.gC
Chemical Formula: $\text{C}_{12}\text{H}_5\text{F}_8\text{N}$
Exact Mass: 315,03 g/mol

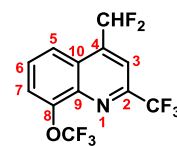


III.3'.gC
Chemical Formula: $\text{C}_{12}\text{H}_7\text{F}_8\text{NO}$
Exact Mass: 333,04 g/mol

tetrafluoroethyl)-2-(trifluoromethyl)quinoline **III.2.gC** was obtained after purification using a gradient of AcOEt in pentane (0-5%) in mixture with the non-cyclized compound, 1,1,1,2,6,6,6-heptafluoro-5-((4-fluorophenyl)amino)hex-4-en-3-one **III.3'.gC** with a ratio of 1:3 (64.7 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.35$ (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-F}} = 5.5$ Hz, 1H, C_8H), 7.97 (s, 1H, C_3H), 7.72 - 7.65 (m, 1H, C_5H), 7.64 - 7.62 (m, 1H, C_7H), 6.33 (dq, $^2J_{\text{H-F}} = 43.8$, $^3J_{\text{H-F}} = 5.4$ Hz, 1H, $\text{C}_4\text{CHF CF}_3$) ppm. HRMS (ESI positive $\text{C}_{12}\text{H}_6\text{F}_8\text{N}$ [$\text{M} + \text{H}$]): calcd 316.0367, found 316.0375.

4-(Difluoromethyl)-8-(trifluoromethoxy)-2-(trifluoromethyl)quinoline III.2.hA

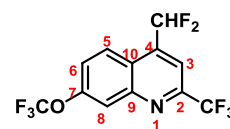
a) TFEDMA **A.1** (1.2 equiv., 0.114 mL, 0.977 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.2 equiv., 0.124 mL, 0.977 mmol); c) *N*-2-(Trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.h** (1 equiv., 1.23 g, 0.815 mmol); and d) 4-(Difluoromethyl)-8-(trifluoromethoxy)-2-(trifluoromethyl)quinoline **III.2.hA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as traces in a mixture with impurities. ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.23 - 7.15$ (m, 2H, $\text{C}_6, \text{C}_7\text{H}$), 7.04 - 6.94 (m, 1H, C_5H), 6.81 (dd, $^4J_{\text{H-F}} = 7.8$, $^4J_{\text{H-F}} = 1.4$ Hz, 1H, C_3H), 6.15 (t, $^2J_{\text{H-F}} = 52.6$ Hz, 1H, C_4CHF_2) ppm.



III.2.hA
Chemical Formula: $\text{C}_{12}\text{H}_5\text{F}_8\text{NO}$
Exact Mass: 331,02 g/mol

4-(Difluoromethyl)-7-(trifluoromethoxy)-2-(trifluoromethyl)quinoline III.2.iA

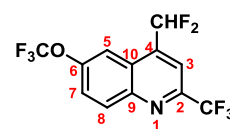
a) TFEDMA **A.1** (1.2 equiv., 0.259 mL, 2.21 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.28 mL, 2.21 mmol); c) 3-(Trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.i** (1 equiv., 500 mg, 1.84 mmol); and d) 4-(Difluoromethyl)-7-(trifluoromethoxy)-2-(trifluoromethyl)quinoline **III.2.iA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 36% yield (219 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.24 (d, $^3J_{\text{H-H}}$ = 9.3 Hz, 1H, C_5H), 8.16 (s, 1H, C_8H), 7.94 (s, 1H, C_3H), 7.65 (dd, $^3J_{\text{H-H}}$ = 9.3, $^4J_{\text{H-H}}$ = 2.4 Hz, 1H, C_6H), 7.18 (t, $^2J_{\text{H-F}}$ = 54.1 Hz, 1H, C_4CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -57.88 (s, C_7OCF_3), -67.89 (s, C_2CF_3), -114.87 (d, $^2J_{\text{F-H}}$ = 54.1 Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 151 (s, C_7), 149.37 (q, $^2J_{\text{C-F}}$ = 35.8 Hz, C_2), 148.63 (s, C_9), 140.65 (t, $^2J_{\text{C-F}}$ = 22.6 Hz, C_4), 125.80 (s, C_5), 123.99 (s, C_6), 123.23 – 123.19 (m, C_{10}), 121.07 (q, $^1J_{\text{C-F}}$ = 276.7 Hz, C_2CF_3), 120.55 (q, $^1J_{\text{C-F}}$ = 260.0 Hz, C_7OCF_3), 120.25 (s, C_8), 114.60 (td, $^3J_{\text{C-F}}$ = 8.0, $^3J_{\text{C-F}}$ = 2.0 Hz, C_3), 112.72 (t, $^1J_{\text{C-F}}$ = 242.0 Hz, C_4CHF_2) ppm. $\text{C}_{12}\text{H}_5\text{F}_8\text{NO}$ (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.



III.2.iA
 Chemical Formula: $\text{C}_{12}\text{H}_5\text{F}_8\text{NO}$
 Exact Mass: 331,02 g/mol
 Yellow solid

4-(Difluoromethyl)-6-(trifluoromethoxy)-2-(trifluoromethyl)quinoline III.2.jA

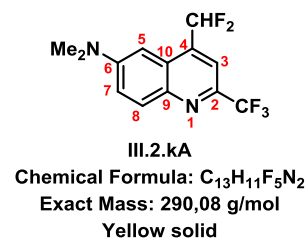
a) TFEDMA **A.1** (1.2 equiv., 0.278 mL, 2.38 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.282 mL, 2.22 mmol); c) 4-(Trifluoromethoxy)-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.j** (1 equiv., 584 mg, 1.85 mmol); and d) 4-(Difluoromethyl)-6-(trifluoromethoxy)-2-(trifluoromethyl)quinoline **III.2.jA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 49% yield (300.3 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.39 (d, $^3J_{\text{H-H}}$ = 9.3 Hz, 1H, C_8H), 7.97 (s, 2H, $\text{C}_3, \text{C}_5\text{H}$), 7.77 (dd, $^3J_{\text{H-H}}$ = 9.3, $^4J_{\text{H-H}}$ = 1.9 Hz, 1H, C_7H), 7.15 (t, $^2J_{\text{H-F}}$ = 54.0 Hz, 1H, C_4CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -57.72 (s, C_6OCF_3), -67.79 (s, C_2CF_3), -115.31 (d, $^2J_{\text{F-H}}$ = 53.9 Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 149.50 (s, C_6), 148.41 (q, $^2J_{\text{C-F}}$ = 35.9 Hz, C_2), 146.02 (s, C_9), 140.46 (t, $^2J_{\text{C-F}}$ = 22.6 Hz, C_4), 133.66 (s, C_8), 125.52 (s, C_{10}), 125.35 (s, C_7), 121.12 (q, $^1J_{\text{C-F}}$ = 276.4 Hz, C_2CF_3), 120.74 (q, $^1J_{\text{C-F}}$ = 260.6 Hz, C_6OCF_3), 115.36 (td, $^3J_{\text{C-F}}$ = 8.0, $^3J_{\text{C-F}}$ = 2.1 Hz, C_3), 113.97 (s, C_5), 112.67 (t, $^1J_{\text{C-F}}$ = 242.0 Hz, C_4CHF_2) ppm. $\text{C}_{12}\text{H}_5\text{F}_8\text{NO}$ (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.



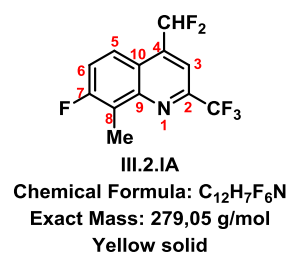
III.2.jA
 Chemical Formula: $\text{C}_{12}\text{H}_5\text{F}_8\text{NO}$
 Exact Mass: 331,02 g/mol
 Yellow solid

4-(Difluoromethyl)-N,N-dimethyl-2-(trifluoromethyl)quinolin-6-amine III.2.kA

a) TFEDMA **A.1** (1.2 equiv., 0.305 mL, 2.61 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.33 mL, 2.61 mmol); c) 1-*N,N*-Dimethyl-4-*N*-(1,1,1-trifluoropropan-2-ylidene)benzene-1,4-diamine **III.1.k** (1 equiv., 500 mg, 2.17 mmol); and d) 4-(Difluoromethyl)-*N,N*-dimethyl-2-(trifluoromethyl)quinolin-6-amine **III.2.kA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 37% yield (235 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.07 (d, $^3J_{\text{H-H}} = 9.5$ Hz, 1H, C₈H), 7.75 (s, 1H, C₃H), 7.43 (dd, $^3J_{\text{H-H}} = 9.5$, $^4J_{\text{H-H}} = 2.8$ Hz, 1H, C₇H), 7.07 (t, $^2J_{\text{H-F}} = 54.5$ Hz, 1H, C₄CHF₂), 6.84 (s, 1H, C₅H), 3.14 (s, 1H, C₆N(CH₃)₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -66.90 (s, C₂CF₃), -117.13 (d, $^2J_{\text{F-H}} = 54.7$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 150.28 (s, C₆), 143.01 – 141.69 (m, C₂ + C₉), 136.12 (t, $^2J_{\text{C-F}} = 21.6$ Hz, C₄), 131.80 (s, C₈), 127.25 (t, $^3J_{\text{C-F}} = 2.5$ Hz, C₁₀), 121.98 (q, $^1J_{\text{C-F}} = 274.0$ Hz, C₂CF₃), 120.46 (s, C₇), 114.48 (td, $^3J_{\text{C-F}} = 8.2$, $^3J_{\text{C-F}} = 2.3$ Hz, C₃), 113.29 (t, $^1J_{\text{C-F}} = 240.4$ Hz, C₄CHF₂), 98.92 (s, C₅), 40.46 (s, C₆N(CH₃)₂) 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.

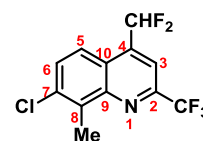
**4-(Difluoromethyl)-7-fluoro-8-methyl-2-(trifluoromethyl)quinoline III.2.IA**

a) TFEDMA **A.1** (1.2 equiv., 0.644 mL, 5.5 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.698 mL, 5.5 mmol); c) 3-Fluoro-2-methyl-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.I** (1 equiv., 1.76 g, 4.59 mmol); and d) 4-(Difluoromethyl)-7-fluoro-8-methyl-2-(trifluoromethyl)quinoline **III.2.IA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 38% yield (488.4 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 7.99 (dd, $^3J_{\text{H-H}} = 9.0$, $^4J_{\text{H-F}} = 5.9$ Hz, 1H, C₅H), 7.88 (s, 1H, C₃H), 7.54 (t, $^3J_{\text{H-H}} = 9.0$ Hz, 1H, C₆H), 7.17 (t, $^2J_{\text{H-F}} = 54.2$ Hz, 1H, C₄CHF₂), 2.75 (d, $^4J_{\text{H-F}} = 2.6$ Hz, 3H, C₈CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -67.78 (s, C₂CF₃), -108.31 – -108.46 (m, C₇F), -114.94 (d, $^2J_{\text{F-H}} = 54.2$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 161.60 (d, $^1J_{\text{C-F}} = 250.2$ Hz, C₇), 148.47 – 147.14 (m, C₂ + C₉), 140.54 (td, $^2J_{\text{C-F}} = 22.3$, $^5J_{\text{C-F}} = 1.8$ Hz, C₄), 123.79 (d, $^2J_{\text{C-F}} = 16.2$ Hz, C₈), 122.26 (d, $^3J_{\text{C-F}} = 10.3$ Hz, C₅ + C₁₀), 121.32 (q, $^1J_{\text{C-F}} = 275.3$ Hz, C₂CF₃), 120.25 (d, $^2J_{\text{C-F}} = 27.2$ Hz, C₆), 113.49 – 112.94 (m, C₃), 112.84 (t, $^1J_{\text{C-F}} = 241.6$ Hz, C₄CHF₂), 9.38 (d, $^3J_{\text{C-F}} = 3.7$ Hz, C₈CH₃) ppm. HRMS (ESI positive) for C₁₂H₈F₆N [M⁺]: calcd 280.0555, found 280.0570. MP: 78.7 – 79.4 °C.



7-Chloro-4-(difluoromethyl)-8-methyl-2-(trifluoromethyl)quinoline III.2.mA

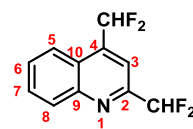
a) TFEDMA **A.1** (1.2 equiv., 0.599 mL, 5.12 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.648 mL, 5.12 mmol); c) 3-Chloro-2-methyl-*N*-(1,1,1-trifluoropropan-2-ylidene)aniline **III.1.m** (1 equiv., 2.01 g, 4.26 mmol); and d) 7-Chloro-4-(difluoromethyl)-8-methyl-2-(trifluoromethyl)quinoline **III.2.mA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a beige amorphous solid in 38% yield (485 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.93 - 7.91$ (m, 2H, C₃, 5H), 7.74 (d, $^3J_{\text{H-H}} = 9.1$ Hz, 1H, C₆H), 7.17 (t, $^2J_{\text{H-F}} = 54.2$ Hz, 1H, C₄CHF₂), 2.93 (s, 3H, C₈CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -67.78$ (s, C₂CF₃), -115.12 (d, $^2J_{\text{F-H}} = 54.1$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 147.53$ (q, $^2J_{\text{C-F}} = 35.8$ Hz, C₂), 147.44 (s, C₉), 140.63 (t, $^2J_{\text{C-F}} = 22.3$ Hz, C₄), 137.44 (s, C₇), 137.10 (s, C₈), 131.35 (s, C₆), 121.50 (s, C₅), 121.27 (q, $^1J_{\text{C-F}} = 275.3$ Hz, C₂CF₃), 119.32 (s, C₁₀), 113.93 - 113.73 (m, C₃), 112.70 (t, $^1J_{\text{C-F}} = 241.7$ Hz, C₄CHF₂), 14.91 (s, C₈CH₃) ppm. C₁₂H₇F₅NCl (295): calcd (%) N 4.73, C 48.70, H 2.36, found N 4.62, C 48.82, H 2.55.

**III.2.mA**

Chemical Formula: C₁₂H₇ClF₅N
Exact Mass: 295.02 g/mol
Beige amorphous solid

3.1.2 From fluorinated ketone (III.1.aa-uu)**2,4-Bis(difluoromethyl)quinoline III.2.aaA**

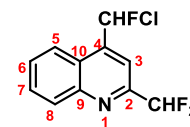
a) TFEDMA **A.1** (1.2 equiv., 0.427 mL, 3.65 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.463 mL, 3.65 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)aniline **III.1.aa** (1 equiv., 515 mg, 3.04 mmol); and d) 2,4-Bis(difluoromethyl)quinoline **III.2.aaA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 77% yield (537 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.23$ (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, C₈H), 8.14 (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, C₅H), 7.92 (s, 1H, C₃H), 7.86 (t, $^3J_{\text{H-H}} = 7.7$ Hz, 1H, C₇H), 7.74 (t, $^3J_{\text{H-H}} = 7.7$ Hz, 1H, C₆H), 7.19 (t, $^2J_{\text{H-F}} = 54.3$ Hz, 1H, C₄CHF₂), 6.81 (t, $^2J_{\text{H-F}} = 55.1$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -114.46$ (d, $^2J_{\text{F-H}} = 55.1$ Hz, C₂CHF₂), -115.16 (d, $^2J_{\text{F-H}} = 54.3$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 152.70$ (t, $^2J_{\text{C-F}} = 27.1$ Hz, C₂), 147.80 (s, C₉), 139.93 (t, $^2J_{\text{C-F}} = 22.2$ Hz, C₄), 130.91 (s, C₇), 130.83 (s, C₈), 129.33 (s, C₆), 124.84 (s, C₁₀), 123.55 (s, C₅), 114.37 (t, $^1J_{\text{C-F}} = 242.0$ Hz, C₄CHF₂), 114.32 - 114.17 (m, C₃), 113.13 (t, $^1J_{\text{C-F}} = 241.2$ Hz, C₂CHF₂) 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.

**III.2.aaA**

Chemical Formula: C₁₁H₇F₄N
Exact Mass: 229.05 g/mol
Yellow solid

4-[Chloro(fluoro)methyl]-2-(difluoromethyl)quinoline III.2.aaB

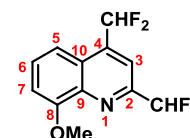
a) Yarovenko's reagent **B.1** (1.2 equiv., 0.56 mL, 3.55 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.2 equiv., 0.45 mL, 3.55 mmol); c) *N*-(1,1,1-Trifluoropropan-2-ylidene)aniline **III.1.aa** (1 equiv., 500 mg, 2.96 mmol); and d) 4-[Chloro(fluoro)methyl]-2-(difluoromethyl)quinoline **III.2.aaB** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a brown solid in 78% yield (567 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.02$ (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, C₈H), 7.88 (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, C₅H), 7.75 (s, 1H, C₃H), 7.62 (t, $^3J_{\text{H-H}} = 7.7$ Hz, 1H, C₇H), 7.51 - 7.42 (m, 2H, C₆H + C₄CHFCl), 6.65 (t, $^2J_{\text{H-F}} = 55.1$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -114.5$ (dd, $^2J_{\text{F-H}} = 55.2$ Hz, $^4J_{\text{F-H}} = 3$ Hz, C₂CHF₂), -138.0 (d, $^2J_{\text{F-H}} = 49$ Hz, C₄CHFCl) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 152.63$ (t, $^2J_{\text{C-F}} = 27$ Hz, C₂), 147.69 (s, C₉), 143.25 (d, $^2J_{\text{C-F}} = 21$ Hz, C₄), 130.80 (s, C₇), 130.70 (s, C₈), 128.96 (s, C₆), 123.68 (d, $^3J_{\text{C-F}} = 3.6$ Hz, C₁₀), 123.06 (s, C₅), 114.33 (t, $^1J_{\text{C-F}} = 241.3$ Hz, C₂CHF₂), 113.0 (dt, $^3J_{\text{C-F}} = 9.6$, $^3J_{\text{C-F}} = 1.9$ Hz, C₃), 97.08 (d, $^1J_{\text{C-F}} = 244.3$ Hz, C₄CHFCl) ppm. HRMS (ESI positive) for $\text{C}_{11}\text{H}_8\text{F}_3\text{NCl}$ [M^+]: calcd 246.0292, found 246.0312.



