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SYNTHESIS OF TRIFLUOROMETHYLATED SCAFFOLDS FOR LEAD STRUCTURE RESEARCH

Von

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aus

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Erklärung

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Eidesstattliche Versicherung

Diese Dissertation wurde eigenständig und ohne unerlaubte Hilfe erarbeitet.

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– FÜR MEINE FAMILIE–

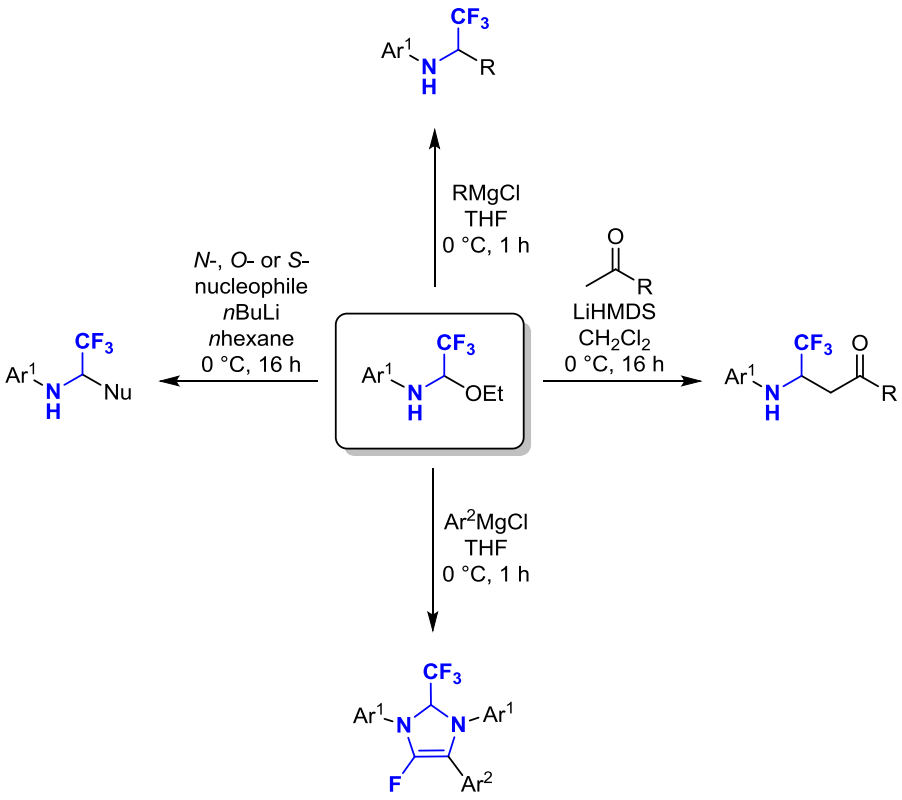
– EVERY REAL STORY IS A NEVERENDING STORY –

MICHAEL ENDE

SUMMARY

The design and synthesis of bioisosteres has become a central instrument in drug development to improve restricting properties of a parent structure without diminishing its biological activity or other beneficial parameters. Especially the replacement of one or more amide bonds in small molecules or peptide mimetics has come to the fore due to the significance of this structural motif in biologically active compounds. Furthermore, amides are often associated with metabolic liabilities as they are susceptible to fast enzymatic hydrolysis. This necessitates the development and synthetic access toward suitable amide mimetics. The concept of trifluoroethylamines has gained in importance as they are metabolically stable isosteres with exceptional properties similar to those of an amide. Despite first examples of successful implementation, synthetic restrictions toward trifluoroethylamines including a small substrate scope and facile hydrolysis of the imine precursors still limit their applicability.

In this context, we envisioned a convenient synthetic strategy toward a broad range of novel fluoroalkylated amines and fluorinated derivatives for possible applications in pharmaceutical research (Scheme 1).



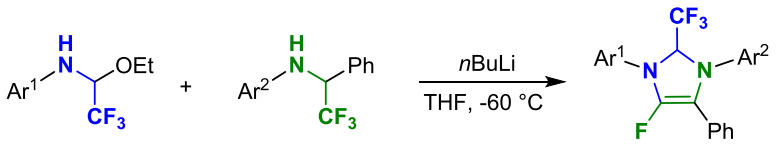
Scheme 1. Syntheses of various functionalized trifluoroethylamine derivatives.

Initially, we focused on developing an efficient approach toward trifluoroethylamines from trifluoromethylated *N*-aryl *N*,*O*-acetals. These *N*-aryl *N*,*O*-acetals are stable imine surrogates and can be reacted with alkyl-, alkenyl- and arylmagnesium reagents to furnish a broad range of functionalized trifluoromethylated amines in good to excellent yield. First attempts toward a stereoselective synthesis of these compounds have been made.

Furthermore, this procedure was successfully extended to the synthesis of novel difluoroalkylated amines, which are also of great interest for medicinal chemistry applications as the difluoromethyl moiety can be used as a hydroxyl bioisostere and, similarly to trifluoromethyl groups, can be implemented to modulate the basicity of adjacent amines.

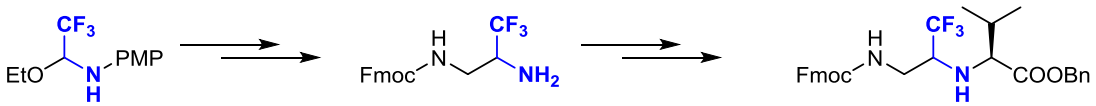
To access novel fluoroalkylated moieties, the conversion of *N*-aryl *N*,*O*-acetals with heteroatom nucleophiles and *in situ* generated lithium enolates was studied. Thus, simple protocols with a broad substrate scope were developed which allow reaction of fluorinated *N*,*O*-acetals with a large variety of *C*- and heteroatom nucleophiles.

In course of the synthesis of trifluoroethylamines, we found that *N*-aryl *N*,*O*-acetals with electron-withdrawing substituents can be treated with aryl magnesium halides to provide *N*-aryl trifluoromethylated imidazole derivatives in an one-pot reaction. At this point, the reaction was studied *via* NMR experiments to elucidate the mechanism pathway, which finally allowed the development of a modified procedure to access highly functionalized imidazole derivatives by reaction of trifluoroethylamines and *N*,*O*-acetals under basic reaction conditions (Scheme 2).



Scheme 2. Synthesis of further functionalized trifluoromethylated imidazole derivatives.

Furthermore, a synthetic strategy toward ψ[CH(CF_3)NH]-Gly dipeptide building blocks was investigated (Scheme 3). Starting from *N*-aryl *N*,*O*-acetal the trifluoromethylated diamine was synthesized in five synthetic steps. First attempts toward the conversion of this diamine precursor by introduction of an appropriate leaving group and its subsequent reaction with a second amino acid were made.



Scheme 3. Synthetic strategy toward ψ[CH(CF_3)NH]-Gly dipeptide building block.

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PUBLICATIONS OF THIS THESIS

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A. Deutsch, H. Glas, A. Hoffmann-Röder* and C. Deutsch*, *RSC Adv.* **2014**, *4*, 9288–9291.

"Synthesis of Functionalized α-Trifluoroethylamine Scaffolds *via Grignard* Addition to *N*-Aryl Hemiaminal Ethers"

A. Deutsch, C. Wagner, C. Deutsch* and A. Hoffmann-Röder*, *Eur. J. Org. Chem.* **2016**, *5*, 930–945.

"Convenient Access to Di- and Trifluoroethylamines for Lead Structure Research"

S. Wunder, **A. Deutsch**, C. Deutsch* and A. Hoffmann-Röder*, *Synthesis* **2016**, *48*, A-J.

"One-Pot Synthesis of Functionalized β-Fluoroalkylated Mannich-Type Products from *N*-Aryl *N*,*O*-Acetals"

A. Deutsch, C. Jessen, C. Deutsch, K. Karaghiosoff and A. Hoffmann-Röder, *Org. Lett.* **2016**, 18, 3474–3477.

"One-Pot Synthesis of Substituted Trifluoromethylated 2,3-Dihydro-1*H*-imidazoles"

ABBREVIATIONS

Å	angstrom
Ac	acetyl
ADME	absorption, distribution, metabolism and excretion
Ar	undefined aryl substituent
ATR	attenuated total reflection (IR)
BAIB	bis(acetoxy)iodobenzene
Bn	benzyl
Bu	butyl
Bz	benzoyl
c	concentration
CA-II	carbonic anhydrase II
CAN	ceric ammonium nitrate
Cat	cathepsin
Cl	clearance
COSY	^{1}H correlation spectroscopy (NMR)
COX-2	cyclooxygenase 2
d	day(s)
δ	chemical shift (NMR)
de	diastereomeric excess
DAST	Diethylaminosulfur trifluoride
DFI	2,2-Difluoro-1,3-dimethylimidazolidine
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent(s)
ESI	electrospray ionisation (HRMS)
Et	ethyl
FDA	Food and Drug Administration
g	gram(s)
h	hour(s)
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HMBC	heteronuclear multiple bond connectivity (NMR)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