III.2.aaB
 Chemical Formula: $\text{C}_{11}\text{H}_7\text{ClF}_3\text{N}$
 Exact Mass: 245.02 g/mol
 Brown solid

2,4-Bis(difluoromethyl)-8-methoxyquinoline III.2.bbA

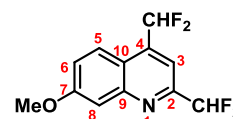
a) TFEDMA **A.1** (1.2 equiv., 0.354 mL, 3.02 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.2 equiv., 0.383 mL, 3.02 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-2-methoxyaniline **III.1.bb** (1 equiv., 502 mg, 2.52 mmol); and d) 2,4-Bis(difluoromethyl)-8-methoxyquinoline **III.2.bbA** was obtained after purification using a gradient of AcOEt in pentane (10-25%) as a yellow solid in 72% yield (473 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.94$ (s, 1H, C₅H), 7.62 (d, $^3J_{\text{H-H}} = 4.2$ Hz, 2H, C₆, C₇H), 7.31 - 7.02 (m, 2H, C₃H + C₄CHF₂), 6.88 (t, $^2J_{\text{H-F}} = 51.4$ Hz, 1H, C₂CHF₂), 4.09 (s, 3H, C₈OCH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -113.42$ (d, $^2J_{\text{F-H}} = 54.9$ Hz, C₂CHF₂), -115.88 (d, $^2J_{\text{F-H}} = 54.3$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 156.17$ (s, C₈), 151.14 (t, $^2J_{\text{C-F}} = 27.7$ Hz, C₂), 140.04 - 139.19 (m, C₄ + C₉), 129.84 (s, C₆), 126.13 (s, C₁₀), 114.92 (s, C₅), 114.72 (t, $^3J_{\text{C-F}} = 7.9$ Hz, C₃), 114.48 (t, $^1J_{\text{C-F}} = 241.9$ Hz, C₂CHF₂), 112.85 (t, $^1J_{\text{C-F}} = 241.1$ Hz, C₄CHF₂), 109.17 (s, C₇), 56.41 (s, C₈OCH₃) ppm. $\text{C}_{12}\text{H}_9\text{F}_4\text{NO}$ (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.



III.2.bbA
 Chemical Formula: $\text{C}_{12}\text{H}_9\text{F}_4\text{NO}$
 Exact Mass: 259.06 g/mol
 Yellow solid

2,4-Bis(difluoromethyl)-7-methoxyquinoline III.2.ccA

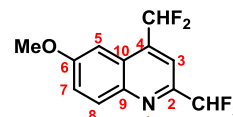
a) TFEDMA **A.1** (1.2 equiv., 0.356 mL, 3.04 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.2 equiv., 0.386 mL, 3.04 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-3-methoxyaniline **III.1.cc** (1 equiv., 505 mg, 2.54 mmol); and d) 2,4-Bis(difluoromethyl)-7-methoxyquinoline **III.2.ccA** was obtained after purification using a gradient of AcOEt in pentane (10-25%) as a yellow solid in 78% yield (515 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.79$ (d, $^3J_{\text{H-H}} = 9.3$ Hz, 1H, C_5H), 7.57 (s, 1H, C_3H), 7.30 (d, $^4J_{\text{H-H}} = 2.6$ Hz, 1H, C_8H), 7.14 (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-H}} = 2.6$ Hz, 1H, C_6H), 6.94 (t, $^2J_{\text{H-F}} = 54.4$ Hz, 1H, C_4CHF_2), 6.62 (t, $^2J_{\text{H-F}} = 55.2$ Hz, 1H, C_2CHF_2), 3.79 (s, 3H, C_8OCH_3) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -114.79$ (d, $^2J_{\text{F-H}} = 54.4$ Hz, C_2CHF_2), -114.95 (d, $^2J_{\text{F-H}} = 55.3$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 161.45$ (s, C_7), 152.86 (t, $^2J_{\text{C-F}} = 26.7$ Hz, C_2), 149.83 (s, C_9), 139.56 (t, $^2J_{\text{C-F}} = 22.2$ Hz, C_4), 124.33 (s, C_5), 122.45 (s, C_6), 119.77 (t, $^3J_{\text{C-F}} = 2.8$ Hz, C_{10}), 114.25 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C_2CHF_2), 113.18 (t, $^1J_{\text{C-F}} = 241.0$ Hz, C_4CHF_2), 111.89 – 111.70 (m, C_3), 108.24 (s, C_8), 55.60 (s, C_8OCH_3) ppm. $\text{C}_{12}\text{H}_9\text{F}_4\text{NO}$ (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.

**III.2.ccA**

Chemical Formula: $\text{C}_{12}\text{H}_9\text{F}_4\text{NO}$
Exact Mass: 259,06 g/mol
Yellow solid

2,4-Bis(difluoromethyl)-6-methoxyquinoline III.2.ddA

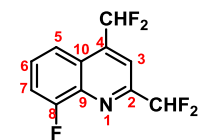
a) TFEDMA **A.1** (1.2 equiv., 0.357 mL, 3.05 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.2 equiv., 0.386 mL, 3.05 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-4-methoxyaniline **III.1.dd** (1 equiv., 506 mg, 2.54 mmol); and d) 2,4-Bis(difluoromethyl)-6-methoxyquinoline **III.2.ddA** was obtained after purification using a gradient of AcOEt in pentane (10-25%) as an orange solid in 71% yield (468 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.15$ (d, $^3J_{\text{H-H}} = 9.3$ Hz, 1H, C_8H), 7.90 (s, 1H, C_3H), 7.53 (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-H}} = 2.5$ Hz, 1H, C_7H), 7.36 (s, 1H, C_5H), 7.16 (t, $^2J_{\text{H-F}} = 54.4$ Hz, 1H, C_4CHF_2), 6.85 (t, $^2J_{\text{H-F}} = 55.2$ Hz, 1H, C_2CHF_2), 4.03 (s, 3H, C_8OCH_3) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -113.99$ (d, $^2J_{\text{F-H}} = 55.3$ Hz, C_2CHF_2), -115.52 (d, $^2J_{\text{F-H}} = 54.4$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 159.77$ (s, C_6), 149.93 (t, $^2J_{\text{C-F}} = 27.0$ Hz, C_2), 143.966 (s, C_9), 138.02 (t, $^2J_{\text{C-F}} = 22.0$ Hz, C_4), 132.11 (s, C_8), 126.21 (s, C_{10}), 123.71 (s, C_7), 114.70 (tt, $^3J_{\text{C-F}} = 8.0$, $^3J_{\text{C-F}} = 1.8$ Hz, C_3), 114.51 (t, $^1J_{\text{C-F}} = 241.9$ Hz, C_2CHF_2), 113.57 (t, $^1J_{\text{C-F}} = 240.8$ Hz, C_4CHF_2), 101.35 (s, C_5), 55.79 (s, C_8OCH_3) ppm. $\text{C}_{12}\text{H}_9\text{F}_4\text{NO}$ (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.

**III.2.ddA**

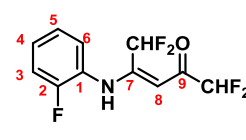
Chemical Formula: $\text{C}_{12}\text{H}_9\text{F}_4\text{NO}$
Exact Mass: 259,06 g/mol
Orange solid

2,4-Bis(difluoromethyl)-8-fluoroquinoline III.2.eeA

a) TFEDMA **A.1** (1.2 equiv., 0.377 mL, 3.22 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.408 mL, 3.22 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-2-fluoroaniline **III.1.ee** (1 equiv., 502 mg, 2.68 mmol); and d) 2,4-Bis(difluoromethyl)-8-fluoroquinoline **III.2.eeA** was obtained after

**III.2.eeA**

Chemical Formula: $\text{C}_{11}\text{H}_6\text{F}_5\text{N}$
Exact Mass: 247,04 g/mol

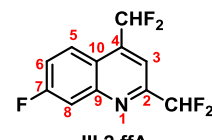
**III.3'.eeA**

Chemical Formula: $\text{C}_{11}\text{H}_8\text{F}_5\text{NO}$
Exact Mass: 265,05 g/mol

purification using a gradient of AcOEt in pentane (0-5%) in mixture with the non-cyclized compound the 1,1,5,5-tetrafluoro-4-((2-fluorophenyl)amino)pent-3-en-2-one **III.3'.eeA** with a ratio of 3:1 in 39% yield (466 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.00 (s, 1H, C_3H), 7.93 (d, $^3J_{\text{H-H}}$ = 8.6 Hz, 1H, C_5H), 7.73 – 7.68 (m, 1H, C_6H), 7.60 – 7.52 (m, 1H, C_7H), 7.17 (t, $^2J_{\text{H-F}}$ = 54.2 Hz, 1H, C_4CHF_2), 6.86 (t, $^2J_{\text{H-F}}$ = 54.8 Hz, 1H, C_2CHF_2) ppm. HRMS (ESI positive) for $\text{C}_{11}\text{H}_7\text{F}_5\text{N}$ [M^+]: calcd 248.0493, found 248.0499.

2,4-Bis(difluoromethyl)-7-fluoroquinoline III.2.ffA

a) TFEDMA **A.1** (1.2 equiv., 0.376 mL, 3.22 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.408 mL, 3.22 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-3-fluoroaniline **III.1.ff** (1 equiv., 501 mg, 2.68 mmol); and d) 2,4-Bis(difluoromethyl)-7-fluoroquinoline **III.2.ffA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 70% yield (464 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.17 (dd, $^4J_{\text{H-}}$

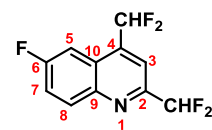
**III.2.ffA**

Chemical Formula: $\text{C}_{11}\text{H}_6\text{F}_5\text{N}$
Exact Mass: 247,04 g/mol
Yellow solid

H = 9.3, $^3J_{\text{H-F}}$ = 5.7 Hz, 1H, C_8H), 7.86 (s, 1H, C_3H), 7.84 (s, 1H, C_5H), 7.57 – 7.49 (m, 1H, C_6H), 7.14 (t, $^2J_{\text{H-F}}$ = 54.2 Hz, 1H, C_4CHF_2), 6.78 (t, $^2J_{\text{H-F}}$ = 55.0 Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -106.41 – -106.96 (m, C_7F), -114.43 (d, $^2J_{\text{F-H}}$ = 54.2 Hz, C_2CHF_2), -114.83 (d, $^2J_{\text{F-H}}$ = 55.0 Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 163.60 (d, $^1J_{\text{C-F}}$ = 253.6 Hz, C_7), 153.93 (t, $^2J_{\text{C-F}}$ = 27.3 Hz, C_2), 149.21 (d, $^3J_{\text{C-F}}$ = 12.7 Hz, C_9), 140.17 (td, $^2J_{\text{C-F}}$ = 22.4, $^5J_{\text{C-F}}$ = 1.1 Hz, C_4), 126.00 (d, $^3J_{\text{C-F}}$ = 9.8 Hz, C_5), 121.79 (d, $^4J_{\text{C-F}}$ = 1.0 Hz, C_{10}), 119.91 (d, $^2J_{\text{C-F}}$ = 25.39 Hz, C_6), 114.54 (d, $^2J_{\text{C-F}}$ = 20.56 Hz, C_8), 114.12 (t, $^1J_{\text{C-F}}$ = 242.9 Hz, C_2CHF_2), 113.86 (m, C_3), 113.23 (t, $^1J_{\text{C-F}}$ = 241.5 Hz, C_4CHF_2) ppm. $\text{C}_{11}\text{H}_6\text{F}_5\text{N}$ (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 III.2.ggA

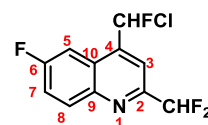
a) TFEDMA **A.1** (1.5 equiv., 0.375 mL, 3.2 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.51 equiv., 0.408 mL, 3.22 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-4-fluoroaniline **III.1.gg** (1 equiv., 400 mg, 2.14 mmol); and d) 2,4-Bis(difluoromethyl)-6-fluoroquinoline **III.2.ggA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 39% yield (205 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.24$ (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-F}} = 5.5$ Hz, 1H, C_8H), 7.92 (s, 1H, C_3H), 7.80 – 7.74 (m, 1H, C_5H), 7.65 – 7.60 (m, 1H, C_7H), 7.09 (t, $^2J_{\text{H-F}} = 54.2$ Hz, 1H, C_4CHF_2), 6.79 (t, $^2J_{\text{H-F}} = 55.0$ Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -107.18$ - -107.24 (m, C_6F), -114.45 (d, $^2J_{\text{F-H}} = 55.0$ Hz, C_2CHF_2), -115.17 (d, $^2J_{\text{F-H}} = 54.2$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 162.01$ (d, $^1J_{\text{C-F}} = 252.9$ Hz, C_6), 152.09 (td, $^2J_{\text{C-F}} = 27.3$, $^6J_{\text{C-F}} = 3.1$ Hz, C_2), 144.98 (s, C_9), 139.56 (td, $^2J_{\text{C-F}} = 22.4$, $^4J_{\text{C-F}} = 6.1$ Hz, C_4), 133.46 (d, $^3J_{\text{C-F}} = 9.6$ Hz, C_8), 125.76 (d, $^3J_{\text{C-F}} = 10.4$ Hz, C_{10}), 121.43 (d, $^2J_{\text{C-F}} = 25.8$ Hz, C_7), 115.28 (t, $^3J_{\text{C-F}} = 7.8$ Hz, C_3), 114.21 (t, $^1J_{\text{C-F}} = 241.3$ Hz, C_2CHF_2), 110.78 (t, $^1J_{\text{C-F}} = 242.0$ Hz, C_4CHF_2), 107.84 (d, $^2J_{\text{C-F}} = 24.0$ Hz, C_5) ppm. $\text{C}_{11}\text{H}_6\text{F}_5\text{N}$ (247): calcd (%) N 5.66, C 53.41, H 2.43, found N 5.67, C 53.42, H 2.57. HRMS (ESI positive) for $\text{C}_{11}\text{H}_7\text{F}_5\text{N}$ [M^+]: calcd 248.0493, found 248.0497. MP: 68.7 – 71.2 °C.

**III.2.ggA**

Chemical Formula: $\text{C}_{11}\text{H}_6\text{F}_5\text{N}$
Exact Mass: 247,04 g/mol
Yellow solid

4-[Chloro(fluoro)methyl]-2-(difluoromethyl)-6-fluoroquinoline III.2.ggB

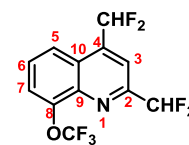
a) Yarovenko's reagent **B.1** (1.2 equiv., 0.597 mL, 2.62 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.2 equiv., 0.332 mL, 2.62 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-4-fluoroaniline **III.1.gg** (1 equiv., 409 mg, 2.19 mmol); and d) 4-[Chloro(fluoro)methyl]-2-(difluoromethyl)-6-fluoroquinoline **III.2.ggB** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a brown liquid in 3% yield, estimated (17 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.26$ (dd, $^3J_{\text{H-H}} = 9.3$, $^4J_{\text{H-F}} = 5.5$ Hz, 1H, C_8H), 7.94 (s, 1H, C_3H), 7.77 (dd, $^3J_{\text{H-F}} = 9.6$, $^4J_{\text{H-H}} = 2.7$ Hz, 1H, C_5H), 7.63 (ddd, $^3J_{\text{H-H}} = 9.3$, $^3J_{\text{H-F}} = 8.0$, $^4J_{\text{H-H}} = 2.7$ Hz, 1H, C_7H), 7.53 (d, $^2J_{\text{H-F}} = 48.9$ Hz, 1H, C_4CHFCl), 6.80 (t, $^2J_{\text{H-F}} = 55.0$ Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -106.78$ - -106.84 (m, C_6F), -114.49 (dd, $^2J_{\text{F-H}} = 55.0$, $^4J_{\text{F-H}} = 2.9$ Hz, C_2CHF_2), -137.65 (d, $^2J_{\text{F-H}} = 48.7$ Hz, C_4CHFCl) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 161.61$ (d, $^1J_{\text{C-F}} = 253.2$ Hz, C_6), 152.11 (t, $^2J_{\text{C-F}} = 27.1$ Hz, C_2), 144.94 (s, C_9), 143.01 (dd, $^2J_{\text{C-F}} = 20.9$, $^4J_{\text{C-F}} = 6.2$ Hz, C_4), 133.56 (d, $^3J_{\text{C-F}} = 9.7$ Hz, C_8), 128.42 (s, C_{10}), 121.43 (d, $^2J_{\text{C-F}} = 25.8$ Hz, C_7), 114.11 (t, $^1J_{\text{C-F}} = 241.0$ Hz, C_2CHF_2), 114.10 (d, $^3J_{\text{C-F}} = 8.8$ Hz, C_3), 107.65 (d, $^2J_{\text{C-F}} = 24.1$ Hz, C_5), 97.09 (d, $^1J_{\text{C-F}} = 244.8$ Hz, C_4CHFCl) ppm. HRMS (ESI positive) for $\text{C}_{11}\text{H}_7\text{F}_4\text{NCl}$ [M^+]: calcd 264.0198, found 264.0198.

**III.2.ggB**

Chemical Formula: $\text{C}_{11}\text{H}_6\text{ClF}_4\text{N}$
Exact Mass: 263,01 g/mol
Brown liquid

2,4-Bis(difluoromethyl)-8-(trifluoromethoxy)quinoline III.2.hhA

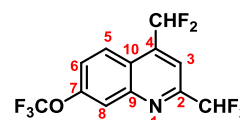
a) TFEDMA **A.1** (1.44 equiv., 0.34 mL, 2.91 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.44 equiv., 0.37 mL, 2.92 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethoxy)aniline **III.1.hh** (1 equiv., 512 mg, 2.02 mmol); and d) 2,4-Bis(difluoromethyl)-8-(trifluoromethoxy)quinoline **III.2.hhA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 39% yield (244 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.11$ (dd, $^3J_{\text{H-H}} = 8.1$, $^4J_{\text{H-H}} = 1.4$ Hz, 1H, C₇H), 8.01 (s, 1H, C₃H), 7.76 – 7.75 (m, 2H, C_{5,6}H), 7.18 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C₄CHF₂), 6.85 (t, $^2J_{\text{H-F}} = 54.8$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -57.55$ (s, C₈OCF₃), -114.12 (d, $^2J_{\text{F-H}} = 54.9$ Hz, C₂CHF₂), -114.91 (d, $^2J_{\text{F-H}} = 54.3$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 153.55$ (t, $^2J_{\text{C-F}} = 28.0$ Hz, C₂), 146.06 (s, C₈), 141.11 (s, C₉), 140.23 (t, $^2J_{\text{C-F}} = 22.5$ Hz, C₄), 128.98 (s, C₅), 126.25 (s, C₁₀), 122.56 (s, C₇), 122.14 (s, C₆), 120.47 (q, $^1J_{\text{C-F}} = 259.6$ Hz, C₈OCF₃), 115.59 (t, $^3J_{\text{C-F}} = 7.9$ Hz, C₃), 114.29 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C₂CHF₂), 112.98 (t, $^1J_{\text{C-F}} = 241.7$ Hz, C₄CHF₂) 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.



III.2.hhA
 Chemical Formula: C₁₂H₆F₇NO
 Exact Mass: 313,03 g/mol
 Yellow solid

2,4-Bis(difluoromethyl)-7-(trifluoromethoxy)quinoline III.2.iiA

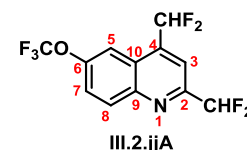
a) TFEDMA **A.1** (1.2 equiv., 0.278 mL, 2.38 mmol); b) $\text{BF}_3 \bullet \text{Et}_2\text{O}$ (1.2 equiv., 0.301 mL, 2.38 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethoxy)aniline **III.1.ii** (1 equiv., 501 mg, 1.98 mmol); and d) 2,4-Bis(difluoromethyl)-7-(trifluoromethoxy)quinoline **III.2.iiA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a light brown liquid in 71% yield (440 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.08$ (d, $^3J_{\text{H-H}} = 9.2$ Hz, 1H, C₅H), 7.93 (s, 1H, C₈H), 7.79 (s, 1H, C₃H), 7.46 (d, $^3J_{\text{H-H}} = 9.2$ Hz, 1H, C₆H), 7.03 (t, $^2J_{\text{H-F}} = 54.2$ Hz, 1H, C₄CHF₂), 6.69 (t, $^2J_{\text{H-F}} = 55.0$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -58.14$ (s, C₇OCF₃), -114.72 (d, $^2J_{\text{F-H}} = 54.1$ Hz, C₂CHF₂), -115.17 (d, $^2J_{\text{F-H}} = 54.9$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 154.12$ (t, $^2J_{\text{C-F}} = 27.3$ Hz, C₂), 150.58 (s, C₇), 148.46 (s, C₉), 140.14 (t, $^2J_{\text{C-F}} = 22.5$ Hz, C₄), 125.76 (s, C₅), 123.13 (s, C₆), 122.95 (s, C₁₀), 120.58 (q, $^1J_{\text{C-F}} = 259.4$ Hz, C₇OCF₃), 120.02 (s, C₈), 114.72 (tt, $^3J_{\text{C-F}} = 8$, $^3J_{\text{C-F}} = 1.8$ Hz, C₃), 114.04 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C₂CHF₂), 113.12 (t, $^1J_{\text{C-F}} = 241.4$ Hz, C₄CHF₂) ppm. C₁₂H₆F₇NO (313): calcd (%) N 4.47, C 45.98, H 1.92, found N 4.49, C 46.13, H 2.15.



III.2.iiA
 Chemical Formula: C₁₂H₆F₇NO
 Exact Mass: 313,03 g/mol
 Light brown liquid

2,4-Bis(difluoromethyl)-6-(trifluoromethoxy)quinoline III.2.jjA

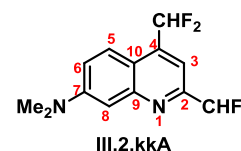
a) TFEDMA **A.1** (1.5 equiv., 0.347 mL, 2.96 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.51 equiv., 0.378 mL, 2.98 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethoxy)aniline **III.1.jj** (1 equiv., 500 mg, 1.98 mmol); and d) 2,4-Bis(difluoromethyl)-6-(trifluoromethoxy)quinoline **III.2.jjA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 58% yield (361 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.30 (d, $^3J_{\text{H-H}}$ = 9.3 Hz, 1H, C₈H), 7.96 – 7.95 (m, 2H, C_{3, 5}H), 7.73 (dd, $^3J_{\text{H-H}}$ = 9.3, $^4J_{\text{H-H}}$ = 1.8 Hz, 1H, C₇H), 7.13 (t, $^2J_{\text{H-F}}$ = 56.0 Hz, 1H, C₄CHF₂), 6.80 (t, $^2J_{\text{H-F}}$ = 55.0 Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -57.71 (s, C₆OCF₃), -114.67 (d, $^2J_{\text{F-H}}$ = 55.0 Hz, C₂CHF₂), -114.88 (d, $^2J_{\text{F-H}}$ = 54.1 Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 153.23 (t, $^2J_{\text{C-F}}$ = 27.5 Hz, C₂), 148.97 (s, C₆), 146.01 (s, C₉), 140.06 (t, $^2J_{\text{C-F}}$ = 22.5 Hz, C₄), 133.17 (s, C₈), 125.23 (s, C₁₀), 124.89 (s, C₇), 120.59 (q, $^1J_{\text{C-F}}$ = 259.2 Hz, C₆OCF₃), 115.64 – 115.49 (m, C₃), 114.32 (s, C₅), 114.08 (t, $^1J_{\text{C-F}}$ = 241.6 Hz, C₂CHF₂), 113.09 (t, $^1J_{\text{C-F}}$ = 240.0 Hz, C₄CHF₂) 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.



III.2.jjA
Chemical Formula: C₁₂H₆F₇NO
Exact Mass: 313.03 g/mol
Yellow solid

2,4-Bis(difluoromethyl)-*N,N*-dimethylquinolin-7-amine III.2.kkA

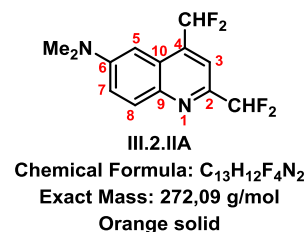
a) TFEDMA **A.1** (1.2 equiv., 0.331 mL, 2.83 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.358 mL, 2.83 mmol); c) 3-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,3-diamine **III.1.kk** (1 equiv., 500 mg, 2.36 mmol); and d) 2,4-Bis(difluoromethyl)-*N,N*-dimethylquinolin-7-amine **III.2.kkA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a brown solid in 15% yield (98.2 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 7.94 (d, $^3J_{\text{H-H}}$ = 9.4 Hz, 1H, C₅H), 7.55 (s, 1H, C₈H), 7.29 (dd, $^3J_{\text{H-H}}$ = 9.4, $^4J_{\text{H-H}}$ = 2.7 Hz, 1H, C₆H), 7.21 (d, $^4J_{\text{H-F}}$ = 2.7 Hz, 1H, C₃H), 7.08 (t, $^2J_{\text{H-F}}$ = 54.6 Hz, 1H, C₄CHF₂), 6.72 (t, $^2J_{\text{H-F}}$ = 55.4 Hz, 1H, C₂CHF₂), 3.13 (s, 6H, C₇N(CH₃)₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -114.59 (d, $^2J_{\text{F-H}}$ = 54.6 Hz, C₂CHF₂), -114.89 (d, $^2J_{\text{F-H}}$ = 55.4 Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 152.95 (t, $^2J_{\text{C-F}}$ = 26.5 Hz, C₂), 151.69 (s, C₇), 150.03 (s, C₉), 139.30 (t, $^2J_{\text{C-F}}$ = 23.9 Hz, C₄), 124.08 (s, C₅), 118.49 (s, C₈), 116.98 (s, C₁₀), 114.56 (t, $^1J_{\text{C-F}}$ = 264.0 Hz, C₂CHF₂), 113.54 (t, $^1J_{\text{C-F}}$ = 240.8 Hz, C₄CHF₂), 109.73 (tt, $^3J_{\text{C-F}}$ = 8.0, $^3J_{\text{C-F}}$ = 2.2 Hz, C₃), 107.26 (s, C₆), 40.38 (s, C₇N(CH₃)₂) 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.



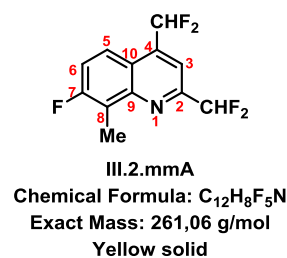
III.2.kkA
Chemical Formula: C₁₃H₁₂F₄N₂
Exact Mass: 272.09 g/mol
Brown solid

2,4-Bis(difluoromethyl)-*N,N*-dimethylquinolin-6-amine III.2.IIA

a) TFEDMA **A.1** (1.2 equiv., 0.331 mL, 2.83 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.358 mL, 2.83 mmol); c) 4-*N*-(1,1-Difluoropropan-2-ylidene)-1-*N,N*-dimethylbenzene-1,4-diamine **III.1.II** (1 equiv., 500 mg, 2.36 mmol); and d) 2,4-Bis(difluoromethyl)-*N,N*-dimethylquinolin-6-amine **III.2.IIA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as an orange solid in 14% yield (91.9 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.01$ (d, $^3J_{\text{H-H}} = 9.4$ Hz, 1H, C_8H), 7.76 (s, 1H, C_3H), 7.42 (dd, $^3J_{\text{H-H}} = 9.5$, $^4J_{\text{H-H}} = 2.7$ Hz, 1H, C_7H), 7.07 (t, $^2J_{\text{H-F}} = 54.6$ Hz, 1H, C_4CHF_2), 6.90 (s, 1H, C_5H), 6.75 (t, $^2J_{\text{H-F}} = 55.5$ Hz, 1H, C_2CHF_2), 3.14 (s, 1H, $\text{C}_6\text{N}(\text{CH}_3)_2$) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -113.38$ (d, $^2J_{\text{F-H}} = 55.5$ Hz, C_2CHF_2), -116.67 (d, $^2J_{\text{F-H}} = 54.6$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 149.96$ (s, C_6), 147.42 (t, $^2J_{\text{C-F}} = 26.8$ Hz, C_2), 141.73 (s, C_9), 136.29 (t, $^2J_{\text{C-F}} = 21.5$ Hz, C_4), 131.36 (s, C_8), 126.89 (s, C_{10}), 120.03 (s, C_7), 114.90 (t, $^1J_{\text{C-F}} = 239.9$ Hz, C_2CHF_2), 114.64 (t, $^3J_{\text{C-F}} = 8.1$ Hz, C_3), 113.69 (t, $^1J_{\text{C-F}} = 241.4$ Hz, C_4CHF_2), 99.55 (s, C_5), 40.53 (s, $\text{C}_6\text{N}(\text{CH}_3)_2$) ppm. $\text{C}_{13}\text{H}_{12}\text{F}_4\text{N}_2$ (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.

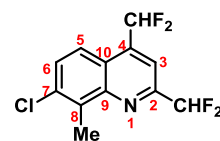
**2,4-Bis(difluoromethyl)-7-fluoro-8-methylquinoline III.2.mmA**

a) TFEDMA **A.1** (1.2 equiv., 0.698 mL, 5.96 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.756 mL, 5.96 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-3-fluoro-2-methylaniline **III.1.mm** (1 equiv., 1 g, 4.97 mmol); and d) 2,4-Bis(difluoromethyl)-7-fluoro-8-methylquinoline **III.2.mmA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a yellow solid in 76% yield (990 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.96$ (dd, $^3J_{\text{H-H}} = 9.0$, $^4J_{\text{H-F}} = 5.9$ Hz, 1H, C_5H), 7.86 (s, 1H, C_3H), 7.47 (t, $^3J_{\text{H-H}} = 9.0$ Hz, 1H, C_6H), 7.13 (t, $^2J_{\text{H-F}} = 54.3$ Hz, 1H, C_4CHF_2), 6.81 (t, $^2J_{\text{H-F}} = 55.1$ Hz, 1H, C_2CHF_2), 2.71 (d, $^4J_{\text{H-F}} = 2.5$ Hz, 3H, C_8CH_3) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -109.41$ (ddd, $^3J_{\text{H-F}} = 8.4$, $^4J_{\text{H-F}} = 5.6$, $^4J_{\text{CH}_3\text{-F}} = 2.7$ Hz, C_7F), -114.20 (d, $^2J_{\text{H-F}} = 55.1$ Hz, C_2CHF_2), -114.56 (d, $^2J_{\text{H-F}} = 54.3$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 161.37$ (d, $^1J_{\text{C-F}} = 249.1$ Hz, C_7), 152.53 (t, $^2J_{\text{C-F}} = 27.5$ Hz, C_2), 148.08 (d, $^3J_{\text{C-F}} = 10.1$ Hz, C_9), 140.19 (t, $^2J_{\text{C-F}} = 21.5$ Hz, C_4), 123.23 (d, $^2J_{\text{C-F}} = 16.1$ Hz, C_8), 122.36 (d, $^3J_{\text{C-F}} = 10.2$ Hz, C_5), 121.85 (s, C_{10}), 119.38 (d, $^2J_{\text{C-F}} = 27.0$ Hz, C_6), 114.58 (t, $^1J_{\text{C-F}} = 241.2$ Hz, C_2CHF_2), 113.12 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C_4CHF_2), 113.12 (s, C_3), 9.34 (d, $^4J_{\text{H-F}} = 3.8$ Hz, C_8CH_3) ppm. $\text{C}_{12}\text{H}_8\text{F}_5\text{N}$ (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 III.2.nnA

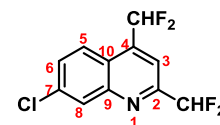
a) TFEDMA **A.1** (1.2 equiv., 0.662 mL, 5.66 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.717 mL, 5.66 mmol); c) 3-Chloro-*N*-(1,1-difluoropropan-2-ylidene)-2-methylaniline **III.1.nn** (1 equiv., 1.03 g, 4.72 mmol); and d) 7-Chloro-2,4-bis(difluoromethyl)-8-methylquinoline **III.2.nnA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as colourless solid in 75% yield (977 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.89 - 7.88$ (m, 2H, $\text{C}_{3,5}\text{H}$), 7.67 (d, $^3J_{\text{H-H}} = 9.1$ Hz, 1H, C_6H), 7.13 (t, $^2J_{\text{H-F}} = 54.3$ Hz, 1H, C_4CHF_2), 6.80 (t, $^2J_{\text{H-F}} = 55.1$ Hz, 1H, C_2CHF_2), 2.88 (s, 3H, C_8CH_3) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -114.17$ (d, $^2J_{\text{F-H}} = 55.1$ Hz, C_2CHF_2), -114.75 (d, $^2J_{\text{F-H}} = 54.3$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 152.34$ (t, $^2J_{\text{C-F}} = 27.6$ Hz, C_2), 147.27 (s, C_9), 140.27 (t, $^2J_{\text{C-F}} = 22.2$ Hz, C_4), 136.83 (s, C_7), 136.57 (s, C_8), 130.56 (s, C_6), 123.48 (s, C_{10}), 121.65 (s, C_5), 114.52 (t, $^1J_{\text{C-F}} = 241.3$ Hz, C_2CHF_2), 113.97 (t, $^3J_{\text{C-F}} = 7.9$ Hz, C_3), 113.08 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C_4CHF_2), 14.84 (s, C_8CH_3) ppm. $\text{C}_{12}\text{H}_8\text{F}_4\text{NCl}$ (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.



III.2.nnA
Chemical Formula: $\text{C}_{12}\text{H}_8\text{ClF}_4\text{N}$
Exact Mass: 277,03 g/mol
Colourless solid

7-Chloro-2,4-bis(difluoromethyl)quinoline III.2.ooA

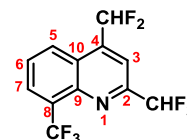
a) TFEDMA **A.1** (1.2 equiv., 3.45 mL, 29.5 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 3.73 mL, 29.5 mmol); c) 3-Chloro-*N*-(1,1-difluoropropan-2-ylidene)aniline **III.1.oo** (1 equiv., 5 g, 24.6 mmol); and d) 7-Chloro-2,4-bis(difluoromethyl)quinoline **III.2.ooA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as colourless solid in 45% yield (2.93 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.20$ (d, $^4J_{\text{H-H}} = 2.1$ Hz, 1H, C_8H), 8.07 (d, $^3J_{\text{H-H}} = 9.0$ Hz, 1H, C_5H), 7.88 (s, 1H, C_3H), 7.67 (dd, $^3J_{\text{H-H}} = 9.0$, $^4J_{\text{H-H}} = 2.1$ Hz, 1H, C_6H), 7.12 (t, $^2J_{\text{H-F}} = 54.2$ Hz, 1H, C_4CHF_2), 6.77 (t, $^2J_{\text{H-F}} = 55.0$ Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -114.73$ (t, $^2J_{\text{F-H}} = 54.4$ Hz, $\text{C}_2\text{CHF}_2 + \text{C}_4\text{CHF}_2$) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 153.83$ (t, $^2J_{\text{C-F}} = 27.3$ Hz, C_2), 148.27 (s, C_9), 140.12 (t, $^2J_{\text{C-F}} = 22.4$ 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_{10}), 114.58 (tt, $^3J_{\text{C-F}} = 8$, $^3J_{\text{C-F}} = 1.8$ Hz, C_3), 114.09 (t, $^1J_{\text{C-F}} = 242.9$ Hz, C_2CHF_2), 113.08 (t, $^1J_{\text{C-F}} = 241.5$ Hz, C_4CHF_2) ppm. $\text{C}_{11}\text{H}_6\text{F}_4\text{NCl}$ (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.



III.2.ooA
Chemical Formula: $\text{C}_{11}\text{H}_6\text{ClF}_4\text{N}$
Exact Mass: 263,01 g/mol
Colourless solid

2,4-Bis(difluoromethyl)-8-(trifluoromethyl)quinoline III.2.ppA

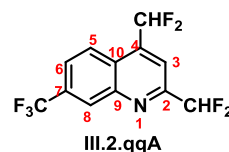
a) TFEDMA **A.1** (1.2 equiv., 0.178 mL, 1.52 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.192 mL, 1.52 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-2-(trifluoromethyl)aniline **III.1.pp** (1 equiv., 0.5 g, 1.26 mmol); and d) 2,4-Bis(difluoromethyl)-8-(trifluoromethyl)quinoline **III.2.ppA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as colourless solid (traces). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.37$ (d, $^2J_{\text{H-H}} = 8.4$ Hz, 1H, C_7H), 8.22 (d, $^2J_{\text{H-H}} = 7.3$ Hz, 1H, C_5H), 8.02 (s, 1H, C_3H), 7.81 (t, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C_6H), 7.18 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C_4CHF_2), 6.84 (t, $^2J_{\text{H-F}} = 54.9$ Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -60.17$ (s, C_8CF_3), -114.25 (d, $^2J_{\text{F-H}} = 56.4$ Hz, C_2CHF_2), -114.36 (d, $^2J_{\text{F-H}} = 54.8$ Hz, C_4CHF_2) ppm. HRMS (ESI positive) for $\text{C}_{12}\text{H}_7\text{F}_7\text{N}$ [M^+]: calcd 298.0461, found 298.0424.



III.2.ppA
Chemical Formula: $\text{C}_{12}\text{H}_6\text{F}_7\text{N}$
Exact Mass: 297,04 g/mol
Colourless solid

2,4-Bis(difluoromethyl)-7-(trifluoromethyl)quinoline III.2.qqA

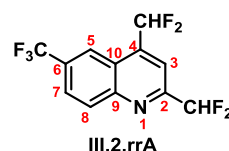
a) TFEDMA **A.1** (1.2 equiv., 0.56 mL, 4.79 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.606 mL, 4.79 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-3-(trifluoromethyl)aniline **III.1.qq** (1 equiv., 0.946 g, 3.99 mmol); and d) 2,4-Bis(difluoromethyl)-7-(trifluoromethyl)quinoline **III.2.qqA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as colourless solid in 28% yield (328.5 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.56$ (s, 1H, C_8H), 8.31 (d, $^3J_{\text{H-H}} = 8.9$ Hz, 1H, C_5H), 8.02 (s, 1H, C_3H), 7.93 (d, $^3J_{\text{H-H}} = 8.7$ Hz, 1H, C_6H), 7.19 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C_4CHF_2), 6.82 (t, $^2J_{\text{H-F}} = 54.9$ Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -63.10$ (s, C_7CF_3), -114.71 (d, $^2J_{\text{F-H}} = 56.4$ Hz, C_2CHF_2), -114.81 (d, $^2J_{\text{F-H}} = 54.8$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 154.19$ (t, $^2J_{\text{C-F}} = 27.5$ Hz, C_2), 146.86 (s, C_9), 140.20 (t, $^2J_{\text{C-F}} = 22.6$ Hz, C_4), 132.69 (q, $^2J_{\text{C-F}} = 33.7$ Hz, C_7), 128.43 (s, C_8), 126.15 (s, C_{10}), 125.08 (s, C_5), 124.85 (s, C_6), 123.54 (q, $^1J_{\text{C-F}} = 272.4$ Hz, C_7CF_3), 116.20 (t, $^3J_{\text{C-F}} = 7.6$ Hz, C_3), 114.02 (t, $^1J_{\text{C-F}} = 242.3$ Hz, C_2CHF_2), 112.98 (t, $^1J_{\text{C-F}} = 241.5$ Hz, C_4CHF_2) ppm. $\text{C}_{12}\text{H}_6\text{F}_7\text{N}$ (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.