HSQC	heteronuclear single quantum coherence (NMR)
HTS	high throughput screening
Hz	hertz (frequency)
IBX	2-iodoxybenzoic acid
IC50	half maximal inhibitory concentration
IR	infra-red
J	coupling constant (NMR)
λ	lambda, wave length unit
LAH	lithium aluminum hydride
LiHMDS	lithium *bis*(trimethylsilyl)amide
LG	leaving group
M	meta
M	molar (*c*)
Me	methyl
min	minute(s)
mol	mole(s)
mp	melting point
MS	mass spectrometry
mTMP	2´-deoxythymidine-5´-monophosphate
mUMP	2´-deoxyuridine-5´-monophosphate
NCE	new chemical entity
n.d.	not detected
NFSI	*N*-fluorobenzenesulfonimide
NMR	nuclear magnetic resonance
Nu	undefined nucleophile
o	ortho
OPA	olefinic peptide nucleic acids
p	para
PDE 5	phosphodiesterase 5
PG	protecting group
Ph	phenyl
PK	pharmacokinetic
PMP	*para*-methoxyphenyl
PNA	peptide nucleic acid
ppm	parts per million (NMR)
Pr	propyl
*p*TSA	*para*-toluenesulfonic acid
R	undefined substituent
Rf	retention factor (TLC)
r.t.	room temperature

SAR	structure-activity relationship
SPPS	solid-phase peptide synthesis
t	(*tert*) tertiary (isomer)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TCCA	trichloroisocyanuric acid
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAF	tetramethylammonium fluoride
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
tR	retention time (HPLC, GC)
W	watt

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INTRODUCTION

I. INTRODUCTION

1. Modern Drug Discovery

The development of new drugs from an initial idea to the launch of a product is known to be a time-consuming task, which can take up to 12 – 15 years and creates costs of about $800 million.[1] In the past decades it has evolved into a highly complex process, involving intensive analysis and optimization steps to create a potential drug candidate, which is subsequently tested in clinical trials. This process is constantly being enhanced by advancements in scientific research, such as the growing identification of novel targets and improved screening methods just to name two. However, pharmaceutical companies still face setbacks and failure of lead structures in late stages of drug development resulting in large financial losses and a lack of new chemical entities (NCEs). Gaining insight into the procedure of early drug discovery as shown in Figure 1 allows a better understanding of the existing limitations and tools used to overcome possible drawbacks. The screening and assay methods described below are not only applied at one stage of the discovery process but recur in many of the development steps.

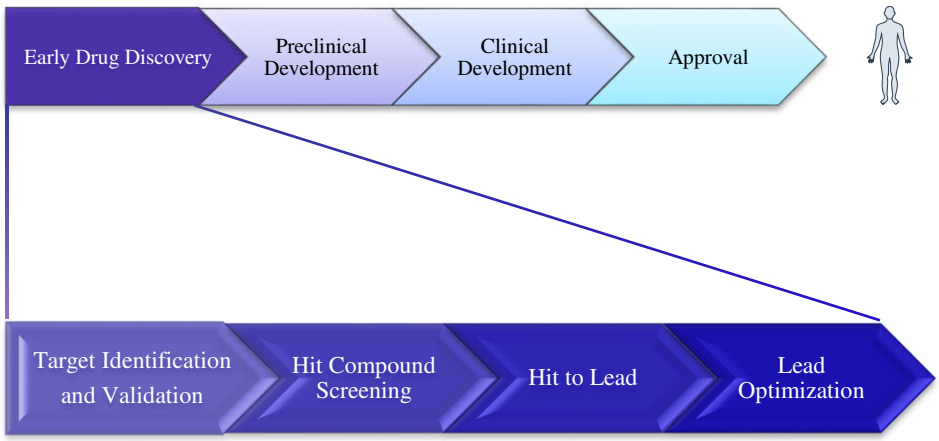


Figure 1. Early drug discovery process from target identification to lead optimization.

1.1 Early drug discovery – from target to preclinical candidate

The first step in developing a novel drug involves the identification and validation of a suitable target that is safe, effective and most importantly drugable. The term drugable refers to a biological entity that binds to a possible drug and reacts with a biological response upon binding to this drug, which can be measured both *in vitro* and *in vivo*. There are three main approaches in target identification: (i) a bioinformatic approach using data mining to identify and rate possible targets, (ii) the search for genetic associations or (iii) phenotype screening. Once identified, a potential target is further validated using *in vitro* and *in vivo* methods such as antisense technology, biological examination of transgenic animals or monoclonal antibodies amongst others. These methods are often combined in a multi-validation approach to maximize the informational outcome.[2]

The target validation process is followed by the screening of hit compounds, which are defined as molecules that show the desired activity during the screening process and retain this activity upon retesting.[3] The current paramount method to identify hit compounds is high-throughput screening (HTS). In this screening process large compound libraries are tested in assays against the target or in cell-based assays. In case of cell-based assays additional screenings using secondary assays are required to confirm the site of action, due to multiple interactions in cells which can result in a false-positive activity of compounds. Despite this promising method, HTS-based hit discovery has a relatively low success rate of 45 – 55%[4-5] and has therefore undergone multiple transformational changes. Novel assay technologies, multipoint and tiered screening strategies are only a few examples which aim at improving the hit identification process.[6] In contrast to HTS, focused or knowledge-based screening requires a preselection of compounds that have a higher potential of activity against the target. Fragment screening typically involves the screening of several thousands of small molecule fragments in high concentration to identify functionalities which exhibit weak activities against the target.[7] Subsequent combination of potent fragments to design molecules with high affinity requires knowledge of the crystal structure of the target. Additionally, nuclear magnetic resonance (NMR) screening has gained attention as a fragment screening method in hit discovery. Protein-ligand interactions can be observed by NMR shifts of signals derived from either the protein or the ligand revealing even weak activities of fragments. Crystal structures of target proteins can also be employed in structure-aided drug design and virtual screening methods, which use docking models of the target and molecules from a virtual compound library to generate a hit compound.[3]

The hit molecules are tested in cell-based assays and animal models to examine both the efficacy and the safety profile. Stable cell lines over-expressing the target or overexpressed recombinant protein assays are well-established to test the activity of a compound. Cell-based assays are used to evaluate molecules interacting with membrane receptors, ion channels and nuclear receptors, while biochemical assays are applied to receptor and enzyme targets to measure the affinity of the hit compound.[8-9] Besides a sufficient affinity toward the target and a tolerable safety profile, the compounds need to fulfill additional requirements to be considered for a hit series. The *Lipinski Rule of Five* aims at ensuring adequate bioavailability of a potential drug. A low molecular weight and a low Log*P* value, a guidance level for lipophilicity affecting the absorption level, are important parameters to ensure compound drugability. Since the lead optimization process often requires further substitution and involves an increase of molecular weight, application of the *Lipinski Rule of Five* is especially important in this early phase of finding a hit series.[10]

Once a hit series is defined further investigation of the binding mode and required dosage is conducted by generating a dose-response curve to determine the half maximal inhibitory concentration. The mode of action and functional groups involved in target binding can be identified by secondary assays and structure-activity relationship (SAR) studies. *In vitro* testing provides important information concerning absorption, distribution, metabolism and excretion (ADME), physicochemical and pharmacokinetic (PK) parameters. This phase of drug development typically ends with a selection of hit compounds having a potency of 100 nM – 5 nM.[3]

The subsequent hit-to-lead phase results in finding potent and selective compounds with sufficient drug-like properties to examine their efficacy in *in vivo* models. Based on information gathered from SAR studies the compounds can be analyzed in more detail in order to identify the core structures responsible for activity and

selectivity. This process can be supplemented by crystallographic and NMR investigations to disclose new binding sites of the target. Similarly, the compounds will be screened in more detail regarding their ADME and PK profiles. These detailed analyses serve the selection of potent candidates for more detailed but costly testing. Key hit structures, which meet the efficacy, selectivity, ADME and physicochemical properties required, are then analyzed concerning their PK properties in rats. At this point it is beneficial to investigate the selectivity of the compounds at the hERG (human ether-à-go-go-related gene) channel, whose inhibition is associated with cardiovascular toxicity.[3]

The final phase in early drug discovery deals with lead optimization, which aims at reversing deficiencies, while maintaining the favorable properties of the selected compounds. This optimization is once again a big synthetic challenge for medicinal chemists and requires the interplay between biological profiling and synthetic strategies. The modified drug properties and synthetic strategies applied during lead optimization will therefore be elucidated more closely in the following chapter.

Further properties of the final drug candidate are examined at the end of this phase as well as in the preclinical development in models of genotoxicity, *in vivo* models, high-dose pharmacology, PK/PD studies, dose linearity and metabolic profiling.[3]After lead discovery, optimization and preclinical development, one or two drug candidates are selected to enter the clinical phases and after successful clinical trial may reach drug approval to be administered to patients.

1.2 Modified drug properties in lead optimization

Active hit compounds which performed well in the initial screens hardly ever exhibit all the required properties of a final drug candidate. Therefore, hit and lead optimization is an indispensable and challenging task for medicinal chemists in order to find a promising candidate with appropriate potency, selectivity, ADME and toxicity characteristics. Numerous properties, which are partially dependent on each other, are evaluated and modulated in this process. They can be clustered in physicochemical, biochemical, PK properties and toxicity. Physicochemical properties can be subdivided in solubility and permeability, which are in turn dependent on the lipophilicity and pK_a values amongst others. Biochemical properties include metabolism, protein and tissue binding, uptake and efflux of the drug. PK properties and toxicity are determined by clearance, half-life, bioavailability, drug-drug interactions and LD_{50} levels.[11]

Aforementioned, the *Lipinski Rule of Five* provides an orientation to minimize absorption issues, which is one of the main factors influencing bioavailability. It states that a drug should have a molecular weight below 500, a distribution coefficient Log*P* below 5, a maximum of 5 hydrogen-bond donors and 10 hydrogen-bond acceptors.[10] This rule has proven to be useful to estimate drug properties, although more recent studies suggest that compounds with Log*P* values below 3 – 4 and a molecular weight below 400 are more successful.[12-14] Increasing lipophilicity often positively affects the binding efficacy of a molecule to the target, but it can likewise result in undesired interactions, creating a lack of selectivity and possible toxic side effects (e.g. hERG channel interaction). On the other hand, highly polar molecules exhibit an enhanced aqueous solubility but diminishing membrane permeability.[15-19]

Another fundamental physicochemical property often altered during lead optimization relies on the ionizability of a compound which in turn is determined by the pK_a value. By modifying the substructure of a molecule to tune its pK_a, the solubility and permeability parameters and thus the absorption and bioavailability of a drug can be improved.[20] Thereby, electron donating or withdrawing groups can be added adjacent to an acidic or basic moiety to alter the electron density at this group.

One of the key aspects of lead optimization concerns the reduction of metabolic liabilities from the lead compound. Metabolism has the biochemical purpose to increase the polarity of the molecule and to alter its solubility to prepare its excretion from the body. However, fast metabolism of administered drugs has a large impact on several pharmacokinetic factors and therefore exhibits a potential restraint for a drug candidate. For instance, a decreased metabolic stability leads to an increase in clearance (Cl) and reduces the exposure of the drug. The PK half-life is directly related to the Cl and the volume of distribution and therefore determines how often a drug should be administered to a patient. What is more, the Cl along with the absorption affects the oral bioavailability (Figure 2).[21]

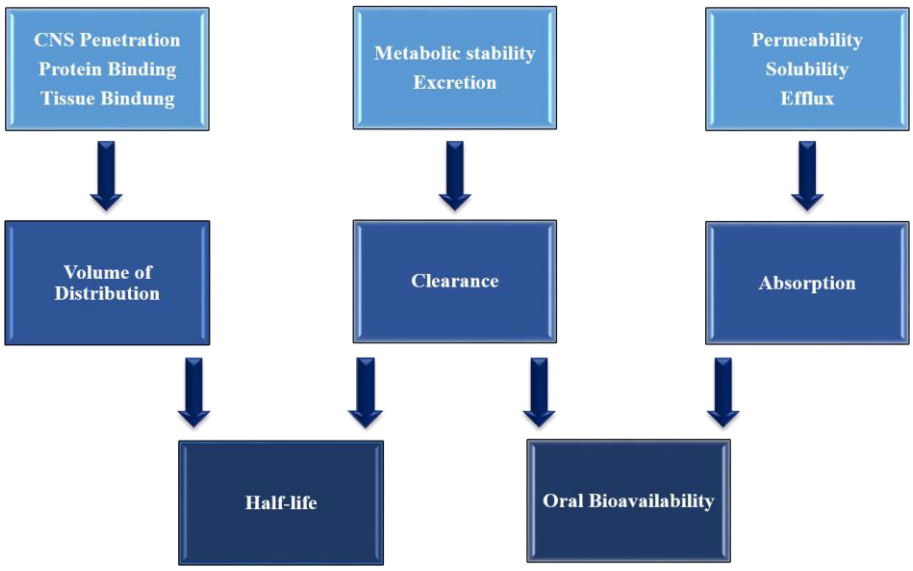


Figure 2. Multilateral influence of physicochemical, biochemical and pharmacokinetic drug properties.[11]

The biological strategies for metabolism are differentiated in phase I and phase II reactions. Phase I metabolism involves modifications of the molecular structure by oxidation/reduction or dealkylation. These reactions are promoted by various enzymes with the most prominent class being monooxygenases, namely the cytochrome P450 and the flavine monooxygenase family. Multiple approaches are applied by medicinal chemists to enhance the metabolic stability of phase I metabolism. Common tools are blocking metabolic sites by adding blocking groups and removing or replacing susceptible sites in the molecule if they are dispensable for target interaction. Cyclization, variation of ring size or chirality can also improve metabolic stability. Since metabolism is also associated with high lipophilicity, reducing lipophilicity of compounds can be an instrument to alter metabolism.

In contrast, Phase II reactions present additions of polar moieties to the molecule structure to enhance its hydrophilicity and hence its elimination from the organism. These polar groups are commonly glucuronic acid,

carboxyl acids, amines or sulfates. Synthetic methods to reduce or hinder these addition reactions include the introduction of electron-withdrawing functionalities, steric hindrance or the implementation of bioisosteric moieties.[11, 21]

The incorporation of fluorine and bioisosteric moieties are of particular interest for lead optimization and widely used throughout medicinal chemistry research. Due to its unique properties, fluorine substitution can be an instrument to alter many physicochemical and metabolic properties of a drug candidate and beyond that can positively contribute to the compound´s binding affinity. Bioisosteric moieties present a tool employed to replace parts of the drug candidate that contribute to metabolic or physicochemical liabilities, while maintaining its biological profile. In the following, both strategies and their effect will be illustrated with examples.

2. Fluorine in Medicinal Chemistry

An important and widely used instrument in lead optimization is the incorporation of one or several fluorine atoms to dedicated positions of drug candidates. Fluorination can improve the metabolic stability, binding affinity and bioavailability of a drug, as well as its physicochemical properties and protein-ligand interactions. Even though organofluorine compounds are practically absent from natural occurring structures, it is estimated that 20 – 25% of all currently tested drugs contain at least one fluorine atom.[22-24] The first successful example of a fluorine substituted compound for pharmaceutical application was reported in 1957 with the synthesis of the anticancer agent 5-fluorouracil.[25] Enzymatically converted into 5-fluoro-2-α-deoxyuridylate, it prevents cellular synthesis of thymidine by acting as a competitive inhibitor of thymidylate synthase, which converts 2´-deoxyuridine-5´-monophosphate (mUMP) into 2´-deoxythymidine-5´-monophosphate (mTMP).[26] Despite this successful implementation, it took until the 1980s for fluorinated drugs to become increasingly prominent in medicinal chemistry research. Until then fluorination was dependent on the use of elementary fluorine which is a harsh and extremely reactive agent and requires precautionary measures and special laboratory equipment. Thus, it was only after the development of the selective fluorination reagent (diethylamino)sulfur trifluoride (DAST) in 1973,[27-28] that mild fluorination reagents allowed an increasing application of fluorine in medicinal chemistry. The invention of DAST was followed by a growing number of nucleophilic fluorination reagents, which converted alcohols and aldehydes into the corresponding mono- and diorganofluorides. Further reagents commonly used are 2,2-difluoro-1,3-dimethylimidazolidine (DFI)[29] and *bis*(2-methoxyethyl) aminosulfur trifluoride (*Deoxofluor*®)[30] (Figure **3**). Electrophilic fluorination reagents like 1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane *bis*(tetrafluoroborate) (*Selectfluor*®) and *N*-fluorobenzene-sulfonimide (NFSI) holding a R_2N-F or R_3N^+-F moiety further extended the synthetic repertoire by allowing electrophilic fluorination to be safely conducted without use of elemental fluorine.[31] Moreover, incorporation of trifluoromethyl groups, which are of growing interest in medicinal chemistry, can be accomplished by using trifluoromethylating reagents such as trifluoroacetamide[32] or the *Ruppert-Prakash* reagent[31].