III.2.qqA
Chemical Formula: $\text{C}_{12}\text{H}_6\text{F}_7\text{N}$
Exact Mass: 297,04 g/mol
Colourless solid

2,4-Bis(difluoromethyl)-6-(trifluoromethyl)quinoline III.2.rrA

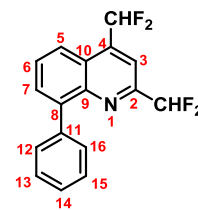
a) TFEDMA **A.1** (1.2 equiv., 0.195 mL, 1.66 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.211 mL, 1.66 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-4-(trifluoromethyl)aniline **III.1.rr** (1 equiv., 328 mg, 1.39 mmol); and d) 2,4-Bis(difluoromethyl)-6-(trifluoromethyl)quinoline **III.2.rrA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a grey solid in 23% yield (93.9 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.46$ (s, 1H, C_5H), 8.37 (d, $^3J_{\text{H-H}} = 8.9$ Hz, 1H, C_8H), 8.04 (dd, $^3J_{\text{H-H}} = 8.9$, $^4J_{\text{H-H}} = 1.8$ Hz, 1H, C_7H), 8.00 (s, 1H, C_3H), 7.20 (t, $^2J_{\text{H-F}} = 54.0$ Hz, 1H, C_4CHF_2), 6.82 (t, $^2J_{\text{H-F}} = 54.9$ Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -62.70$ (s, C_6CF_3), -114.48 (d, $^2J_{\text{F-H}} = 54.0$ Hz, C_2CHF_2), -114.98 (d, $^2J_{\text{F-H}} = 54.9$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 154.90$ (t, $^2J_{\text{C-F}} = 27.4$ Hz, C_2), 148.77 (s, C_9), 141.09 (t, $^2J_{\text{C-F}} = 22.5$ Hz, C_4), 132.14 (s, C_8), 131.11 (q, $^2J_{\text{C-F}} = 33.1$ Hz, C_6), 126.76 (q, $^3J_{\text{C-F}} = 2.9$ Hz, C_7), 123.95 (t, $^3J_{\text{C-F}} = 2.5$ Hz, C_{10}), 123.65 (q, $^1J_{\text{C-F}} = 272.9$ Hz, C_6CF_3), 121.81 (s, C_5), 115.71 (tt, $^3J_{\text{C-F}} = 7.6$, $^3J_{\text{C-F}} = 2.2$ Hz, C_3), 113.94 (t, $^1J_{\text{C-F}} = 243.4$ Hz, C_2CHF_2), 112.93 (t, $^1J_{\text{C-F}} = 241.9$ Hz, C_4CHF_2) ppm. $\text{C}_{12}\text{H}_6\text{F}_7\text{N}$ (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.



III.2.rrA
Chemical Formula: $\text{C}_{12}\text{H}_6\text{F}_7\text{N}$
Exact Mass: 297,04 g/mol
Grey solid

2,4-Bis(difluoromethyl)-8-phenylquinoline III.2.ssA

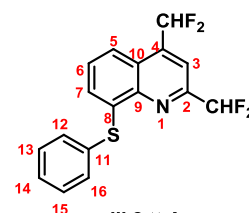
a) TFEDMA **A.1** (1.2 equiv., 0.403 mL, 3.45 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.437 mL, 3.45 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-2-phenylaniline **III.1.ss** (1 equiv., 704 mg, 2.87 mmol) and d) 2,4-Bis(difluoromethyl)-8-phenylquinoline **III.2.ssA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as colourless solid in 28% yield (248.9 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.16$ (dd, $^3J_{\text{H-H}} = 8.5$, $^4J_{\text{H-H}} = 1.5$ Hz, 1H, C_5H), 8.00 (s, 1H, C_3H), 7.92 (dd, $^3J_{\text{H-H}} = 7.2$, $^4J_{\text{H-H}} = 1.3$ Hz, 1H, C_7H), 7.85 – 7.77 (m, 1H, C_6H), 7.76 – 7.70 (m, 2H, $\text{C}_{12, 16}\text{H}$), 7.58 – 7.45 (m, 3H, $\text{C}_{13, 14, 15}\text{H}$), 7.24 (t, $^2J_{\text{H-F}} = 54.3$ Hz, 1H, C_4CHF_2), 6.74 (t, $^2J_{\text{H-F}} = 55.1$ Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -113.70$ (d, $^2J_{\text{F-H}} = 55.1$ Hz, C_2CHF_2), -114.97 (d, $^2J_{\text{F-H}} = 54.3$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 152.18$ (t, $^2J_{\text{C-F}} = 27.8$ Hz, C_2), 145.30 (s, C_9), 142.28 (s, C_{11}), 140.04 (t, $^2J_{\text{C-F}} = 22.0$ Hz, C_4), 138.65 (s, C_8), 131.61 (s, C_7), 131.02 (s, $\text{C}_{13, 15}$), 129.09 (s, C_6), 128.06 (s, $\text{C}_{12, 16}$), 127.84 (s, C_{14}), 125.29 (s, C_{10}), 122.83 (s, C_5), 114.68 (t, $^1J_{\text{C-F}} = 240.9$ Hz, C_2CHF_2), 114.17 (t, $^3J_{\text{C-F}} = 8.0$ Hz, C_3), 113.25 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C_4CHF_2) ppm. $\text{C}_{17}\text{H}_{11}\text{F}_4\text{N}$ (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.

**III.2.ssA**

Chemical Formula: $\text{C}_{17}\text{H}_{11}\text{F}_4\text{N}$
Exact Mass: 305,08 g/mol
Colourless solid

2,4-Bis(difluoromethyl)-8-(phenylsulfanyl)quinoline III.2.ttA

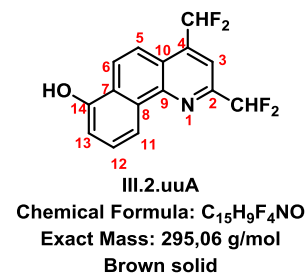
a) TFEDMA **A.1** (1.2 equiv., 0.253 mL, 2.16 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.274 mL, 2.16 mmol); c) *N*-(1,1-Difluoropropan-2-ylidene)-2-(phenylsulfanyl)aniline **III.1.tt** (1 equiv., 500 mg, 1.8 mmol) and d) 2,4-Bis(difluoromethyl)-8-(phenylsulfanyl)quinoline **III.2.ttA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as colourless solid in 52% yield (308.7 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.99$ (s, 1H, C_3H), 7.82 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C_5H), 7.66 (dd, $^3J_{\text{H-H}} = 6.4$, $^4J_{\text{H-H}} = 3.0$ Hz, 2H, $\text{C}_{12, 16}\text{H}$), 7.53 – 7.49 (m, 3H, $\text{C}_{13, 14, 15}\text{H}$), 7.47 (t, $^3J_{\text{H-H}} = 8.0$ Hz, 1H, C_6H), 7.17 (t, $^2J_{\text{H-F}} = 54.3$ Hz, 1H, C_4CHF_2), 7.06 (d, $^3J_{\text{H-H}} = 7.6$ Hz, 1H, C_7H), 6.89 (t, $^2J_{\text{H-F}} = 54.9$ Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -113.66$ (d, $^2J_{\text{F-H}} = 55.0$ Hz, C_2CHF_2), -115.22 (d, $^2J_{\text{F-H}} = 54.2$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 151.47$ (t, $^2J_{\text{C-F}} = 27.7$ Hz, C_2), 143.85 (s, C_9), 143.02 (s, C_8), 140.20 (t, $^2J_{\text{C-F}} = 22.2$ Hz, C_4), 136.16 (s, $\text{C}_{12, 16}$), 130.89 (s, C_{11}), 130.11 (s, $\text{C}_{13, 15}$), 129.64 (s, C_{14}), 129.33 (s, C_6), 126.16 (s, C_7), 125.13 (s, C_{10}), 119.37 (s, C_5), 114.86 (t, $^3J_{\text{C-F}} = 7.9$ Hz, C_3), 114.31 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C_2CHF_2), 112.87 (t, $^1J_{\text{C-F}} = 241.4$ Hz, C_4CHF_2) ppm. $\text{C}_{17}\text{H}_{11}\text{F}_4\text{NS}$ (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.

**III.2.ttA**

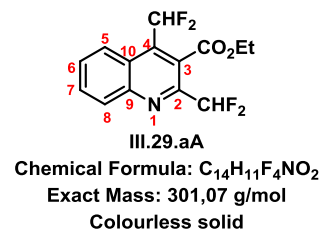
Chemical Formula: $\text{C}_{17}\text{H}_{11}\text{F}_4\text{NS}$
Exact Mass: 337,05 g/mol
Colourless solid

2,4-Bis(difluoromethyl)benzo[h]quinolin-7-ol III.2.uuA

a) TFEDMA **A.1** (1.2 equiv., 0.298 mL, 2.55 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 0.323 mL, 2.55 mmol); c) 5-[(1,1-Difluoropropan-2-ylidene)amino]-1-naphthol **III.1.uu** (1 equiv., 500 mg, 2.13 mmol) and d) 2,4-Bis(difluoromethyl)benzo[h]quinolin-7-ol **III.2.uuA** was obtained after purification using a gradient of AcOEt in pentane (0-5%) as a brown solid in 51% yield (321.7 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.90$ (d, $^3J_{\text{H-H}} = 8.3$ Hz, 1H, C₁₁H), 8.39 (d, $^3J_{\text{H-H}} = 9.4$ Hz, 1H, C₅H), 8.04 (s, 1H, C₃H), 7.93 (d, $^3J_{\text{H-H}} = 9.4$ Hz, 1H, C₆H), 7.61 (t, $^3J_{\text{H-H}} = 8.0$ Hz, 1H, C₁₂H), 7.25 (t, $^2J_{\text{H-F}} = 54.4$ Hz, 1H, C₄CHF₂), 7.11 (d, $^3J_{\text{H-H}} = 7.6$ Hz, 1H, C₁₃H), 6.92 (t, $^2J_{\text{H-F}} = 55.3$ Hz, 1H, C₂CHF₂), 5.43 (br s, 1H, OH) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -113.93$ (d, $^2J_{\text{F-H}} = 55.3$ Hz, C₂CHF₂), -114.96 (d, $^2J_{\text{F-H}} = 54.4$ Hz, C₄CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 151.71$ (s, C₁₄), 151.27 (t, $^2J_{\text{C-F}} = 27.2$ Hz, C₂), 146.29 (s, C₉), 139.47 (t, $^2J_{\text{C-F}} = 22.2$ Hz, C₄), 132.81 (s, C₈ + C₁₀), 128.23 (s, C₁₂), 124.51 (s, C₅), 123.57 (s, C₇), 118.94 (s, C₆), 117.77 (s, C₁₁), 114.73 (tt, $^3J_{\text{C-F}} = 7.6$, $^3J_{\text{C-F}} = 2.2$ Hz, C₃), 114.60 (t, $^1J_{\text{C-F}} = 241.0$ Hz, C₂CHF₂), 113.24 (s, C₁₃), 113.06 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C₄CHF₂) 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.

**3.1.3 From fluorinated acetoacetate (III.28)****Ethyl-2,4-bis(difluoromethyl)quinoline-3-carboxylate III.29.aA**

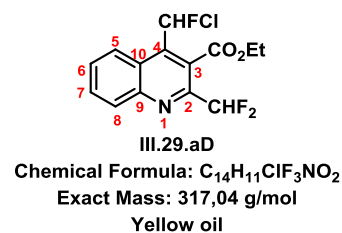
a) TFEDMA **A.1** (1.2 equiv., 3.26 mL, 27.9 mmol); b) $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.2 equiv., 3.53 mL, 27.9 mmol); c) Ethyl-4,4-difluoro-3-(phenylamino)but-2-enoate **III.28.a** (1 equiv., 5.6 g, 23.2 mmol); and d) Ethyl-2,4-bis(difluoromethyl)quinoline-3-carboxylate **III.29.aA** was obtained after purification using a gradient of AcOEt in cyclohexane (0-5%) as colourless solid in 89% yield (6.54 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.40$ (dd, $^3J_{\text{H-H}} = 8.6$, $^5J_{\text{H-F}} = 1.4$ Hz, 1H, C₅H), 8.23 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C₈H), 7.88 (ddd, $^3J_{\text{H-H1}} = 8.4$, $^3J_{\text{H-H4}} = 7.0$, $^4J_{\text{H-H2}} = 1.2$ Hz, 1H, C₆H), 7.76 (ddd, $^3J_{\text{H-H2}} = 8.3$, $^3J_{\text{H-H3}} = 7.0$, $^4J_{\text{H-H1}} = 1.0$ Hz, 1H, C₇H), 7.19 (t, $^2J_{\text{H-F}} = 52.9$ Hz, 1H, C₄CHF₂), 6.93 (t, $^2J_{\text{H-F}} = 54.6$ Hz, 1H, C₂CHF₂), 4.53 (q, $^3J_{\text{H-H}} = 7.2$ Hz, 2H, C₃OCH₂CH₃), 1.44 (t, $^3J_{\text{H-H}} = 7.2$ Hz, 3H, C₃OCH₂CH₃) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -109.64$ (dd, $^2J_{\text{F-H}} = 53.0$, $^5J_{\text{F-H}} = 2.0$ Hz, C₄CHF₂), -115.25 (d, $^2J_{\text{F-H}} = 54.6$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 165.32$ (s, C₃CO), 148.26 (t, $^2J_{\text{C-F}} = 25.3$ Hz, C₂), 147.56 (s, C₁₀), 137.17 (t, $^2J_{\text{C-F}} = 23.3$ Hz, C₄), 131.84 (s, C₆), 130.80 (s, C₈), 129.99 (s, C₇), 125.43 (t, $^4J_{\text{C-F}} = 3.7$ Hz, C₅), 124.21 (t, $^3J_{\text{C-F}} = 6.6$ Hz, C₃), 123.57 (s, C₉), 114.08 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C₂CHF₂), 112.93 (t, $^1J_{\text{C-F}} = 241.4$ Hz, C₄CHF₂), 63.30 (s, C₃OCH₂CH₃), 14.03 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2988-2901 (C_{sp3}H), 1721 (C=O_{ester}). C₁₄H₁₁F₄NO₂ (301): calcd (%) N 4.65, C 55.82, H 3.68, found N 4.63, C 55.86, H 3.78. MP: 65.5 – 66.7 °C.



Ethyl-4-(chlorofluoromethyl)-2-(difluoromethyl)quinoline-3-carboxylate
III.29.aD

Far was freshly prepared according to the procedure part 1.

a) *N*-(2-Chloro-1,2-difluoroethylidene)-*N*-methylmethanaminium tetrafluoroborate **D.2** (1.30 equiv., 1.19 g, 5.2 mmol); b) Ethyl-4,4-difluoro-3-(phenylamino)but-2-enoate **III.28.a** (1 equiv., 1.56 g, 3.87 mmol); and d) Ethyl-4-(chlorofluoromethyl)-2-(difluoromethyl)quinoline-3-carboxylate **III.29.aD** was obtained after purification using a gradient of AcOEt in cyclohexane (0-5%)

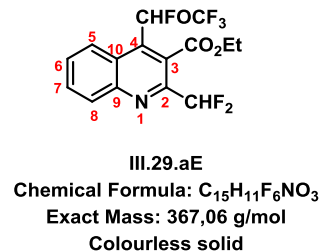


as a yellow oil in 85% yield (1.04 g). 1H NMR (400 MHz, $CDCl_3$) δ_H = 8.48 (d, $^3J_{H-H}$ = 8.6 Hz, 1H, C_5H), 8.23 (d, $^3J_{H-H}$ = 7.9 Hz, 1H, C_8H), 7.88 (ddd, $^3J_{H-H1}$ = 8.4, $^3J_{H-H4}$ = 6.9, $^4J_{H-H2}$ = 1.3 Hz, 1H, C_6H), 7.77 (ddd, $^3J_{H-H2}$ = 8.4, $^3J_{H-H3}$ = 6.9, $^4J_{H-H1}$ = 1.3 Hz, 1H, C_7H), 7.62 (d, $^2J_{H-F}$ = 48.6 Hz, 1H, C_4CHFCI), 6.93 (t, $^2J_{H-F}$ = 54.6 Hz, 1H, C_2CHF_2), 4.61 – 4.44 (m, 2H, $C_3OCH_2CH_3$), 1.45 (t, $^3J_{H-H}$ = 7.2 Hz, 3H, $C_3OCH_2CH_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -115.30 (d, $^2J_{F-H}$ = 54.6 Hz, C_2CHF_2), -133.91 (d, $^2J_{F-H}$ = 48.6 Hz, C_4CHFCI) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 165.40 (s, C_3CO), 148.30 (t, $^2J_{C-F}$ = 25.2 Hz, C_2), 147.71 (s, C_{10}), 140.20 (d, $^2J_{C-F}$ = 21.2 Hz, C_4), 131.77 (s, C_6), 131.02 (s, C_8), 129.71 (s, C_7), 125.43 (d, $^4J_{C-F}$ = 5.7 Hz, C_5), 123.07 (s, C_9), 122.10 (d, $^3J_{C-F}$ = 5.3 Hz, C_3), 114.03 (t, $^1J_{C-F}$ = 244.1 Hz, C_2CHF_2), 96.76 (d, $^1J_{C-F}$ = 244.6 Hz, C_4CHFCI), 63.26 (s, $C_3OCH_2CH_3$), 14.04 (s, $C_3OCH_2CH_3$) ppm. IR ν (cm^{-1}): 2987-2907 ($C_{sp^3}H$), 1727 ($C=O_{ester}$). $C_{14}H_{11}F_3ClNO_2$ (317): calcd (%) N 4.41, C 52.93, H 3.49, found N 4.32, C 52.63, H 3.59.

Ethyl-2-(difluoromethyl)-4-(fluoro(trifluoromethoxy)methyl)quinoline-3-carboxylate III.29.aE

Far was freshly prepared according to the procedure part 1.