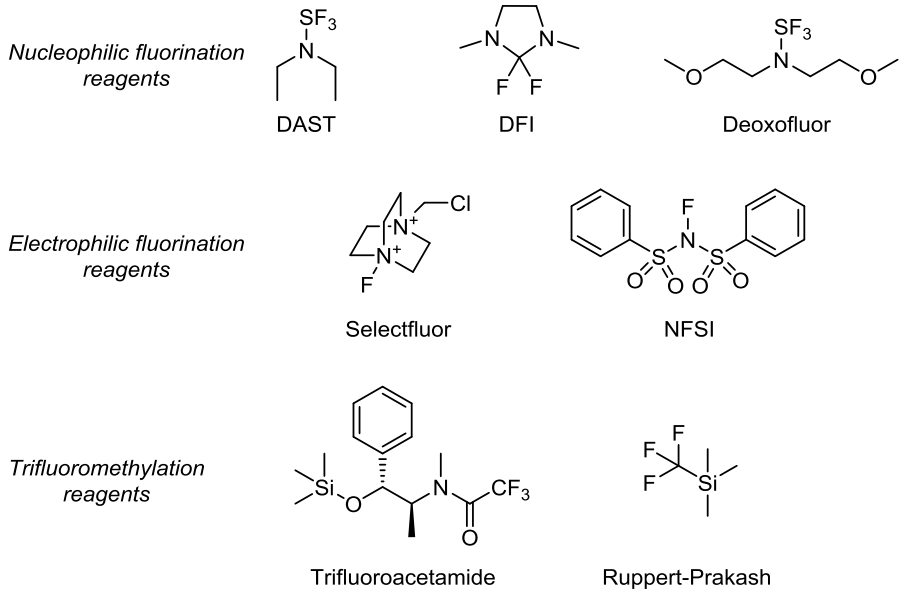
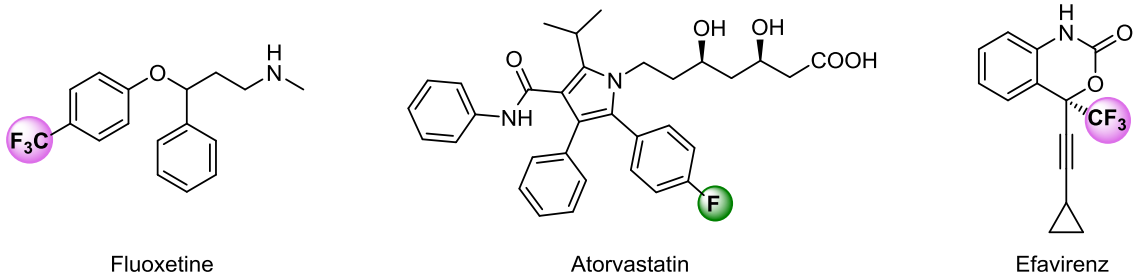


Figure 3. Examples of selective fluorination reagents.

These strategic fluorination methods fostered the design and investigation of diverse fluorinated compounds, the most prominent and significant examples will be discussed below (Figure 4). Fluoxetine is commonly known as *Prozac*® and acts as an antidepressant by selectively inhibiting the serotonin uptake activating its specific receptor. During lead structure optimization SAR studies showed a 6-fold increase in activity by trifluoromethylation of the *para*-position.[33] This increase in activity is not fully understood, however it is believed that the conformational change introduced upon introduction of the trifluoromethyl group enhances the binding affinity to the serotonin transporter.[34]

Efavirenz is a non-nucleoside reverse transcriptase inhibitor which is used in antiretroviral therapy in the treatment of patients infected with HIV. SAR studies indicated that the trifluoromethyl moiety at the tertiary stereogenic center has a large effect on the pK_a and the ionization of the carbamate, responsible for the enhanced potency.[35]

The effect of fluorination was also studied in the case of atorvastatin, a lipid-lowering agent featuring a fluorine substitution in *para*-position of a phenyl substituent. During lead optimization this fluorinated substitution pattern was found to be superior to hydroxyl, hydrogen and methoxy substitution resulting in a 2- to 10-fold increase in potency.[36] This effect could later be elucidated by crystal structure analysis of atorvastatin in the active pocket of the HMG-CoA reductase, displaying a favorable interaction of the C–F bond with the guanidinium side chain of Arg_{590} (see crystal structure depicted in Figure 4).[37] While it is beyond dispute that the unique properties of fluorine can have a large impact on many factors relevant for drug development and fine-tuning, there are only few examples where the influence of fluorine substitution is fully understood.



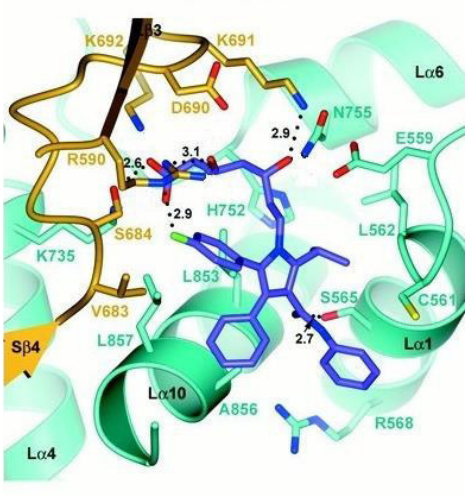


Figure 4. Examples of fluorinated drugs and crystal structure of atorvastatin in the binding pocket of the HMG-CoA reductase.[38]

2.1 Physicochemical properties

2.1.1 Modulation of pK_a

Fluorination of an active lead structure can be a useful instrument to alter its physicochemical properties. It is often replaced with hydrogen in the modified structures resulting in a similar potency, albeit very different properties concerning *van der Waals* radius and electronegativity.[39] Due to its pronounced electronegativity, fluorine substitution considerably influences pK_a values of neighboring functional moieties.[40-41] Modification of the pK_a, in turn, may affect many relevant parameters including solubility, lipophilicity, binding potency and selectivity, as well as ADME restrictions including hERG potassium channel interactions.[42-44]

As demonstrated in Figure 5, *Niel et al.* investigated the influence of fluorine substitution comparing a series of piperidinyl and piperazinyl indole 5-TH_{1D} receptor inhibitors, which showed large potential in the treatment of migraine. Comparing the piperazine and piperidine analogs (**1** and **2**), it was found that the piperidine compound **2** exhibits a lower bioavailability and absorption. By introducing a fluorine in C-4 position of the piperidine ring (compound **3**), its pK_a could by shifted toward the pK_a of the corresponding piperazine analog, inducing improved bioavailability and absorption.[45]

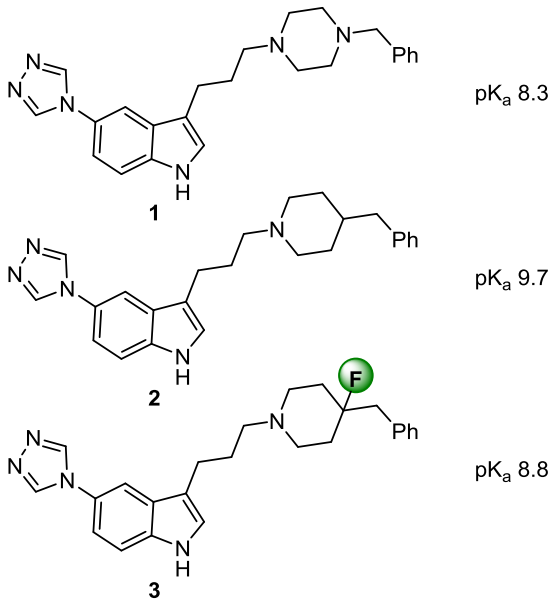


Figure 5. pK_a values of piperazine **1**, piperidine **2** and 4-fluoropiperidine **3** inhibitors of the 5-TH_{1D} receptor.

Studies on predicting pK_a values of basic amines by substitution with fluorine, oxygen, nitrogen and sulfur functionalities to optimize physical properties in drug-discovery research demonstrated that the pK_a of amines can be tuned by position and number of substituted fluorine atoms. In open-chain molecules the value decreases by approximately 1.7 units with increasing number of fluorine atoms in the series $CH_3CH_2NH_2$ (pK_a 10.7) → $FCH_2CH_2NH_2$ (pK_a 9.0) → $F_2CHCH_2NH_2$ (pK_a 7.3) → $F_3CCH_2NH_2$ (pK_a 5.7). This can be explained by a rising destabilization of the protonated ammonium form when increasing fluorination. This effect decreases with growing distance to the amine functionality, but is even notable for δ-substitution.[41] Fluorine can also be

used to increase the acidity of functionalities as observed by fluorine substitution in close proximity to alcohols, carboxylic acids, heterocycles and phenols.

2.1.2 Influence on lipophilicity

Apart from influencing the ADME parameters by pK_a modification of adjacent functionalities, fluorine substitution directly affects lipophilicity and solubility. The absorption and distribution of orally administered drugs is to a high degree dependent on sufficient lipophilicity to enable the compound to pass through the cell lipid membrane, while simultaneously exhibiting good solubility. However, the effect of fluorine substitution on the lipophilicity is by no means easy to predict and can differ strongly depending on the substrate. Monofluorination and trifluorination are found to decrease lipophilicity in small saturated alkanes due to their strong C-F and C-CF_3 bond dipoles, whereas aromatic fluorination, introduction of perfluoroalkyl groups and fluorination adjacent to π-bonds enhance lipophilicity.[46] The exchange of hydrogen with fluorine was found to increase the logD value by approximately 0.25 units. This effect was even more significant when the fluorine was located near a basic amine.[47]

Jacobs et al. investigated the effect of fluorination on the activity and lipophilicity of leukotriene receptor inhibitors. They observed a loss of potency toward the inhibition of the leukotriene receptor after extension of an alkyl chain length to enhance lipophilicity of the original substrate. Therefore, they addressed the loss in activity by fluorination of the parent compound. The fluorinated compound shows a 10-fold increase in potency compared to non-fluorinated analogs *in vitro*, which is a result of the enhanced lipophilicity.[48]

2.1.3 Conformational changes

Since the *van der Waals* radius of fluorine (1.47 Å) lies between that of a hydrogen (1.20 Å) and an oxygen atom (1.52 Å),[39] substitution of hydrogen and hydroxyl groups are often well tolerated without major changes in potency. In contrast, substitution of a methyl by a trifluoromethyl moiety leads to profound changes in conformation due to a larger steric demand. Studies investigating *van der Waals* volumes of trifluoromethyl groups suggest they are similar to an ethyl, isopropyl or even *tert*-butyl group depending on the method employed.[49-51]

Comparing the conformation of methoxyphenyl and trifluoromethoxyphenyl groups illustrates the large steric demand. Whereas anisol adopts a planar conformation due to the preferred conjugation of the oxygen p-orbital with the π-system of the aromatic ring, the trifluoromethoxy moiety is rotated out of plane because of its larger steric demand and stereoelectronic properties, favoring a sp^3 hybridization of the oxygen atom.[52] Furthermore the influence of the preferred conformation owing to fluorination can be demonstrated by 1,2-difluoroethane, in which the fluorine atoms adopt a gauche orientation. In this orientation, the C-F bonds are antiperiplanar to the C-H-bonds resulting in a stabilizing hyperconjugative ($\sigma \rightarrow \sigma^*$) interaction (Figure 6).

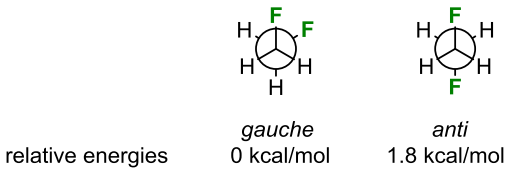


Figure 6. *Gauche* effect of 1,2-difluoroethane.[53]

Such conformational effects should be included in lead structure research to optimize the binding efficacy. A natural conformation close to the bound ligand-protein structure may result in a minimal loss of energy and optimal binding properties.[53] This was confirmed by a conformational study of fluorinated analogs of the HIV-1 protease inhibitor Indinavir. It was shown that the *gauche* effect stabilizes the carbon backbone of the *syn*, *syn* fluorinated analog resulting in similar activities of the fluorinated and non-fluorinated compounds in contrast to the *syn*, *anti* analogs.[54]

2.2 Metabolic stability

Improving the metabolic stability of active lead structures is a key challenge in lead optimization. Fluorination can enhance metabolic stability by blocking sites susceptible to degradation. A particularly interesting example is the discovery of the cholesterol inhibitor ezetimib, in which fluorine substitution is used to reduce oxidative degradation by cytochrome P450 monooxygenases. Examination of the potent radiolabeled substrate SCH 48461 during lead optimization exhibits several sites susceptible to metabolism (Figure 7). This resulted in a compound mixture even more potent than the parent drug itself. To enhance both the metabolic stability and *in vivo* potency, those metabolic modifications beneficial for potency were introduced in the substrate, while susceptible sites not affecting the potency were blocked by incorporation of fluorine. Fluorine substitution in *para*-position of phenyl rings is commonly used to prevent phenyl oxidation by deactivation of the aromatic system. These modifications finally lead to ezetimib, a 400-fold more potent drug with improved metabolic stability.[55-57]

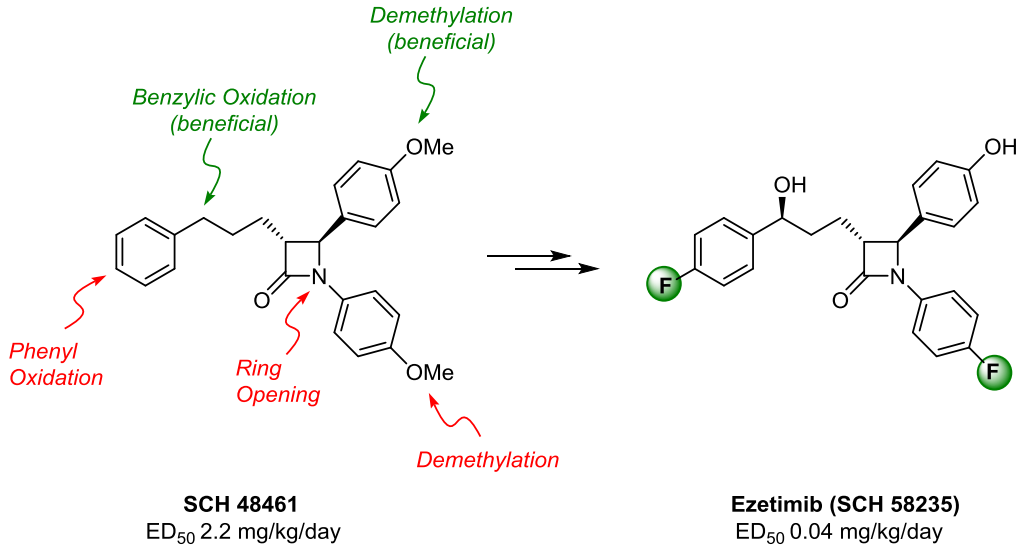


Figure 7. Metabolically susceptible sites of SCH 48461 and discovery of ezetimib.[55-57]

The strong stabilizing effect of fluorine can also be adverse, as was demonstrated in the case of celecoxib. Celecoxib is an inhibitor of cyclooxygenase-2 (COX-2), which is administered to treat patients with arthritis amongst others. In contrast to the discovery of exetimib, the synthesized substrates showed an exceeding metabolic stability which could be attributed to the fluorine substituent of the phenyl ring. Replacing this fluorine atom by a metabolically more labile methyl moiety reduced the half-life of the drug to an acceptable time of 3.5 hours (Figure 8).[58-59]

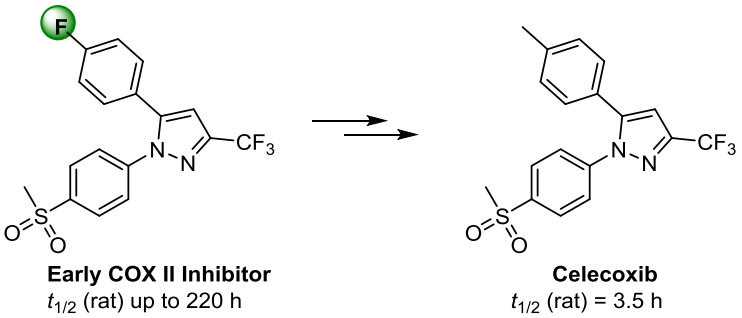


Figure 8. Development of celecoxib by replacing fluorine with a methyl moiety.[58-59]

Fluorination can also be applied to enhance the hydrolytic stability of a compound as exemplified by the lead optimization of prostacyclin (PGI_2), used to treat vascular diseases. The substrate features an enol ether which is susceptible to hydrolysis and thus limits the applicability despite its high potency. Introduction of a fluorine atom adjacent to the hydrolytic site (7-F-PGI_2) reduced the electron density of the enol ether and significantly increases its half-life. Further fluorination (AFP-07) could multiply this effect by increasing the half-life of the unfluorinated species from 10 minutes to 90 days for the difluorinated analog (Figure 9).[60-62]