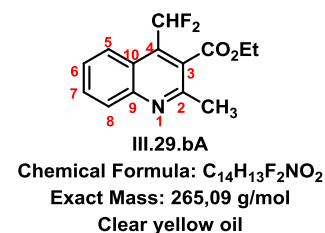
a) *N*-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate **E.2** (1.57 equiv., 1.7 g, 6.1 mmol); b) Ethyl-4,4-difluoro-3-(phenylamino)but-2-enoate **III.28.a** (1 equiv., 1.56 g, 3.87 mmol); and d) Ethyl-2-(difluoromethyl)-4-(fluoro(trifluoromethoxy)methyl)quinoline-3-carboxylate **III.29.aE** was obtained after purification using a gradient of AcOEt in cyclohexane (0-20%) as colourless solid in 97% yield (1.38 g). 1H NMR (400 MHz, $CDCl_3$) δ_H = 8.41 (d, $^3J_{H-H}$ = 8.6 Hz, 1H, C_5H), 8.23 (d, $^3J_{H-H}$ = 8.4 Hz, 1H, C_8H), 7.93 – 7.82 (m, 1H, C_7H), 7.82 – 7.67 (m, 1H, C_6H), 7.28 (d, $^2J_{H-F}$ = 54.8 Hz, 1H, $C_4CHFOCF_3$), 6.95 (t, $^2J_{H-F}$ = 54.6 Hz, 1H, C_2CHF_2), 4.61 – 4.45 (m, 2H, $C_3OCH_2CH_3$), 1.44 (t, $^3J_{H-H}$ = 7.2 Hz, 3H, $C_3OCH_2CH_3$) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -59.39 (d, $^4J_{F-F}$ = 4.9 Hz, $C_4CHFOCF_3$), -114.33 – -116.46 (m, A_2B_2 , $\Delta\nu$ = 485.13 Hz, C_2CHF_2), -120.55 (dq, $^2J_{F-H}$ = 54.9, $^4J_{F-F}$ = 4.8, $^5J_{F-H}$ = 2.1 Hz, $C_4CHFOCF_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 165.28 (s, C_3CO), 148.35 (t, $^2J_{C-F}$ = 25.3 Hz, C_2), 147.68 (s, C_9), 136.42 (d, $^2J_{C-F}$ = 24.1 Hz, C_4), 131.91 (s, C_7), 130.87 (s, C_8), 130.02 (s, C_6), 125.63 (d, $^4J_{C-F}$ = 4.9 Hz, C_5), 123.97 (d, $^3J_{C-F}$ = 6.2 Hz, C_3), 123.46 (s, C_{10}), 121.08 (qd, $^1J_{C-F}$ = 262.6, $^3J_{C-F}$ = 1.7 Hz, $C_4CHFOCF_3$), 114.05 (t, $^1J_{C-F}$ = 244.1 Hz, C_2CHF_2), 103.11 (dq, $^1J_{C-F}$ = 232.2, $^3J_{C-F}$ = 3.9 Hz, $C_4CHFOCF_3$), 63.42 (s, $C_3OCH_2CH_3$), 13.90 (s, $C_3OCH_2CH_3$) ppm. IR ν (cm^{-1}): 2991-2943 ($C_{sp^3}H$), 1727 ($C=O_{ester}$). $C_{15}H_{11}F_6NO_3$ (367): calcd (%) N 3.81, C 49.06, H 3.02, found N 3.74, C 49.23, H 3.18. MP: 43.3 - 44.8 °C.



Ethyl-4-(difluoromethyl)-2-methylquinoline-3-carboxylate III.29.bA*Addition of H₂SO₄*

a) TFEDMA **A.1** (1.2 equiv., 0.207 mL, 1.77 mmol); b) BF₃•Et₂O (1.2 equiv., 0.224 mL, 1.77 mmol); c) Ethyl-3-(phenylamino)but-2-enoate **III.28.b** (1 equiv., 0.466 g, 1.47 mmol); d) H₂SO₄ (20 equiv., 18 M, 1.64 mL, 29.5 mmol) and stirred for an additional 12 h; and e) Traces of the ethyl-4-(difluoromethyl)-2-methylquinoline-3-carboxylate

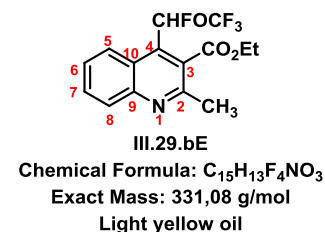
III.29.bA were obtained after purification using a gradient of AcOEt in cyclohexane (0-80%) as a clear yellow oil. ¹H NMR (500 MHz, CDCl₃) δ_H = 8.25 (dd, ³J_{H-H} = 8.5, ⁵J_{H-F} = 1.6 Hz, 1H, C₅H), 8.09 (d, ³J_{H-H} = 8.4 Hz, 1H, C₈H), 7.79 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H4} = 6.9, J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.63 (ddd, ³J_{H-H1} = 8.3, ³J_{H-H3} = 6.9, ⁴J_{H-H2} = 1.2 Hz, 1H, C₆H), 7.10 (t, ²J_{H-F} = 53.3 Hz, 1H, C₄CHF₂), 4.51 (q, ³J_{H-H} = 7.2 Hz, 2H, C₃OCH₂CH₃), 2.77 (s, 3H, C₂CH₃), 1.45 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -110.31 (dd, ²J_{F-H} = 53.2, ⁵J_{F-H} = 1.9 Hz, C₄CHF₂) ppm. ¹³C NMR (126 MHz, CDCl₃) δ_C = 167.51 (s, C₃CO), 154.78 (s, C₂), 148.29 (s, C₁₀), 134.78 (t, ²J_{C-F} = 22.6 Hz, C₄), 130.97 (s, C₇), 129.72 (s, C₈), 127.73 (s, C₆), 126.54 (t, ³J_{C-F} = 6.0 Hz, C₃), 124.79 (t, ⁴J_{C-F} = 2.9 Hz, C₅), 121.72 (s, C₉), 113.38 (t, ¹J_{C-F} = 241.2 Hz, C₄CHF₂), 62.67 (s, C₃OCH₂CH₃), 23.83 (s, C₂CH₃), 14.26 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2986-2929 (C_{sp3}H), 1726 (C=O_{ester}). C₁₄H₁₃F₂NO₂ (265): calcd (%) N 5.28, C 63.39, H 4.94, found N 4.89, C 63.62, H 5.21.

**Ethyl-4-[fluoro(trifluoromethoxy)methyl]-2-methylquinoline-3-carboxylate III.29.bE***Addition of H₂SO₄*

Far was freshly prepared according to the procedure part 1.

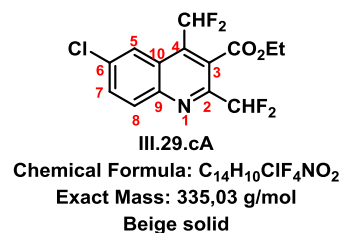
a) N-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-N-methylmethanaminium tetrafluoroborate **E.2** (1.59 equiv., 1.7 g, 6.1 mmol); b) Ethyl-3-(phenylamino)but-2-enoate **III.28.b** (1 equiv., 1.21 g, 3.82 mmol); d) H₂SO₄ (10 equiv., 18 M, 2.12 mL, 38.2 mmol) and stirred for an additional 4 h; and e) Ethyl-4-[fluoro(trifluoromethoxy)methyl]-2-methylquinoline-3-carboxylate

III.29.bE was obtained after purification using a gradient of AcOEt in cyclohexane (0-20%) in 27% yield (346 mg) as a light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ_H = 8.25 (d, ³J_{H-H} = 8.6 Hz, ⁵J_{H-F} = 1.5, 1H, C₅H), 8.09 (dd, ³J_{H-H} = 8.5, ⁶J_{H-F} = 0.6 Hz, 1H, C₈H), 7.79 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.63 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H3} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.16 (d, ²J_{H-F} = 55.1 Hz, 1H, C₄CHFOCF₃), 4.58 - 4.44 (m, 2H, C₃OCH₂CH₃), 2.77 (s, 3H, C₂CH₃), 1.44 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -59.28 (d, ⁴J_{F-F} = 5.2 Hz, C₄CHFOCF₃), -121.02 (dq, ²J_{F-H} = 55.1, ⁴J_{F-F} = 5.0, ⁵J_{F-H} = 1.9 Hz, C₄CHFOCF₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 167.32 (s, C₃CO), 154.81 (s, C₂), 148.41 (s, C₁₀), 134.01 (d, ²J_{C-F} = 23.4 Hz, C₄), 131.04 (s, C₇), 129.79 (s, C₈), 127.77 (s, C₆), 126.45 (d, ³J_{C-F} = 5.7 Hz, C₃), 124.90 (d, ⁴J_{C-F} = 3.9 Hz, C₅), 121.52 (s, C₉), 121.11 (qd, ¹J_{C-F} = 262.2, ³J_{C-F} = 1.7 Hz, C₄CHFOCF₃), 103.55 (dq, ¹J_{C-F} = 232.2, ³J_{C-F} = 3.9 Hz, C₄CHFOCF₃), 62.76 (s, C₃OCH₂CH₃), 23.96 (s, C₂CH₃), 14.12 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2987 (C_{sp3}H), 1727 (C=O_{ester}). HRMS (ESI positive) for C₁₅H₁₄F₄NO₃ [M⁺]: calcd 332.0904, found 332.0898.



6-Chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylate III.29.cA*Addition of H₂SO₄*

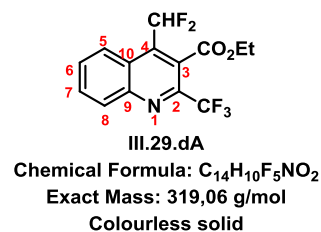
a) TFEDMA **A.1** (1.2 equiv., 0.58 mL, 4.96 mmol); b) BF₃•Et₂O (1.2 equiv., 0.628 mL, 4.96 mmol); c) Ethyl-3-[(4-chlorophenyl)amino]-4,4-difluorobut-2-enoate **III.28.c** (1 equiv., 1.52 g, 4.13 mmol); d) H₂SO₄ (10 equiv., 18 M, 2.29 mL, 41.3 mmol) and stirred for an additional 4 h; and e) 6-Chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylate **III.29.cA** was obtained after purification using a gradient of AcOEt in cyclohexane (0-5%) as a beige solid in 26%



yield (358 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.39 (dd, ⁴J_{H-H} = 3.7, ⁵J_{H-F} = 1.8 Hz, 1H, C₅H), 8.17 (d, ³J_{H-H} = 9.0 Hz, 1H, C₈H), 7.83 (dd, ³J_{H-H} = 9.0, ⁴J_{H-H} = 2.2 Hz, 1H, C₇H), 7.12 (t, ²J_{H-F} = 52.0 Hz, 1H, C₄CHF₂), 6.91 (t, ²J_{H-F} = 54.5 Hz, 1H, C₂CHF₂), 4.53 (q, ³J_{H-H} = 7.2 Hz, 1H, C₃OCH₂CH₃), 1.45 (t, ³J_{H-H} = 7.2 Hz, 1H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -109.66 (dd, ²J_{F-H} = 52.8, ⁵J_{F-H} = 1.7 Hz, C₄CHF₂), -115.46 (d, ²J_{F-H} = 54.5 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.91 (s, C₃CO), 148.53 (t, ²J_{C-F} = 25.5 Hz, C₂), 145.99 (s, C₆), 137.61 – 135.84 (m, C₄ + C₁₀), 132.99 (s, C₇), 132.22 (s, C₈), 125.09 (t, ³J_{C-F} = 6.7 Hz, C₃), 124.63 (t, ⁴J_{C-F} = 4.2 Hz, C₅), 124.18 (s, C₉), 113.86 (t, ¹J_{C-F} = 245.4 Hz, C₂CHF₂), 112.69 (t, ¹J_{C-F} = 241.5 Hz, C₄CHF₂), 63.53 (s, C₃OCH₂CH₃), 14.04 (s, C₃OCH₂CH₃) ppm. IR ν (cm⁻¹): 2990-2941 (C_{sp3}H), 1721 (C=O_{ester}). C₁₄H₁₀F₄NC₁₀O₂ (335): calcd (%) N 4.17, C 50.09, H 3.00, found N 3.98, C 49.59, H 3.19. MP: 71.9 - 74.3 °C.

Ethyl-4-(difluoromethyl)-2-(trifluoromethyl)quinoline-3-carboxylate III.29.dA

a) TFEDMA **A.1** (1.2 equiv., 0.176 mL, 1.51 mmol); b) BF₃•Et₂O (1.2 equiv., 0.191 mL, 1.51 mmol); c) Ethyl-4,4,4-trifluoro-3-(phenylamino)but-2-enoate **III.28.d** (1 equiv., 406 mg, 1.26 mmol); and d) Ethyl-4-(difluoromethyl)-2-(trifluoromethyl)quinoline-3-carboxylate **III.29.dA** was obtained after purification using a gradient of AcOEt in cyclohexane (0-5%) as colourless solid in 80% yield (316 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.44 (dd, ³J_{H-H} = 8.6, ⁵J_{H-F} = 2.0 Hz,



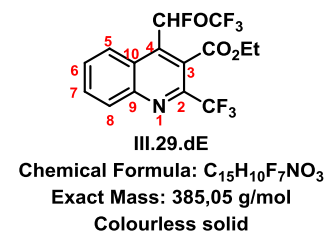
1H, C₅H), 8.31 (dd, ³J_{H-H} = 8.5, ⁶J_{H-F} = 0.6 Hz, 1H, C₈H), 7.95 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.83 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H3} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.13 (t, ²J_{H-F} = 52.8 Hz, 1H, C₄CHF₂), 4.52 (q, ³J_{H-H} = 7.2 Hz, 2H, C₃OCH₂CH₃), 1.44 (t, ³J_{H-H} = 7.2 Hz, 3H, C₃OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -64.17 (s, C₂CF₃), -109.48 (dd, ²J_{F-H} = 52.7, ⁵J_{F-H} = 2.0 Hz, C₄CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 164.90 (s, C₃CO), 147.30 (s, C₁₀), 143.72 (q, ²J_{C-F} = 35.0 Hz, C₂), 137.33 (t, ²J_{C-F} = 23.5 Hz, C₄), 132.19 (s, C₆), 131.17 (s, C₈), 130.75 (s, C₇), 125.37 (t, ⁴J_{C-F} = 3.7 Hz, C₅), 124.04 (s, C₉), 123.97 (s, C₃), 121.03 (q, ¹J_{C-F} = 276.7 Hz, C₂CF₃), 112.86 (t, ¹J_{C-F} = 241.8 Hz, C₄CHF₂), 63.56 (s, C₃OCH₂CH₃), 13.99 (s, C₃OCH₂CH₃). IR ν (cm⁻¹): 2987-2901 (C_{sp3}H), 1731 (C=O_{ester}). C₁₄H₁₀F₅NO₂ (319): calcd (%) N 4.39, C 52.67, H 3.16, found N 4.39, C 52.80, H 3.27. MP: 79.8 - 80.8 °C.

Ethyl-4-[fluoro(trifluoromethoxy)methyl]-2-(trifluoromethyl)quinoline-3-carboxylate III.29.dE

Far was freshly prepared according to the procedure part 1.

a) *N*-(1,2-Difluoro-2-(trifluoromethoxy)ethylidene)-*N*-methylmethanaminium tetrafluoroborate **E.2** (1.57 equiv., 852 mg, 3.06 mmol); b) Ethyl 4,4,4-trifluoro-3-(phenylamino)but-2-enoate **III.28.d** (1 equiv., 503 mg, 1.94 mmol); and d) Ethyl-4-[fluoro(trifluoromethoxy)methyl]-2-(trifluoromethyl)quinoline-3-carboxylate **III.29.dE** was obtained after purification using a gradient

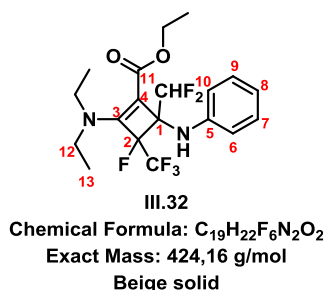
of AcOEt in cyclohexane (0-20%) as colourless solid in 74% yield (551 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.45 (d, ³J_{H-H} = 8.6 Hz, 1H, C₅H), 8.31 (dd, ³J_{H-H} = 8.5, ⁶J_{H-F} = 0.6 Hz, 1H, C₈H), 7.95 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.84 (ddd, ³J_{H-H2} = 8.4,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

**Ethyl 2-(diethylamino)-4-(difluoromethyl)-3-fluoro-4-(phenylamino)-3-(trifluoromethyl)cyclobut-1-ene-1-carboxylate III.32**

Addition of H₂SO₄.

a) Ishikawa's reagent **C.1** (1.2 equiv., 0.867 mL, 3.11 mmol); b) BF₃•Et₂O (1.2 equiv., 0.394 mL, 3.11 mmol); c) Ethyl-4,4-difluoro-3-(phenylamino)but-2-enoate **III.28.a** (1 equiv., 1.04 g, 2.59 mmol); d) H₂SO₄ (10 equiv., 18 M, 1.44 mL, 25.9 mmol) and stirred for an additional 4 h; and e) Ethyl 2-(diethylamino)-4-(difluoromethyl)-3-fluoro-4-(phenylamino)-3-(trifluoromethyl)cyclobut-1-ene-1-carboxylate **III.32** was obtained after purification using a gradient of AcOEt in cyclohexane (0-

5%) as a beige solid in 26% yield (287 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 7.23 – 7.11 (m, 2H, C₇, ₉H), 6.85 – 6.79 (m, 1H, C₈H), 6.74 (d, ³J_{H-H} = 8.3 Hz, 2H, C₆, ₁₀H), 6.53 – 6.20 (m, 1H, C₁CHF₂), 4.84 (s, 1H, NH), 4.13 – 3.93 (m, 2H, C₁₁OCH₂CH₃), 3.73 – 3.34 (m, 4H, C₁₂H), 1.21 (t, ³J_{H-H} = 7.1 Hz, 6H, C₁₃H), 1.16 (t, ³J_{H-H} = 7.1 Hz, 3H, C₁₁OCH₂CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -72.52 (d, ³J_{F-F} = 9.4 Hz, C₂CF₃), -126.98 – -129.35 (m, C₁CHF₂), -169.42 – -169.73 (m, C₂F) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 162.20 (d, ⁴J_{C-F} = 6.8 Hz, C₁₁), 147.26 (d, ²J_{C-F} = 18.2 Hz, C₁), 143.92 (s, C₅), 129.09 (s, C₇, ₉), 121.74 (qd, ¹J_{C-F} = 283.8, ²J_{C-F} = 32.7 Hz, C₂CF₃), 119.86 (s, C₆, ₁₀), 117.24 (s, C₈), 113.03 (td, ¹J_{C-F} = 249.1, ³J_{C-F} = 2.2 Hz, C₁CHF₂), 94.85 (ddd, ¹J_{C-F} = 249.4, ²J_{C-F} = 30.8, ³J_{C-F} = 4.1 Hz, C₂), 90.12 (dt, ²J_{C-F} = 19.2, ³J_{C-F} = 3.6 Hz, C₄), 66.31 (ddd, ²J_{C-F} = 22.9, ²J_{C-F} = 20.8, ³J_{C-F} = 18.6 Hz, C₁), 60.11 (s, C₁₁OCH₂CH₃), 45.09 (s, C₁₂), 14.16 (s, C₁₃ + C₁₁OCH₂CH₃) ppm. C₁₉H₂₂F₆N₂O₂ (424): calcd (%) N 6.60, C 53.77, H 5.23, found N 6.70, C 53.81, H 5.29. MP: 77.9-78.9 °C.