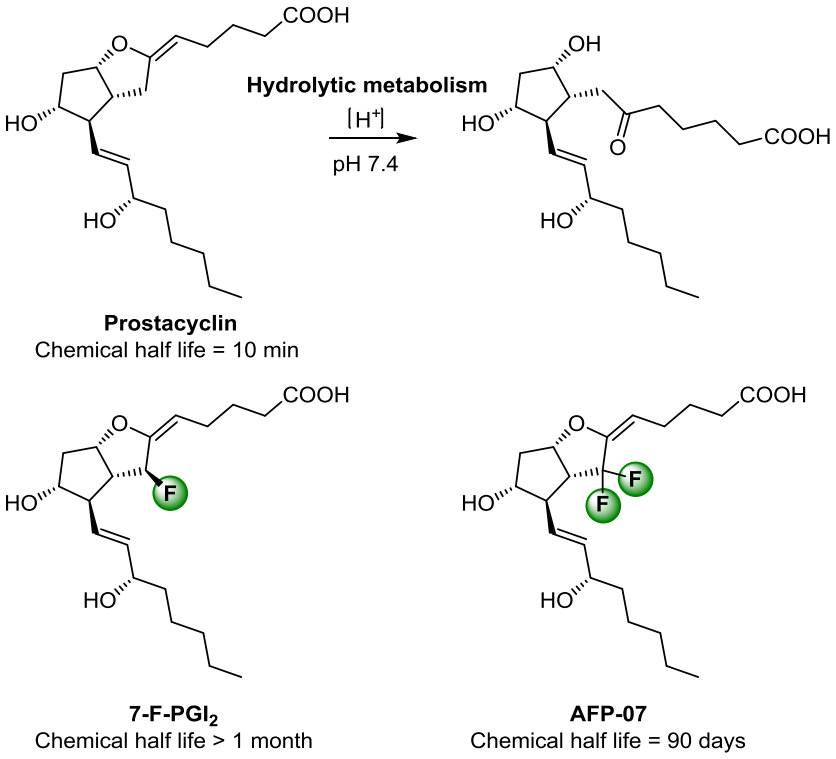
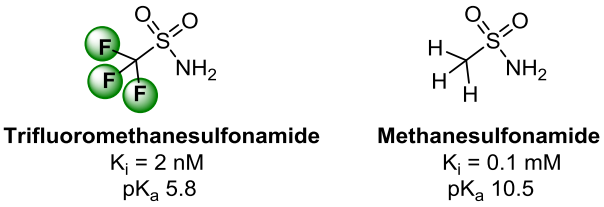


Figure 9. Hydrolytic metabolism of prostacyclin and chemical half-lives of prostacyclin analogs at pH 7.4.[60-62]

2.3 Binding affinity

Fluorine substitution can have a great influence on the binding affinity of a drug. On the one hand, fluorine-induced modification of polarity and other physiochemical properties of the drug can indirectly affect the potency of a drug. On the other hand, fluorine is also known to interact directly in ligand-protein binding.

As previously discussed, fluorine substitution can be used as a tool to manipulate the lipophilicity, polarity and pK_a of a given drug, thereby influencing its uptake and bioavailability. However, these modifications can also influence the binding affinity of the compound, as is illustrated by comparison of fluorinated and non-fluorinated inhibitors of carbonic anhydrase II (CAII). The metalloenzyme CAII catalyzes the hydration of CO_2 to bicarbonate and a proton. Sulfonamides have been studied as inhibitors of CAII, since they can bind to Zn^{2+} in the active site in their deprotonated state as $R\text{-}SO_2NH^-$. *Maren* and *Conroy* compared the binding affinities for aliphatic sulfonamides and trifluoromethanesulfonamide as a function of the pK_a value (see Figure 10). They found that the higher acidity of the fluorinated sulfonamide corresponds to its greatly enhanced binding affinity. Trifluoromethanesulfonamide (pK_a 5.8) is dissociated at neutral pH due to the strong electron withdrawing effect of the trifluoromethyl moiety, illustrating an indirect influence of fluorine modification on drug potency.[63]

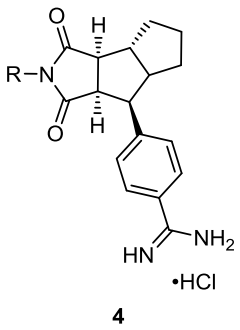


Trifluoromethanesulfonamide
K_i = 2 nM
pK_a 5.8

Methanesulfonamide
K_i = 0.1 mM
pK_a 10.5

Figure 10. Binding affinity and pK_a values for carbonic anhydrase inhibitors.

Fluorine is also known to interact directly with the ligand-protein binding as illustrated by the previously discussed example of the drug atorvastatin. A further example is represented by fluorine-containing inhibitors of the thrombin receptor (Figure 11). *Diederich* and co-workers studied the influence of fluorine substitution on the binding affinity of various tricyclic thrombin inhibitors. They discovered that proper positioning of fluorine substituents within the hydrophobic binding pocket of the receptor strongly enhances the binding affinity of these compounds. The *para*-fluorinated analog **4** showed a 5-fold higher binding affinity compared to the parent non-fluorinated species, which can be explained by a favorable polar interaction of the fluorine atom and the H–C_α–C═O group of the Asn_{98} in the X-ray structure of the serine protease.[64-65] Similarly, attractive fluorine interactions with carbonyl moieties in other ligand-protein binding patterns, especially in inhibitors of p38 kinase, where shown to positively affect binding affinities.[66-67]



4

R	K_i (μM)
benzyl	0.27
2-fluorobenzyl	0.50
3-fluorobenzyl	0.36
4-fluorobenzyl	0.057

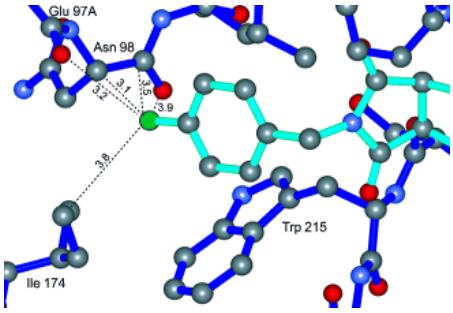


Figure 11. Class of inhibitors of thrombin and effect of fluorination position on the binding affinity. X-ray structure of 4-fluorobenzyl-substituted inhibitor in the thrombin active site.[64-65]

The possibility to use fluorine substitution as a synthetic tool to modulate physiochemical properties, metabolic stability and binding affinity has led to a steadily rising number of prominent fluorine containing drugs in recent years. Promoting the understanding of the effect of fluorine substitution in lead structures, together with advances in synthetic fluorine-organic chemistry, will certainly result in the development of more novel, highly effective fluorinated drugs.

3. Bioisosteres in Medicinal Chemistry

The concept of bioisosterism is another commonly used technique to modulate specific properties of drug candidates, such as selectivity, toxicity and ADME parameters, while maintaining their bioactivity.[68-71] In this process the susceptible moiety in the compound is exchanged by another functional group exhibiting similar biological properties. The idea of bioisosterism emerged from the concept of isosterism, which was coined by *Langmuir* in 1919.[72] During his studies on the properties of various molecules, *Langmuir* observed that certain molecules like CO_2 and N_2O exhibit similar physical properties. Based on his observations he defined a group of 21 isosteres. This concept was later extended by *Grimm´s* Hydride Replacement Law in 1925 and *Erlenmeyer's* definition of isosteres as atoms, ions and molecules in which the peripheral layers of electrons are identical.[73-75] It was also *Erlenmeyer*, who first illustrated examples of bioisosterism in experimental studies with antibodies (Figure 12). He studied the reaction of various diazonium ions **5** with the tyrosine phenol ring of proteins **6**, showing that the antibodies can neither differentiate between thienyl and phenyl substitution nor between *O*-, *N*- or CH_2-linkages connecting the two aromatic systems.[76-77]