3.2 Typical procedure C for the synthesis of quinoline derivatives (III.16, 17 and III.2.aaA)

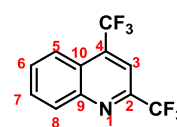
To a solution of enamine (1 equiv) in neat was added H₂SO₄ (10 equiv., 18 M) slowly. The reaction mixture was heated at 50 °C. After 4 h, the mixture was cooled down to room temperature and diluted in water and Et₂O was added. Organic layer was extracted with Et₂O, dried over Na₂SO₄ and concentrated under vacuum.

The following experiments were carried out according to *Typical Procedure C*. Data are reported as: a) Enamine (**III.8, 10 and 12**); b) H₂SO₄; c) yield and aspect.

Individual analysis for each compound (**III.16, 17 and III.2.aaA**) is given below.

2,4-Bis(trifluoromethyl)quinoline III.16

a) 1,1,1,5,5-Hexafluoro-4-(phenylamino)pent-3-en-2-one **III.12** (1 equiv., 279 mg, 0.991 mmol); b) H₂SO₄ (10 equiv., 18 M, 0.55 mL, 9.91 mmol); c) Traces of the 2,4-bis(trifluoromethyl)quinoline **III.16** were obtained as colourless solid. ¹H NMR (400 MHz, CDCl₃) δ_H 8.36 (d, ³J_{H-H} = 8.4 Hz, 1H, C₈H), 8.24 (d, ³J_{H-H} = 8.8 Hz, 1H, C₅H), 8.03 (s, 1H, C₃H), 7.95 (t, ³J_{H-H} = 7.7 Hz, 1H, C₇H), 7.84 (t, ³J_{H-H} = 7.1 Hz, 1H, C₆H) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -61.46 (s, C₄CF₃), -67.65 (s, C₂CF₃) ppm.

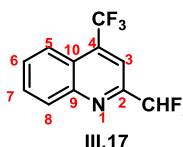


III.16

Chemical Formula: C₁₁H₅F₆N
Exact Mass: 265,03 g/mol
Colourless solid

2-(Difluoromethyl)-4-(trifluoromethyl)quinoline III.17

a) 1,1,1,5,5-Pentafluoro-4-(phenylamino)pent-3-en-2-one **III.8** (1 equiv., 496 mg, 1.87 mmol); b) H₂SO₄ (10 equiv., 18 M, 1.04 mL, 18.7 mmol); c) 2-(Difluoromethyl)-4-(trifluoromethyl)quinoline **III.17** was obtained as a brown solid in 90% yield (416 mg). ¹H NMR (400 MHz, CDCl₃) δ_H 8.26 (d, ³J_{H-H} = 8.5 Hz, 1H, C₅H), 8.20 (d, ³J_{H-H} = 8.5 Hz, 1H, C₈H), 8.03 (s, 1H, C₃H), 7.89 (ddd, ³J_{H-H4} = 8.4, ³J_{H-H2} = 7.0, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.78 (ddd, ³J_{H-H3} = 8.3, ³J_{H-H1} = 7.0, ⁴J_{H-H2} = 1.1 Hz, 1H, C₆H), 6.82 (t, ²J_{H-F} = 55.0 Hz, 1H, C₂CHF₂) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -61.53 (d, ⁴J_{F-H} = 1.9 Hz, C₄CF₃), -114.50 (d, ²J_{F-H} = 54.9 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 152.40 (t, ²J_{C-F} = 27.3 Hz, C₂), 148.14 (s, C₉), 136.38 (q, ²J_{C-F} = 32.4 Hz, C₄), 131.23 (s, C₇), 130.85 (s, C₈), 129.88 (s, C₆), 124.26 (d, ⁴J_{C-F} = 2.1 Hz, C₅), 123.71 (s, C₁₀), 123.22 (q, ¹J_{C-F} = 274.9 Hz, C₄CF₃), 114.64 - 114.23 (m, C₃), 114.15 (t, ¹J_{C-F} = 241.5 Hz, C₂CHF₂) ppm. C₁₁H₆F₅N (247): calcd (%) N 5.67, C 53.45, H 2.45, found N 5.16, C 52.97, H 2.82. MP: 51.2 - 52.4 °C.

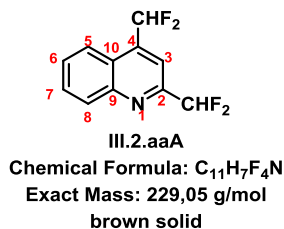


III.17

Chemical Formula: C₁₁H₆F₅N
Exact Mass: 247,04 g/mol
Brown solid

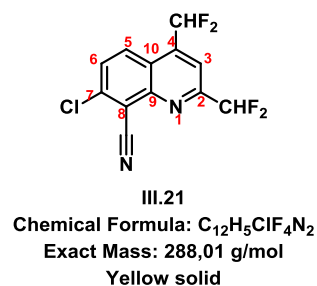
2,4-Bis(difluoromethyl)quinoline III.2.aaA

a) 1,1,5,5-Tetrafluoro-4-(phenylamino)pent-3-en-2-one **III.10** (1 equiv., 41 mg, 0.166 mmol); b) H₂SO₄ (10 equiv., 18 M, 0.0921 mL, 1.66 mmol); c) 2,4-Bis(difluoromethyl)quinoline **III.2.aaA** was obtained as a brown solid in 64% yield (24.3 mg). **Analysis sees part 3.1.2.**

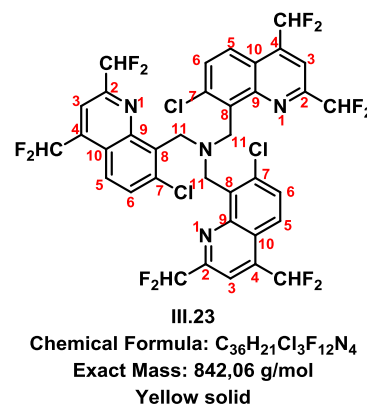
**3.3 Functionalization in position 8 of quinoline derivatives****7-Chloro-2,4-bis(difluoromethyl)quinoline-8-carbonitrile III.21 and Tris({[7-chloro-2,4-bis(difluoromethyl)quinolin-8-yl]methyl})amine III.23**

To a solution of 7-chloro-2,4-bis(difluoromethyl)-8-methylquinoline **III.2.nnA** (1 equiv., 300 mg, 1.08 mmol) and aqueous hydrogen bromide (HBr) (48%) (3 equiv., 0.368 mL, 3.24 mmol) in carbon tetrachloride (CCl₄) (4.5 mL) was added dropwise aqueous hydrogen peroxide (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 1 h. Then, MeCN (2 mL), aqueous ammonia (NH₃) (35%) (50.2 equiv., 3 mL, 54.3 mmol), and iodine (I₂) (2.5 equiv., 685 mg, 2.7 mmol) were added to the mixture and it was heated at 60 °C. After 14 h, the reaction mixture was cooled down to room temperature and quenched by saturated aqueous solution of Na₂S₂O₃. Organic layer was extracted with DCM, washed with water and brine, then dried over Na₂SO₄ and concentrated under vacuum. The mixture was purified by column chromatography using a gradient of AcOEt in cyclohexane (0-15%).

7-Chloro-2,4-bis(difluoromethyl)quinoline-8-carbonitrile **III.21** was isolated as a yellow solid in 29% yield (91 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.36 (d, ³J_{H-H} = 9.1 Hz, 1H, C₅H), 8.03 (s, 1H, C₃H), 7.85 (d, ³J_{H-H} = 9.1 Hz, 1H, C₆H), 7.14 (t, ²J_{H-F} = 51.0 Hz, 1H, C₄CHF₂), 6.88 (t, ²J_{H-F} = 51.7 Hz, 1H, C₂CHF₂) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -113.56 (d, ²J_{F-H} = 53.8 Hz, C₂CHF₂), -114.48 (d, ²J_{F-H} = 54.6 Hz, C₄CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 155.77 (t, ²J_{C-F} = 28.3 Hz, C₂), 147.88 (s, C₉), 142.63 (s, C₇), 141.07 (t, ²J_{C-F} = 22.9 Hz, C₄), 130.33 (s, C₆), 129.10 (s, C₅), 123.23 (s, C₁₀), 116.48 (t, ³J_{C-F} = 7.9 Hz, C₃), 114.62 (s, CN), 113.66 (t, ¹J_{C-F} = 242.9 Hz, C₂CHF₂), 113.55 (s, C₈), 112.89 (t, ¹J_{C-F} = 242.3 Hz, C₄CHF₂) ppm. HRMS (ESI positive) for C₁₂H₆F₄N₂Cl [M⁺]: calcd 289.0150 found 289.0164. MP: 116 - 116.5 °C.

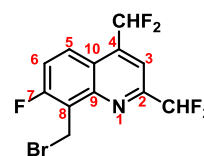


Tris({[7-chloro-2,4-bis(difluoromethyl)quinolin-8-yl]methyl})amine **III.23** was isolated as a yellow solid in 10% yield (94.5 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 7.95$ (d, $^3J_{\text{H-H}} = 9.1$ Hz, 3H, C_5H), 7.82 (s, 3H, C_3H), 7.57 (d, $^3J_{\text{H-H}} = 9.1$ Hz, 3H, C_6H), 7.11 (t, $^2J_{\text{H-F}} = 54.2$ Hz, 3H, C_4CHF_2), 6.39 (t, $^2J_{\text{H-F}} = 55.1$ Hz, 3H, C_2CHF_2), 4.49 (s, 6 H, C_{11}H) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -114.15$ (d, $^2J_{\text{F-H}} = 55.1$ Hz, C_2CHF_2), -114.67 (d, $^2J_{\text{F-H}} = 54.2$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 152.45$ (t, $^2J_{\text{C-F}} = 27.7$ Hz, C_2), 147.95 (s, C_9), 140.13 (t, $^2J_{\text{C-F}} = 22.3$ Hz, C_4), 139.25 (s, C_7), 136.72 (s, C_8), 130.92 (s, C_6), 123.33 (s, C_5), 123.01 (s, C_{10}), 114.28 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C_2CHF_2), 113.96 (t, $^3J_{\text{C-F}} = 7.9$ Hz, C_3), 113.08 (t, $^1J_{\text{C-F}} = 241.4$ Hz, C_4CHF_2), 50.30 (s, C_{11}) ppm. HRMS (ESI positive) for $\text{C}_{36}\text{H}_{22}\text{F}_{12}\text{N}_4\text{Cl}_3$ $[\text{M}^+]$: calcd 843.0713 found 843.0716. MP: 120 - 121 °C.



8-(Bromomethyl)-2,4-bis(difluoromethyl)-7-fluoroquinoline **III.24**.

Method A: To a solution of 2,4-bis(difluoromethyl)-7-fluoro-8-methylquinoline **III.2.mmA** (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 H_2O (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, and then turned into a colourless suspension after 10 min under light. Saturated aqueous solution of sodium thiosulfate ($\text{Na}_2\text{S}_2\text{O}_3$) was added to the reaction mixture, and the product was extracted with AcOEt. The combined extracts were washed with brine and dried over Na_2SO_4 . The organic phase was concentrated under reduced pressure.



III.24
Chemical Formula: $\text{C}_{12}\text{H}_7\text{BrF}_5\text{N}$
Exact Mass: 338,97 g/mol
Colourless solid

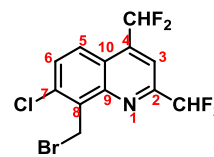
Method B: To a mixture of 2,4-bis(difluoromethyl)-7-fluoro-8-methylquinoline **III.2.mmA** (1 equiv., 300 mg, 1.15 mmol), NaIO_4 (1.5 equiv., 368 mg, 1.72 mmol) and LiBr (1.5 equiv., 149 mg, 1.72 mmol) was added aq. H_2SO_4 (2%) (6 mL). The reaction mixture was heated at 95 °C for 6 h. The reaction mixture was then cooled to room temperature and extracted with AcOEt. The combined organic layers were washed with saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ then water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

In both cases the reaction mixture was purified by column chromatography using a gradient of AcOEt in cyclohexane (0-15%) to provide the 8-(bromomethyl)-2,4-bis(difluoromethyl)-7-fluoroquinoline **III.24** as colourless solid in respectively 63% (**Method A**) and 50% (**Method B**) yield. ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.17$ (dd, $^3J_{\text{H-H}} = 9.4$, $^4J_{\text{H-F}} = 5.7$ Hz, 1H, C_5H), 7.93 (s, 1H, C_3H), 7.55 (t, $^3J_{\text{H-H}} = 9.1$ Hz, 1H, C_6H), 7.14 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C_4CHF_2), 6.86 (t, $^2J_{\text{H-F}} = 55.0$ Hz, 1H, C_2CHF_2), 5.22 (d, $^4J_{\text{H-F}} = 1.6$ Hz, 2H, $\text{C}_8\text{CH}_2\text{Br}$) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -106.81$ - -106.85 (m, C_7F), -114.12 (d, $^2J_{\text{F-H}} = 54.1$ Hz, C_2CHF_2), -114.52 (d, $^2J_{\text{F-H}} = 55.0$ Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 161.55$ (d, $^1J_{\text{C-F}} = 257.1$ Hz, C_7), 153.60 (t, $^2J_{\text{C-F}} = 27.7$ Hz, C_2), 146.39 (d, $^3J_{\text{C-F}} = 8.3$ Hz, C_9), 140.59 (td, $^2J_{\text{C-F}} = 22.5$, $^5J_{\text{C-F}} = 1.5$ Hz, C_4), 125.95 (d, $^2J_{\text{C-F}} = 10.7$ Hz, C_8), 122.95 (d, $^3J_{\text{C-F}} = 13.7$ Hz, C_5), 122.14 (s, C_{10}), 119.74 (d, $^2J_{\text{C-F}} = 25.7$ Hz, C_6), 114.26 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C_2CHF_2), 114.36 - 114.18 (m, C_3), 113.20 (t, $^1J_{\text{C-F}} = 241.7$ Hz, C_4CHF_2), 20.07 (d, $^3J_{\text{C-F}} = 4.6$ Hz, $\text{C}_8\text{CH}_2\text{Br}$). $\text{C}_{12}\text{H}_7\text{F}_5\text{NBr}$ (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 III.25

Method A : The same previous procedure was used on the 7-chloro-2,4-bis(difluoromethyl)-8-methylquinoline **III.2.nna** (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 **III.2.nna** (1 equiv., 302 mg, 1.09 mmol).



III.25
Chemical Formula: $C_{12}H_7BrClF_4N$
Exact Mass: 354,94 g/mol
Colourless solid

In both cases the reaction mixture was purified by column chromatography using a gradient of AcOEt in cyclohexane (0-15%) to provide the 8-(bromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline **III.25** as colourless solid in respectively 68% (**Method A**) and 55% (**Method B**) yield. 1H NMR (400 MHz, $CDCl_3$) δ_H = 8.08 (d, $^3J_{H-H}$ = 9.1 Hz, 1H, C_5H), 7.96 (s, 1H, C_3H), 7.75 (d, $^3J_{H-H}$ = 9.1 Hz, 1H, C_6H), 7.14 (t, $^2J_{H-F}$ = 54.1 Hz, 1H, C_4CHF_2), 6.85 (t, $^2J_{H-F}$ = 54.9 Hz, 1H, C_2CHF_2), 5.36 (s, 1H, C_8CH_2Br) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -114.27 - -114.56 (m, C_2CHF_2 + C_4CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 153.37 (t, $^2J_{C-F}$ = 27.8 Hz, C_2), 145.97 (s, C_9), 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_{10}), 115.04 - 114.85 (m, C_3), 114.21 (t, $^1J_{C-F}$ = 242.4 Hz, C_2CHF_2), 113.05 (t, $^1J_{C-F}$ = 241.8 Hz, C_4CHF_2), 25.08 (s, C_8CH_2Br). $C_{12}H_7F_4NBrCl$ (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 III.26

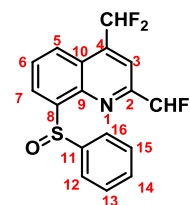
To a solution of 8-(bromomethyl)-7-chloro-2,4-bis(difluoromethyl)quinoline **III.25** (1 equiv., 370 mg, 1.04 mmol) in aqueous H_2SO_4 (70%) (3962 mg) at 110 °C was added aqueous HNO_3 (65%) (321 mg) dropwise. CAUTION: a release of brown toxic gas was observed. The reaction mixture was stirred for 17 h, and then the reaction mixture was cooled down and poured into ice. The precipitate was filtered off, washed with water and dried under vacuum. The solid was triturated into pentane to remove all impurities. 7-Chloro-2,4-bis(difluoromethyl)quinoline-8-carboxylic acid **III.26** was obtained as a beige solid in 64% yield (77.7 mg). 1H NMR (400 MHz, $CDCl_3$) δ_H = 9.55 (br s, 1H, OH), 8.22 (d, $^3J_{H-H}$ = 9.0 Hz, 1H, C_5H), 8.00 (s, 1H, C_3H), 7.84 (d, $^3J_{H-H}$ = 9.1 Hz, 1H, C_6H), 7.18 (t, $^2J_{H-F}$ = 53.9 Hz, 1H, C_4CHF_2), 6.84 (t, $^2J_{H-F}$ = 54.7 Hz, 1H, C_2CHF_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ_F = -114.47 (d, $^2J_{F-H}$ = 53.9 Hz, C_2CHF_2), -115.22 (d, $^2J_{F-H}$ = 54.7 Hz, C_4CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ_C = 167.41 (s, C_8CO_2H), 153.70 (t, $^2J_{C-F}$ = 27.8 Hz, C_2), 145.41 (s, C_9), 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_{10}), 115.48 (t, $^3J_{C-F}$ = 7.9 Hz, C_3), 113.30 (t, $^1J_{C-F}$ = 243.4 Hz, C_2CHF_2), 112.74 (t, $^1J_{C-F}$ = 242.3 Hz, C_4CHF_2) ppm. $C_{12}H_6F_4NO_2Cl$ (307): calcd (%) N 4.55, C 46.80, H 1.95 found N 4.56, C 46.41, H 2.06. MP: 158 - 159 °C.