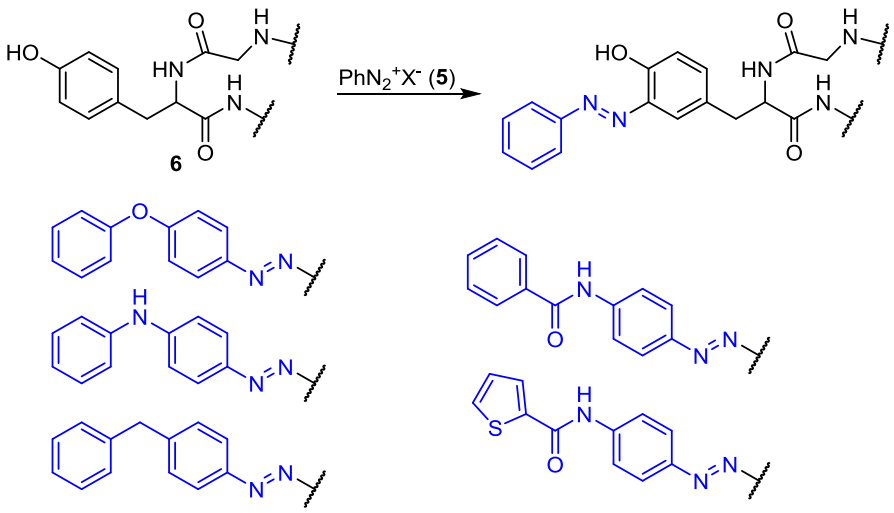
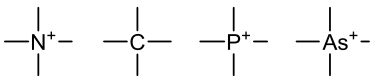


Figure 12. Reaction of diazonium ions **5** with the tyrosine phenol ring of proteins **6**.[77]

Despite this early research, the term bioisosterism itself was defined by *Friedman* in 1950 as isosteric atoms and molecules, which exhibit similar biological properties.[78] As research progressed it was observed that the applicability of bioisosterism is not always dependent on similarity concerning structural properties but instead focuses on biochemical mimicry. This led to a distinction of two classes of bioisosteres: classical bioisosteres that follow the earlier defined rules of isosteric behavior and non-classical bioisosteres which mimic the replaced moiety by biochemical functional aspects without displacing large overlap in steric and electronic properties.[79] Classical bioisosteres are distinguished by the number of bonds affected through the formal replacement process and are therefore structured in mono-, di- and trivalent atoms and groups, tetrasubstituted atoms and ring equivalents. Non-classical bioisosteres are clustered in rings, noncyclic isosteres and exchangeable groups. An outline of classical bioisosteres is depicted in Table 1:[80]

Table 1. *Selected examples of classical bioisosteres*[80]

Classical bioisosteres	
Monovalent bioisosteres:	*Trivalent atoms and groups:*
H and F	─CH═, ─N═
OH and NH	─P═, ─As═
F, OH, NH or CH_3 for H	*Tetrasubstituted atoms:*
SH, OH	
Cl, Br, CF_3	
Divalent bioisosteres:	*Ring equivalents:*
─C═S, ─C═O, ─C═NH, ─C═C─	

The replacement of functional groups in a lead compound by bioisosteric moieties can have a significant influence on the properties of the drug candidate. Bioisosteres are known to tune the ADME criteria by affecting physiochemical properties like polarizability, polarity, lipophilicity and pK_a values and improving the metabolic stability of compounds, if susceptible sites are replaced by more stable functionalities. However, depending on the functionality of the replaced group and the binding mode of the ligand to the target, effects of bioisosteric replacements can vary substantially. Taking this into account, the implementation of bioisosteres in drug design will be highlighted based on specific examples in the following.

3.1 Physicochemical properties

One of the major challenges in lead development represents the optimization of lipid permeability, which is mostly influenced by the physicochemical properties of lipophilicity and hydrogen bonding. Next to amide moieties, which will be discussed in detail later, guanidine and amidine groups are often responsible for poor lipid permeability. Guanidines and amidines are commonly used in inhibitors of serine proteases. They are highly basic moieties, which are protonated under physiological conditions and lead to very poor membrane permeability. To reduce the basic pK_a of about 13 – 14, the adjacent CH_2 to the guanidine or amidine moiety can be replaced by either isosteric oxygen (pK_a 7 – 7.5) or a carbonyl group (pK_a 8). The resulting oxyguanidines have been successfully used as thrombin inhibitors (Figure 13a, compound **7**),[81-82] while acylguanidines are structural elements of a family of histamine H_2 agonists.[83-84]

Direct replacement of the basic amidino moiety has been studied for a series of factor Xa inhibitors, which finally led to the development of the anticoagulant apixaban (Figure 13b). Replacement of an arginine residue involved in direct ligand-protein binding usually results in a loss or reduction of potency. Yet there are cases, such as apixaban, where this loss in potency is compensated by a great improvement of PK properties. It was shown, that a series of neutral bioisosteres revealed a reduced potency compared to 3-amidino parent compound. This was presumably a result of a disappearing favorable interaction of the amidino substituent with the carboxylic side chain of the Asparagine Asp_{189}. However, the good pharmacokinetic profile of the

4-methoxyphenyl substituted drug candidate and its sufficient potency (K_i = 11 nM) permitted clinical testing of the compound and its Food and Drug Administration (FDA) approval in 2011.[85-86]

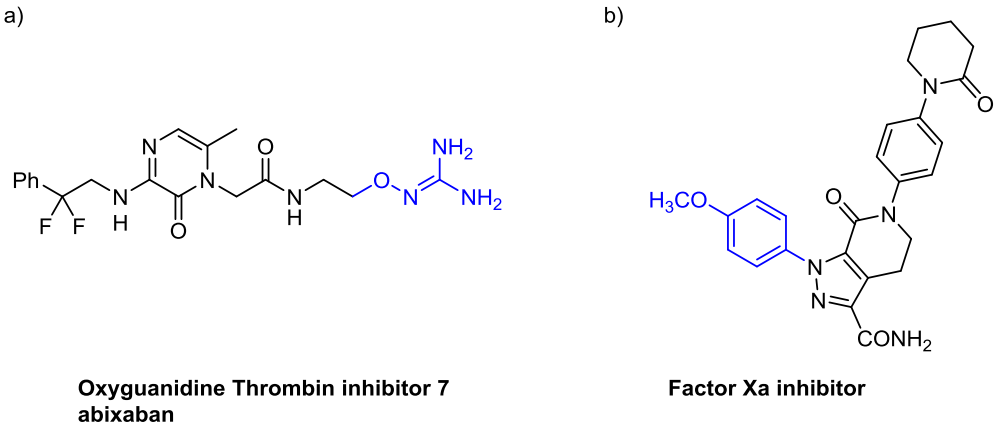


Figure 13. Structures of potent guanidine and arginine inhibitors.

Another prominent example of a bioisosteric replacement to alter the physicochemical properties of a compound is represented by the development of losartan (Figure 14). Early antagonists of the angiotensin II receptor (compound **8**) bearing a carboxylic acid demonstrated promising effects on the blood pressure, if administered intravenously, but showed no oral activity. During lead optimization, various bioisosteric replacements for the carboxylic moiety were evaluated to improve oral activity and metabolic stability. The introduction of a tetrazole moiety finally resulted in a 10-fold increase in potency compared to the carboxylic analog, due to an increase in lipophilicity of the tetrazole ring and a slight increase in pK_a resulting in a suppression of ionization.[87-88]

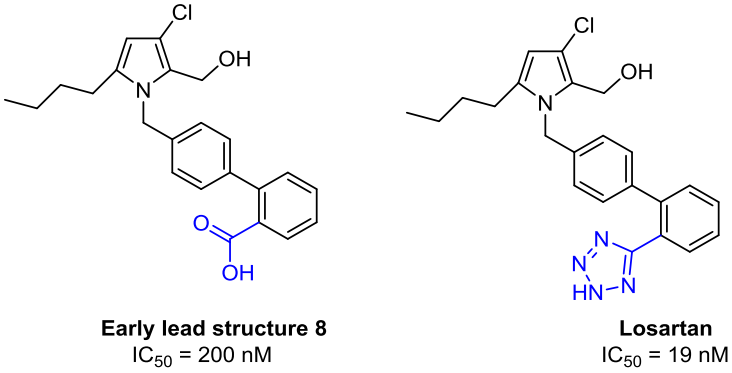


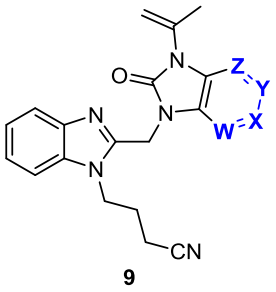
Figure 14. Structure of early angiotensin II receptor antagonists and tetrazole bioisostere losartan.[87-88]