III.26
Chemical Formula: $C_{12}H_6ClF_4NO_2$
Exact Mass: 307,00 g/mol
Beige solid

8-(Benzenesulfinyl)-2,4-bis(difluoromethyl)quinoline III.27

Iron (III) chloride (FeCl_3) (0.03 equiv., 1.59 mg, 0.00979 mmol) and 2,4-bis(difluoromethyl)-8-(phenylsulfanyl)quinoline **III.2.ttA** (1 equiv., 110 mg, 0.326 mmol) were dissolved in MeCN (1 mL) and stirred for 5 min. To this solution was added periodic acid (H_5IO_6) (1.1 equiv., 81.8 mg, 0.359 mmol) at once. The reaction mixture was stirred at room temperature for 3 h. Then it was quenched by the addition of a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ and extracted with DCM. Organic layers were dried over Na_2SO_4 and concentrated under vacuum. 8-(Benzenesulfinyl)-2,4-bis(difluoromethyl)quinoline

**III.27**

Chemical Formula: $\text{C}_{17}\text{H}_{11}\text{F}_4\text{NOS}$
Exact Mass: 353,05 g/mol
Brown solid

III.27 was obtained as a sticky brown solid in 79% yield (91.2 mg). ^1H NMR (400 MHz, CDCl_3) δ_{H} = 8.61 (dd, $^3J_{\text{H-H}} = 7.3$, $^4J_{\text{H-H}} = 1.2$ Hz, 1H, C₇H), 8.22 (dd, $^3J_{\text{H-H}} = 8.5$, $^4J_{\text{H-H}} = 1.3$ Hz, 1H, C₅H), 7.96 (d, $^3J_{\text{H-H}} = 7.5$ Hz, 1H, C₆H), 7.93 (s, 1H, C₃H), 7.91 – 7.87 (m, 2H, C_{12, 16}H), 7.41 – 7.31 (m, 3H, C_{13, 14, 15}H), 7.14 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C₄CHF₂H), 6.81 (t, $^2J_{\text{H-F}} = 55.0$ Hz, 1H, C₂CHF₂H) ppm. ^{19}F NMR (376 MHz, CDCl_3) δ_{F} = -113.77 – -115.99 (m, C₄CHF₂), -113.36 – -117.48 (m, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) δ_{C} = 152.39 (dd, $^2J_{\text{C-F1}} = 28.2$, $^2J_{\text{C-F2}} = 26.2$ Hz, C₂), 145.60 (s, C₉), 145.42 (s, C₁₁), 143.42 (s, C₈), 140.52 (t, $^2J_{\text{C-F}} = 22.5$ Hz, C₄), 131.28 (s, C₁₄), 129.60 (s, C₅), 129.09 (s, C_{13, 15}), 126.66 (s, C₇), 125.93 (s, C_{6, 12, 16}), 124.93 (s, C₁₀), 115.39 – 115.08 (m, C₃), 113.45 (t, $^1J_{\text{C-F}} = 243.4$ Hz, C₄CHF₂), 112.79 (t, $^1J_{\text{C-F}} = 241.9$ Hz, C₂CHF₂) ppm. $\text{C}_{17}\text{H}_{11}\text{F}_4\text{NOS}$ (353): calcd (%) N 3.96, C 57.79, H 3.14, found N 3.94, C 57.64, H 3.32.

3.4 Typical procedure D for the saponification reaction

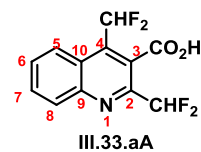
To a stirred solution of potassium hydroxide (KOH) in 60% ethanol aqueous solution was added quinoline. The reaction mixture was stirred under reflux for 4 h. The mixture was quenched with concentrated hydrochloric acid (HCl) until pH 1. EtOH was removed under vacuum and organics compounds were extracted with AcOEt, washed with water, dried over Na_2SO_4 , and concentrated under reduced pressure.

The following experiments were carried out according to **Typical Procedure D**. Data are reported as: a) KOH; b) ethanol aqueous solution; c) quinoline; and d) yield and aspect.

Individual analysis for each compound (**III.33**) is given below.

2,4-Bis(difluoromethyl)quinoline-3-carboxylic acid III.33.aA

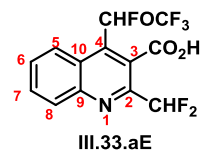
a) KOH (8 equiv., 10.6 g, 189 mmol); b) ethanol aqueous solution (187 ml); c) Ethyl-2,4-bis(difluoromethyl)quinoline-3-carboxylate **III.29.aA** (1 equiv., 7.14 g, 23.7 mmol); and d) Desire compound 2,4-Bis(difluoromethyl)quinoline-3-carboxylic acid **III.33.aA** was obtained as colourless solid in 99% yield (6.44 g). ^1H NMR (400 MHz, DMSO) δ_{H} = 8.39 (d, $^3J_{\text{H-H}} = 7.7$ Hz, 1H, C₅H), 8.27 (d, $^3J_{\text{H-H}} = 7.8$ Hz, 1H, C₈H), 8.07 – 7.99 (m, 1H, C₆H), 7.97 – 7.88 (m, 1H, C₇H), 7.70 (t, $^2J_{\text{H-F}} = 52.1$ Hz, 1H, C₄CHF₂), 7.27 (t, $^2J_{\text{H-F}} = 53.7$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, DMSO) δ_{F} = -106.25 (dd, $^2J_{\text{F-H}} = 52.0$, $^5J_{\text{F-H}} = 1.7$ Hz, C₄CHF₂), -110.60 (d, $^2J_{\text{F-H}} = 53.7$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, DMSO) δ_{C} = 166.11 (s, C₃CO), 147.73 (t, $^2J_{\text{C-F}} = 24.2$ Hz, C₂), 146.40 (s, C₁₀), 135.53 (t, $^2J_{\text{C-F}} = 22.7$ Hz, C₄), 132.02 (s, C₆), 130.33 (s, C₇), 130.20 (s, C₈), 125.21 (t, $^3J_{\text{C-F}} = 6.1$ Hz, C₃), 124.74 (s, C₅), 123.07 (s, C₉), 113.02 (t, $^1J_{\text{C-F}} = 241.7$ Hz, C₂CHF₂), 112.87 (t, $^1J_{\text{C-F}} = 240.4$ Hz, C₄CHF₂) ppm. IR ν (cm⁻¹): 3418 (OH), 1696 (C=O_{acid}). C₁₂H₇F₄NO₂ (273): calcd (%) N 5.13, C 52.76, H 2.58, found N 5.03, C 52.80, H 2.75. MP: 183.1 – 184 °C.



III.33.aA
Chemical Formula: C₁₂H₇F₄NO₂
Exact Mass: 273,04 g/mol
Colourless solid

2-(Difluoromethyl)-4-[fluoro(trifluoromethoxy)methyl]quinoline-3-carboxylic acid III.33.aE

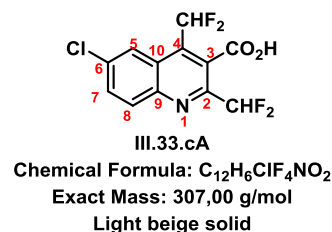
a) KOH (8 equiv., 305 mg, 5.45 mmol); b) ethanol aqueous solution (5.40 ml); c) Ethyl-2-(difluoromethyl)-4-[fluoro(trifluoromethoxy)methyl]quinoline-3-carboxylate **III.29.aE** (1 equiv., 250 mg, 0.681 mmol); and d) Desire compound 2-(difluoromethyl)-4-[fluoro(trifluoromethoxy)methyl]quinoline-3-carboxylic acid **III.33.aE** was obtained as a light beige solid in 86% yield (197 mg). ^1H NMR (400 MHz, DMSO) δ_{H} = 8.38 (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, C₅H), 8.28 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C₈H), 8.04 (t, $^3J_{\text{H-H}} = 7.7$ Hz, 1H, C₆H), 7.96 (t, $^3J_{\text{H-H}} = 7.5$ Hz, 1H, C₇H), 7.88 (d, $^2J_{\text{H-F}} = 54.0$ Hz, 1H, C₄CHFOCF₃), 7.30 (t, $^2J_{\text{H-F}} = 53.7$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, DMSO) δ_{F} = -57.85 (d, $^4J_{\text{F-F}} = 4.8$ Hz, C₄CHFOCF₃), -114.57 – -116.64 (m, A₂B₂, $\Delta\nu = 459.45$ Hz, C₂CHF₂), -122.18 – -122.61 (m, C₄CHFOCF₃) ppm. ^{13}C NMR (101 MHz, DMSO) δ_{C} = 166.04 (s, C₃CO), 147.96 (t, $^2J_{\text{C-F}} = 23.8$ Hz, C₂), 146.51 (s, C₉), 134.67 (d, $^2J_{\text{C-F}} = 23.3$ Hz, C₄), 132.12 (s, C₇), 130.43 (s, C₆), 130.34 (s, C₈), 125.59 – 125.22 (m, C₃), 124.71 (d, $^4J_{\text{C-F}} = 3.9$ Hz, C₅), 122.86 (s, C₁₀), 120.55 (qd, $^1J_{\text{C-F}} = 261.6$, $^3J_{\text{C-F}} = 1.2$ Hz, C₄CHFOCF₃), 112.80 (t, $^1J_{\text{C-F}} = 241.5$ Hz, C₂CHF₂), 103.06 (dq, $^1J_{\text{C-F}} = 230.2$, $^3J_{\text{C-F}} = 3.8$ Hz, C₄CHFOCF₃) ppm. IR ν (cm⁻¹): 2920 (C_{sp3}H), 1714 (C=O_{acid}). C₁₃H₇F₆NO₃ (339): calcd (%) N 4.13, C 46.03, H 2.08, found N 4.02, C 46.87, H 2.39. MP: 183.3 – 185.5 °C.



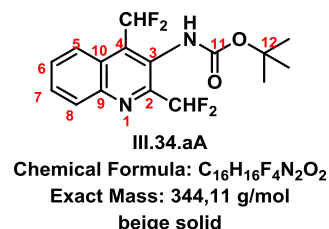
III.33.aE
Chemical Formula: C₁₃H₇F₆NO₃
Exact Mass: 339,03 g/mol
Light beige solid

6-Chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylic acid III.33.cA

a) KOH (8 equiv., 0.585 g, 10.4 mmol); b) ethanol aqueous solution (10.30 ml); c) 6-Chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylate **III.29.cA** (1 equiv., 0.583 g, 1.3 mmol); and d) Desire compound 6-chloro-2,4-bis(difluoromethyl)quinoline-3-carboxylic acid **III.33.cA** was obtained as a light beige solid in 41% yield (531 mg). ^1H NMR (400 MHz, Acetone- d_6) δ_{H} = 8.45 (dd, $^4J_{\text{H-H}} = 3.7$, $^5J_{\text{H-F}} = 1.8$ Hz, 1H, C₅H), 8.30 (d, $^3J_{\text{H-H}} = 9.0$ Hz, 1H, C₈H), 8.04 (dd, $^3J_{\text{H-H}} = 9.0$, $^4J_{\text{H-H}} = 2.2$ Hz, 1H, C₇H), 7.63 (t, $^2J_{\text{H-F}} = 52.3$ Hz, 1H, C₄CHF₂), 7.20 (t, $^2J_{\text{H-F}} = 54.1$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, Acetone- d_6) δ_{F} = -111.47 (d, $^2J_{\text{F-H}} = 52.2$ Hz, C₄CHF₂), -116.87 (d, $^2J_{\text{F-H}} = 54.1$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, Acetone- d_6) δ_{C} = 166.01 (s, C₃CO), 149.66 (t, $^2J_{\text{C-F}} = 24.7$ Hz, C₂), 146.77 (s, C₆), 136.89 (t, $^2J_{\text{C-F}} = 23.4$ Hz, C₄), 136.61 (s, C₁₀), 133.57 (s, C₇), 133.43 (s, C₈), 126.53 (t, $^3J_{\text{C-F}} = 6.4$ Hz, C₃), 125.03 (s, C₉), 124.94 (t, $^4J_{\text{C-F}} = 3.7$ Hz, C₅), 114.20 (t, $^1J_{\text{C-F}} = 242.1$ Hz, C₂CHF₂), 114.05 (t, $^1J_{\text{C-F}} = 240.4$ Hz, C₄CHF₂) ppm. IR ν (cm⁻¹): 2918 (C_{sp3}H), 1725-1706 (C=O_{acid}). C₁₂H₆F₄NO₂ (307): calcd (%) N 4.55, C 46.85, H 1.97, found N 4.43, C 47.22, H 2.27. MP: 236.2 – 237.2 °C.

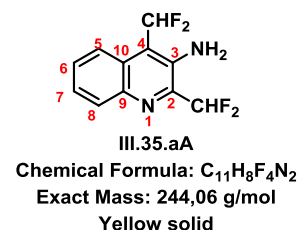
**3.5 Post functionalization in position 3 of quinoline derivatives****Carbamate synthesis: *t*-butyl *N*-[2,4-bis(difluoromethyl)quinolin-3-yl]carbamate III.34.aA**

To a solution of 2,4-bis(difluoromethyl)quinoline-3-carboxylic acid **III.33.aA** (1 equiv., 802 mg, 2.56 mmol) in *tert*-butyl alcohol (10 mL) was added NEt₃ (1.6 equiv., 0.552 mL, 4.09 mmol) and DPPA (1.3 equiv., 0.718 mL, 3.32 mmol). The reactor was not totally sealed in order to let the gas moving and the mixture was stirred at 100 °C overnight. The reaction mixture was cooled down and diluted with water. Organic layer was extracted with AcOEt, washed with a solution of NaHCO₃ followed by brine, dried over Na₂SO₄ and concentrated under vacuum. Compound was purified by flash chromatography using a gradient of AcOEt in cyclohexane (0-20%). The *t*-butyl-*N*-[2,4-bis(difluoromethyl)quinolin-3-yl]carbamate **III.34.aA** was obtained as a beige solid in 64% yield (0.567 g). ^1H NMR (400 MHz, CDCl₃) δ_{H} = 8.47 (d, $^3J_{\text{H-H}} = 7.9$ Hz, 1H, C₅H), 8.16 (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, C₈H), 7.82 (t, $^3J_{\text{H-H}} = 7.4$ Hz, 1H, C₇H), 7.73 (t, $^3J_{\text{H-H}} = 7.5$ Hz, 1H, C₆H), 7.21 (t, $^2J_{\text{H-F}} = 53.7$ Hz, 1H, C₄CHF₂), 6.85 (t, $^2J_{\text{H-F}} = 54.2$ Hz, 1H, C₂CHF₂), 6.65 (s, 1H, NH), 1.69 – 1.20 (m, 9H, *t*-Bu) ppm. ^{19}F NMR (376 MHz, CDCl₃) δ_{F} = -112.09 (s, C₄CHF₂), -113.57 (d, $^2J_{\text{F-H}} = 52.5$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl₃) δ_{C} = 154.31 (s, C₁₁), 149.51 – 146.66 (m, C₂), 146.01 (s, C₁₀), 137.39 – 134.67 (m, C₄), 130.46 (s, C_{7,8}), 129.61 (s, C₆), 127.05 (s, C₉), 125.59 (t, $^4J_{\text{C-F}} = 3.9$ Hz, C₅), 125.13 (s, C₃), 116.89 (t, $^1J_{\text{C-F}} = 240.1$ Hz, C₂CHF₂), 112.55 (t, $^1J_{\text{C-F}} = 238.5$ Hz, C₄CHF₂), 82.57 (s, C₁₂), 28.14 (s, *t*-Bu) ppm. IR ν (cm⁻¹): 3675 (NH), 2978-2901 (C_{sp3}H), 1704 (C=O_{ester}). C₁₆H₁₆F₄N₂O₂ (344): calcd (%) N 8.14, C 55.81, H 4.68, found N 8.01, C 56.22, H 4.79. MP: 135.6 – 136.5 °C.



Deprotection reaction: 2,4-bis(difluoromethyl)quinolin-3-amine III.35.aA

t-Butyl-*N*-[2,4-bis(difluoromethyl)quinolin-3-yl]carbamate **III.34.aA** (1 equiv., 566 mg, 1.32 mmol) was dissolved in DCE (4.53 mL) and treated with TFA (20.9 equiv., 2.04 mL, 27.5 mmol). After 4 hr at room temperature, the mixture was quenched with water and a solution of NaHCO₃ until neutral pH. Organic layer was extracted with DCM, washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. 2,4-Bis(difluoromethyl)quinolin-3-amine **III.35.aA** was



obtained as a yellow solid in 98% yield (315 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.00 (dd, ³J_{H-H} = 8.3, ⁴J_{H-H} = 1.1 Hz, 1H, C₅H), 7.83 (d, ³J_{H-H} = 8.6 Hz, 1H, C₈H), 7.62 – 7.57 (m, 1H, C₆H), 7.51 (ddd, ³J_{H-H2} = 8.2, ³J_{H-H3} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.43 (t, ²J_{H-F} = 53.7 Hz, 1H, C₄CHF₂), 6.84 (t, ²J_{H-F} = 54.2 Hz, 1H, C₂CHF₂), 5.08 (s, 2H, NH₂) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -116.50 (d, ²J_{F-H} = 56.4 Hz, C₄CHF₂), -116.63 (d, ²J_{F-H} = 52.6 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 141.95 (t, ²J_{C-F} = 26.1 Hz, C₂), 140.35 (s, C₉), 137.10 (s, C₃), 130.85 (s, C₅), 129.93 (s, C₆), 126.92 (t, ³J_{C-F} = 4.9 Hz, C₁₀), 126.21 (s, C₇), 119.97 (s, C₈), 118.65 (t, ¹J_{C-F} = 239.4 Hz, C₂CHF₂), 114.58 (t, ²J_{C-F} = 20.4 Hz, C₄), 113.90 (t, ¹J_{C-F} = 234.9 Hz, C₄CHF₂) ppm. IR ν (cm⁻¹): 3533-3238 (NH + C_{sp2}H), 1635-1591 (C=C). C₁₁H₈F₄N₂ (244): calcd (%) N 11.37, C 54.11, H 3.30, found N 11.34, C 54.19, H 3.39. MP: 68.3 - 70.3 °C.

Typical procedure E for the Sandmeyer reaction

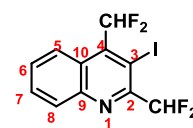
In a solution of 2,4-bis(difluoromethyl)quinolin-3-amine **III.35.aA** (1 equiv.) in dry MeCN, was added under argon copper precursor (1 equiv.). The suspension was stirred for 10 min and *tert*-butyl nitrite (*t*-BuONO) (4 equiv.) was added. The mixture was stirred for 20 min at room temperature. Then the flask was fitted with a reflux condenser and heated at 60 °C for 4 h. After cooling to room temperature, the mixture was diluted with saturated aqueous NaHCO₃ and extracted with AcOEt. Organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure.

The following experiments were carried out according to **Typical Procedure E**. Data are reported as: a) Amine; b) MeCN; c) Copper precursor; d) *t*-BuONO; and e) yield and aspect.

Individual analysis for each compound (**III.36-37.aA**) is given below.

2,4-Bis(difluoromethyl)-3-iodoquinoline III.36.aA

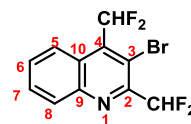
a) 2,4-Bis(difluoromethyl)quinolin-3-amine **III.35.aA** (1 equiv., 231 mg, 0.475 mmol); b) MeCN (4.97 mL); c) Copper (I) iodide (CuI) (1 equiv., 90.4 mg, 0.475 mmol); d) *t*-BuONO (4 equiv., 0.228 mL, 1.9 mmol); and e) 2,4-Bis(difluoromethyl)-3-iodoquinoline **III.36.aA** was obtained as colourless solid after purification on flash chromatography using a gradient of AcOEt in cyclohexane (0-20%) in 65% yield (109 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.44 (d, ³J_{H-H} = 8.1 Hz, 1H, C₅H), 8.23 (d, ³J_{H-H} = 8.4 Hz, 1H, C₈H), 7.87 (ddd, ³J_{H-H1} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.75 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H3} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.51 (t, ²J_{H-F} = 52.7 Hz, 1H, C₄CHF₂), 7.06 (t, ²J_{H-F} = 54.0 Hz, 1H, C₂CHF₂) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -109.46 (dd, ²J_{F-H} = 52.7, ⁵J_{F-H} = 2.4 Hz, C₄CHF₂), -115.42 (d, ²J_{F-H} = 54.0 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 150.58 (t, ²J_{C-F} = 23.4 Hz, C₂), 147.13 (s, C₁₀), 141.31 (t, ²J_{C-F} = 24.0 Hz, C₄), 131.38 (s, C₆), 130.66 (s, C₈), 129.87 (s, C₇), 126.04 (s, C₉), 124.51 (t, ⁴J_{C-F} = 5.2 Hz, C₅), 121.69 (t, ¹J_{C-F} = 242.4 Hz, C₄CHF₂), 115.50 (t, ¹J_{C-F} = 244.5 Hz, C₂CHF₂), 89.31 (t, ³J_{C-F} = 8.1 Hz, C₃) ppm. C₁₁H₆IF₄N (355): calcd (%) N 3.94, C 37.21, H 1.70, found N 3.96, C 37.33, H 1.78. MP: 87.1-87.9 °C.



Chemical Formula: C₁₁H₆F₄IN
Exact Mass: 354,95 g/mol
Colourless solid

3-bromo-2,4-bis(difluoromethyl)quinoline III.37.aA

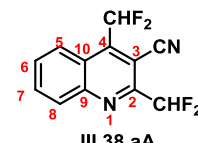
a) 2,4-Bis(difluoromethyl)quinolin-3-amine **III.35.aA** (1 equiv., 245 mg, 1 mmol); b) MeCN (10.5 mL); c) Copper (II) bromide (CuBr₂) (0.5 equiv., 112 mg, 0.502 mmol); d) *t*-BuONO (4 equiv., 0.481 mL, 4.01 mmol); and e) 3-Bromo-2,4-bis(difluoromethyl)quinoline **III.37.aA** was obtained as colourless solid after purification on flash chromatography using a gradient of AcOEt in cyclohexane (0-5%) in 50% yield (153 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 8.45 (dd, ³J_{H-H} = 8.6, ⁵J_{H-F} = 2.0 Hz, 1H, C₅H), 8.24 (d, ³J_{H-H} = 8.2 Hz, 1H, C₈H), 7.87 (ddd, ³J_{H-H2} = 8.4, ³J_{H-H4} = 6.9, ⁴J_{H-H1} = 1.3 Hz, 1H, C₇H), 7.77 (ddd, ³J_{H-H1} = 8.5, ³J_{H-H3} = 6.9, ⁴J_{H-H2} = 1.3 Hz, 1H, C₆H), 7.59 (t, ²J_{H-F} = 52.9 Hz, 1H, C₄CHF₂), 7.06 (t, ²J_{H-F} = 53.8 Hz, 1H, C₂CHF₂) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -111.19 (dd, ²J_{F-H} = 52.9, ⁵J_{F-H} = 2.3 Hz, C₄CHF₂), -116.95 (d, ²J_{F-H} = 53.8 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 148.80 (t, ²J_{C-F} = 23.7 Hz, C₂), 146.53 (s, C₁₀), 137.87 (t, ²J_{C-F} = 24.4 Hz, C₄), 131.20 (s, C₇), 130.90 (s, C₈), 130.19 (s, C₆), 125.97 (s, C₉), 124.78 (t, ⁴J_{C-F} = 4.8 Hz, C₅), 115.80 (t, ¹J_{C-F} = 193.9 Hz, C₄CHF₂), 114.95 (t, ³J_{C-F} = 7.7 Hz, C₃), 113.88 (t, ¹J_{C-F} = 196.9 Hz, C₂CHF₂) ppm. C₁₁H₆BrF₄N (308): calcd (%) N 4.55, C 42.89, H 1.96, found N 4.47, C 43.05, H 2.13. MP: 68.8 - 70 °C.



III.37.aA
Chemical Formula: C₁₁H₆BrF₄N
Exact Mass: 306,96 g/mol
Colourless solid

2,4-Bis(difluoromethyl)quinoline-3-carbonitrile III.38.aA

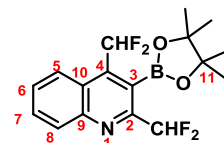
a) 2,4-Bis(difluoromethyl)quinolin-3-amine **III.35.aA** (1 equiv., 247 mg, 1.01 mmol); b) MeCN (5 mL); c) Copper (I) cyanide (CuCN) (1 equiv., 90.6 mg, 1.01 mmol); d) *t*-BuONO (4 equiv., 0.485 mL, 4.05 mmol); and e) 2,4-Bis(difluoromethyl)quinoline-3-carbonitrile **III.38.aA** was obtained as colourless solid after purification on flash chromatography using a gradient of AcOEt in cyclohexane (0-5%) in 47% yield (121 mg). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.51$ (dd, $^3J_{\text{H-H}} = 8.6$, $^5J_{\text{H-F}} = 1.7$ Hz, 1H, C₅H), 8.30 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C₈H), 8.04 (ddd, $^3J_{\text{H-H2}} = 8.4$, $^3J_{\text{H-H4}} = 7.0$, $^4J_{\text{H-H1}} = 1.3$ Hz, 1H, C₇H), 7.89 (ddd, $^3J_{\text{H-H1}} = 8.4$, $^3J_{\text{H-H3}} = 7.0$, $^4J_{\text{H-H2}} = 1.2$ Hz, 1H, C₆H), 7.47 (t, $^2J_{\text{H-F}} = 52.4$ Hz, 1H, C₄CHF₂), 6.93 (t, $^2J_{\text{H-F}} = 53.6$ Hz, 1H, C₂CHF₂) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -109.07$ (dd, $^2J_{\text{F-H}} = 52.4$, $^5J_{\text{F-H}} = 2.0$ Hz, C₄CHF₂), -113.13 (d, $^2J_{\text{F-H}} = 53.7$ Hz, C₂CHF₂) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 150.64$ (t, $^2J_{\text{C-F}} = 26.9$ Hz, C₂), 148.16 (s, C₉), 144.60 (t, $^2J_{\text{C-F}} = 24.6$ Hz, C₄), 134.07 (s, C₇), 131.14 and (2 * s, C_{6,8}), 125.70 (t, $^4J_{\text{C-F}} = 3.8$ Hz, C₅), 123.07 (s, C₁₀), 114.09 (t, $^1J_{\text{C-F}} = 243.4$ Hz, C₂CHF₂), 113.23 (t, $^1J_{\text{C-F}} = 242.7$ Hz, C₄CHF₂), 112.20 (s, C₃CN), 102.62 (t, $^3J_{\text{C-F}} = 6.6$ Hz, C₃) ppm. IR ν (cm⁻¹): 2988-2901 (C_{sp3}H), 2234 (CN). C₁₂H₆F₄N₂ (254): calcd (%) N 11.02, C 56.70, H 2.38, found N 10.96, C 56.28, H 2.43. MP: 130.6 – 132.3 °C.



III.38.aA
 Chemical Formula: C₁₂H₆F₄N₂
 Exact Mass: 254,05 g/mol
 Colourless solid

Introduction of boronic ester: 2,4-bis(difluoromethyl)-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline III.39.aA

In a solution of 2,4-bis(difluoromethyl)-3-iodoquinoline **III.36.aA** (1 equiv., 2.42 g, 6.82 mmol) and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3 equiv., 4.17 mL, 20.4 mmol) in anhydrous THF (10 ml) was added dropwise at -10 °C and *i*PrMgCl.LiCl (1.5 equiv., 1.3 M, 7.86 mL, 10.2 mmol). The reaction mixture was allowed to warm up overnight. The reaction was quenched with a saturated aqueous solution of ammonium chloride (NH₄Cl) and aqueous phase was extracted with Et₂O. Combined organic layers were washed with NH₄Cl and brine, dried over Na₂SO₄ and concentrated under reduced pressure. 2,4-Bis(difluoromethyl)-3-(tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline **III.39.aA** was obtained after purification on column chromatography using a gradient of AcOEt in cyclohexane (0-5%) as colourless solid in 54% yield (1.31 g). ^1H NMR (400 MHz, CDCl_3) $\delta_{\text{H}} = 8.30$ (d, $^3J_{\text{H-H}} = 8.5$ Hz, 1H, C₅H), 8.21 (d, $^3J_{\text{H-H}} = 8.4$ Hz, 1H, C₈H), 7.86 – 7.80 (m, 1H, C₇H), 7.71 (t, $^3J_{\text{H-H}} = 7.2$ Hz, 1H, C₆H), 7.34 (t, $^2J_{\text{H-F}} = 53.9$ Hz, 1H, C₄CHF₂), 6.98 (t, $^2J_{\text{H-F}} = 55.2$ Hz, 1H, C₂CHF₂), 1.45 (s, 12H, Bpin) ppm. ^{19}F NMR (376 MHz, CDCl_3) $\delta_{\text{F}} = -108.94$ (d, $^2J_{\text{F-H}} = 53.8$ Hz, C₄CHF₂), -112.64 (d, $^2J_{\text{F-H}} = 55.2$ Hz, C₂CHF₂) ppm. ^{11}B NMR (128 MHz, CDCl_3) $\delta_{\text{B}} = 31.01$ (s, Bpin) ppm. ^{13}C NMR (101 MHz, CDCl_3) $\delta_{\text{C}} = 154.17$ (t, $^2J_{\text{C-F}} = 24.8$ Hz, C₂), 147.70 (s, C₉), 144.29 (t, $^2J_{\text{C-F}} = 21.9$ Hz, C₄), 131.15 (s, C₇), 130.67 (s, C₈), 129.12 (s, C₆), 124.57 (t, $^4J_{\text{C-F}} = 2.9$ Hz, C₅), 124.07 (s, C₁₀), 114.83 (t, $^1J_{\text{C-F}} = 242.4$ Hz, C₄CHF₂), 114.57 (t, $^1J_{\text{C-F}} = 241.4$ Hz, C₂CHF₂), 85.62 (s, C₁₁), 25.19 (s, C₁₁CH₃) ppm. C₁₇H₁₈F₄NBO₂ (355): calcd (%) N 3.94, C 57.49, H 5.11, found N 4.01, C 57.68, H 5.20. MP: 82.6-83.5 °C.



III.39.aA
 Chemical Formula: C₁₇H₁₈BF₄NO₂
 Exact Mass: 355,14 g/mol
 Colourless solid

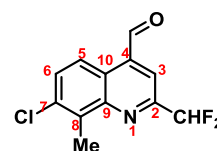
3.6 Unexpected side product

7-Chloro-2-(difluoromethyl)-8-methylquinoline-4-carbaldehyde III.19 and 7-chloro-8-methylquinoline-2,4-dicarbaldehyde III.20

7-Chloro-2,4-bis(difluoromethyl)-8-methylquinoline **III.2.nnA** (1 equiv., 209 mg, 0.755 mmol) was dissolved in H₂SO₄ (70%) (24.5 equiv., 1814 mg, 18.5 mmol), the mixture was heated at 140 °C and vanadium pentoxide (V₂O₅) (0.013 equiv., 1.78 mg, 0.00981 mmol) and cobalt acetate (Co(OAc)₂) (0.007 equiv., 0.935 mg, 0.00528 mmol) were added. Nitric acid (HNO₃) (65%) (5.38 equiv., 255 mg, 4.06 mmol) was added and a bubbling of air was started (to remove the resulting nitrous gases). The reaction mixture was stirred under air flow for 4 days. After completion, the reaction mixture was cooled down and poured into ice water. Organic layer was extracted with AcOEt, washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The mixture was purified by column chromatography using a gradient of AcOEt in cyclohexane (0-5%). Two compounds were isolated:

7-Chloro-2-(difluoromethyl)-8-methylquinoline-4-carbaldehyde

III.19 as a yellow solid in 19% yield (37.2 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 10.51 (s, 1H, C₄CHO), 8.86 (d, ³J_{H-H} = 9.2 Hz, 1H, C₅H), 8.11 (s, 1H, C₃H), 7.76 (d, ³J_{H-H} = 9.2 Hz, 1H, C₆H), 6.86 (t, ²J_{H-F} = 55.1 Hz, 1H, C₂CHF₂), 2.91 (s, 3H, C₈CH₃) ppm. ¹⁹F NMR (376 MHz, CDCl₃) δ_F = -114.17 (d, ²J_{F-H} = 55.1 Hz, C₂CHF₂) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 192.11 (s, C₄CHO), 152.88 (t, ²J_{C-F} = 27.8 Hz, C₂), 147.99 (s, C₉), 138.92 (s, C₄), 136.99 (s, C₇), 136.42 (s, C₈), 132.11 (s, C₆), 123.30 (s, C₁₀), 122.87 (s, C₅), 121.61 (s, C₃), 114.40 (t, ¹J_{C-F} = 241.3 Hz, C₂CHF₂), 14.97 (s, C₈CH₃) ppm. IR ν (cm⁻¹): 2924-2857 (C_{sp3}H), 1699 (C=O_{aldehyde}), 1590 (C=N); 1504 (C=C). C₁₂H₈F₂NCIO (255): calcd (%) N 5.48, C 56.38, H 3.15, found N 5.19, C 55.95, H 3.37. MP: 78.3 – 79.2 °C.

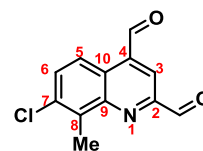


III.19

Chemical Formula: C₁₂H₈ClF₂NO
Exact Mass: 255,03 g/mol
Yellow solid

7-Chloro-8-methylquinoline-2,4-dicarbaldehyde **III.20** as a yellow

solid in 14% yield (25 mg). ¹H NMR (400 MHz, CDCl₃) δ_H = 10.50 (s, 1H, C₄CHO), 10.29 (s, 1H, C₂CHO), 8.93 (d, ³J_{H-H} = 9.2 Hz, 1H, C₅H), 8.40 (s, 1H, C₃H), 7.82 (d, ³J_{H-H} = 9.2 Hz, 1H, C₆H), 3.00 (s, 3H, C₈CH₃) ppm. ¹³C NMR (101 MHz, CDCl₃) δ_C = 192.95 (s, C₄CHO), 192.45 (s, C₂CHO), 152.53 (s, C₂), 148.73 (s, C₉), 138.48 (s, C₄), 137.25 (s, C₇), 137.13 (s, C₈), 133.34 (s, C₆), 124.41 (s, C₁₀), 123.28 (s, C₅), 122.27 (s, C₃), 15.10 (s, C₈CH₃) ppm. IR ν (cm⁻¹): 2833 (C_{sp3}H), 1707-1698 (C=O_{aldehyde}), 1501 (C=N); 1426 (C=C_{ar}). C₁₂H₈NCIO₂ (233): calcd (%) N 5.99, C 61.69, H 3.45, found N 5.66, C 61.07, H 3.73. MP: 160.7 - 161 °C.



III.20

Chemical Formula: C₁₂H₈ClNO₂
Exact Mass: 233,02 g/mol
Yellow solid

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Development and Biological evaluation of novel fluorinated ingredients for modern crop protection

Résumé en français

Ce doctorat a permis la conception de nouvelles molécules destinées aux développements de futurs produits phytosanitaires. Tout d'abord, la synthèse d' α,α -difluoro- β -hydroxy cétones a été réalisée. Motif déjà reconnu dans le domaine pharmaceutique, nous voulions étendre son champ d'application à l'agrochimie. Une série de composés possédant une activité biologique en tant qu'agonistes des récepteurs GABA a été synthétisée. Ils ont été obtenus à l'issue d'une synthèse convergente nécessitant une réaction de couplage entre un aldéhyde aromatique et un intermédiaire α,α -difluoro- β -trifluorométhylidihydroxy cétone. L'analyse biologique de nos produits a fait ressortir un type de famille spécifique. Une approche pro-drug a débuté afin d'en affiner la structure et d'en faire ressortir un hit. Dans un second temps, le développement d'une série de quinoléines substituées par des groupements fluorés en position 2 et 4 a été conduit. Ces molécules peu décrites dans la littérature furent synthétisées dans des conditions douces avec de bons rendements et une complète régiosélectivité, inspirée par les réactions de Combes et de Meth-Cohn utilisant un Réactif Fluoroalkyl Amine (FARs). La post-fonctionnalisation en position 3 et 8 a permis l'exemplification de ces composés. Une étude physico-chimique réalisée sur une série homogène a apporté des informations complémentaires sur leurs propriétés électroniques. Bien qu'aucune molécule n'ait montré d'activité biologique, nous avons pu lors de ce projet réaliser la synthèse de nouvelles quinoléines et évaluer l'intérêt des FARs dans la synthèse de molécules inconnues de la littérature jusqu'à ce jour.

Mots-clés : GABA, agonistes, pro-drug, quinoléines, FARs, Combes, Meth-Cohn, post-fonctionnalisation, propriétés physico-chimiques.

Résumé en anglais

This PhD thesis allowed the conception of new molecules for the development of novel phytosanitary ingredients. First, the synthesis of α,α -difluoro- β -hydroxy ketones was performed. Since this motif is already known in the pharmaceutical field, we decided to extend their application to the agrochemical field. A series of compounds with biological activities as GABA agonist receptors was synthesized. They were obtained by a convergent method after a coupling reaction between benzaldehydes and α,α -difluoro- β -trifluoromethylidihydroxy ketone intermediates. Biological analysis highlighted a specific family of compounds. A pro-drug approach was applied to tune the structure and allowed the discovery of a hit. Second, the development of a series of 2,4-(fluoroalkyl)-substituted quinoline derivatives was conducted. Scarcely described in literature, these molecules were obtained under smooth conditions, with good yields and a complete regioselectivity, inspired by Combes and Meth-Cohn reactions using Fluoroalkyl Amino Reagents (FARs). Post-functionalization in position 3 and 8 allowed us to increase the scope of the reaction. A physico-chemical study gave complementary informations on their electronical properties. Although none of these molecules have shown biological activity, we have during this project realized the synthesis of new quinolines and evaluated the use of FARs in the synthesis of unknown fluorinated molecules.

Keywords: GABA, agonists, pro-drug, quinolines, FARs, Combes, Meth-Cohn, Post-functionalization, physico-chemical properties.