3.2 Metabolic stability

As mentioned before, rapid metabolism is mostly a consequence of an unfavorable overall lipophilicity or unstable metabolic sites in the lead compound. The introduction of bioisosteric moieties is a helpful tool to enhance and tune the metabolic stability of a compound and is therefore widely used in modern drug design. One common metabolic derivatization is the hydroxylation of phenyl rings, which can be avoided by proper substitution, e.g. upon replacement of a CH-group with a nitrogen atom. This was evaluated in a series of

benzimidazole-based inhibitors **9** of the respiratory syncytial virus (RSV). After exchanging the CH moiety in all four available positions of the benzimidazole the antiviral activity and cytotoxicity of the compounds were compared (Table 2). The incorporation of a nitrogen atom had a strong effect on the metabolic stability and the solubility of the drug, while the potency of the inhibitors was clearly dependent on the position of the substitution. After further optimization a clinical candidate emerged based on the structure of a 6-aza-benzimidazol-2-one scaffold.[89-90]

Table 2. *RSV inhibition activity and cytotoxicity found in a series of RSV fusion inhibitors*



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W	**X**	**Y**	**Z**	**Inhibition of RSC replication EC_{50} (nM)**	**Cytotoxicity CC_{50} (µM)**
CH	CH	CH	CH	5	13
N	CH	CH	CH	3	>216
CH	**N**	**CH**	**CH**	**7**	**236**
CH	CH	CH	N	200	264

The development and implementation of phenol and catechol isosteres has been of particular interest due to their potential activity as agonists and antagonists of biogenic amines, such as adrenaline, serotonine and dopamine. Phenol can be hydroxylated in *ortho*- and *para*-position forming catechols which can subsequently be oxidized by CYP 450 enzymes to *ortho*- and *para*-quinones. These active metabolites have the potential to bind irreversibly to proteins resulting in an increased toxicity of the drugs. Thus, bioisosteric replacements using phenol isosteres as dopamine D1/D5 antagonists are particularly interesting (Figure 15).

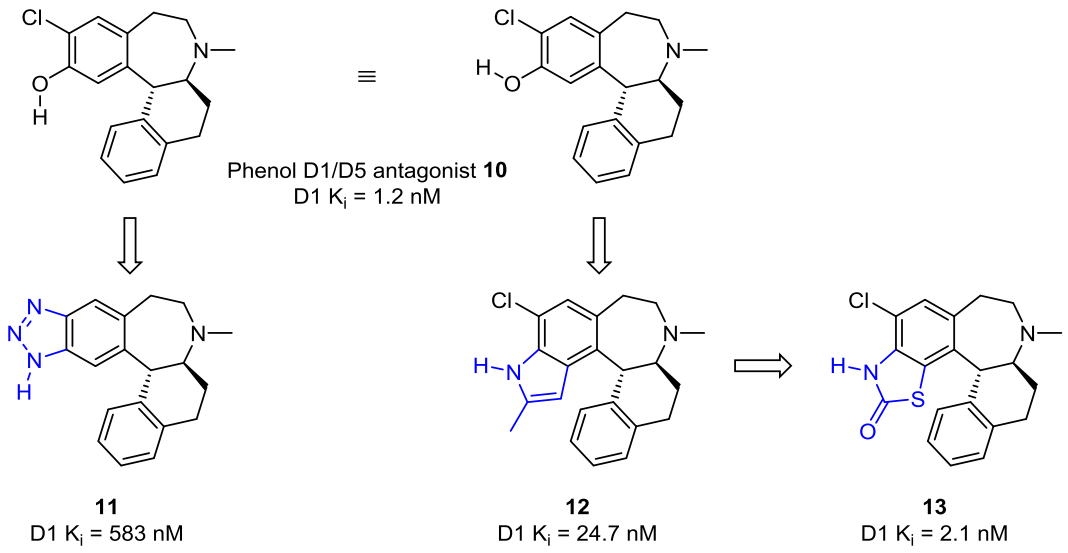


Figure 15. Phenolic and phenol mimetics in dual dopamine D1/D5 antagonists.

The original phenol-containing compound **10** showed poor oral bioavailability due to oxidation of the phenol moiety and was therefore replaced by different heterocyclic isosteres. The two initial isosteres (**11** and **12**) gave insight into the preferred orientation of compound **10** and its H-bonding in the binding pocket of the enzyme, as illustrated by comparison of the corresponding binding affinities.[91] Further optimization of potency resulted

in the development of compound **13**, demonstrating improved metabolic stability and similar potency when compared to the original phenolic antagonist.[91]

3.3 Binding affinity

Bioisosteric replacement is not only a means to enhance the ADME and toxicity parameters of drugs, but it can also directly affect the binding affinity toward the target. The binding affinity is highly dependent on various interactions, like hydrogen bonds, ionic and *van der Waals* interactions of the drug with its receptor, enzyme or ion channel. The development of bioisosteres of the phosphodiesterase 5 (PDE5) inhibitor sildenafil, better known as *Viagra*®, which is used to treat erectile dysfunction, is a particularly interesting example (Figure 16). Entering a highly profitable market encouraged increased research efforts toward new therapeutics with a longer duration of action and higher potency. These resulted in the development of the bioisosteric analog vardenafil which exhibits a 32-fold higher potency despite only small structural differences in the heterocycle.[92-93] One explanation was found in binding studies of co-crystals of PDE5 and the drugs, revealing two interactions of the heterocycles of vardenafil and sildenafil with Tyr_{612} *via* a hydrogen bond over a water bridge and a hydrophobic interaction of the heterocycle and the tyrosine ring. Thus, the hydrophobic interaction between vardenafil and the Tyr_{612} was much stronger compared to the interaction with sildenafil.[94]

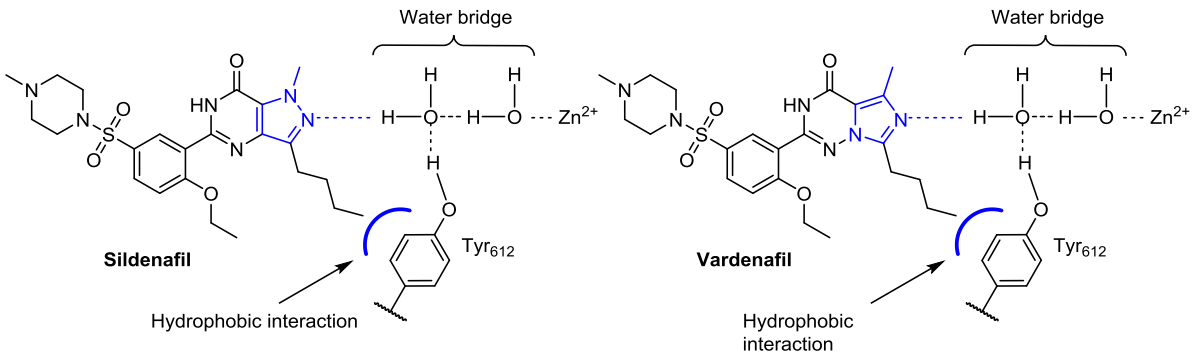


Figure 16. Structure of PDE5 inhibitors sildenafil and vardenafil and schematic depiction of interactions of Tyr_{612} with sildenafil and vardenafil. Dotted lines illustrate hydrogen bonds between nitrogen of the heterocycle and water, which is also forming hydrogen bonds with the phenolic hydroxyl moiety of Tyr_{612}. The blue line illustrates hydrophobic interaction between the heterocycle and the aromatic ring of Tyr_{612}.[94]

The collected examples illustrate that bioisosteric replacements can have a substantial effect on both the potency and stability of a drug candidate, while demonstrating structural similarity to the parent compound. On the other hand, bioisosteres can exhibit essential structural differences from their analog, yet eliminate deficient properties of the replaced functionality. An appropriate selection of bioisosteric replacements and their success is therefore hard to foresee. Nevertheless, bioisosteres have become one of the most useful tools in tuning active compounds toward drug candidates.

Amide moieties present an exceptional functional group in medicinal chemistry and will therefore be discussed in the next chapter. Due to their biological activity, they have a large scope of application in drug research. However, amides are often susceptible toward enzymatic hydrolysis fostering the search for appropriate bioisosteres, a few of which will be discussed in the following.

4. Amide Bond Replacements and Peptidomimetics

Amide bond replacements are of particular interest in bioisosteric research due to the increasing demand for peptide-based drugs and the development of peptidomimetics. Additionally, in the context of small molecule research, replacing an amide bond with a different moiety is a common tool to modulate polarity and bioavailability. Since amide bonds are naturally present in peptide backbones they are susceptible to hydrolysis by multiple enzymes which cleave the amide bonds into their amino acid building blocks. Consequentially, amide containing drug candidates often show poor metabolic stability and bioavailability demonstrating an urgent need for stable surrogates with improved stability toward proteolytic cleavage. There are many isosteric replacements of amides featuring diverse properties known that find versatile applications in lead compound optimization. A brief synopsis of different amide surrogates is presented in Figure 17.

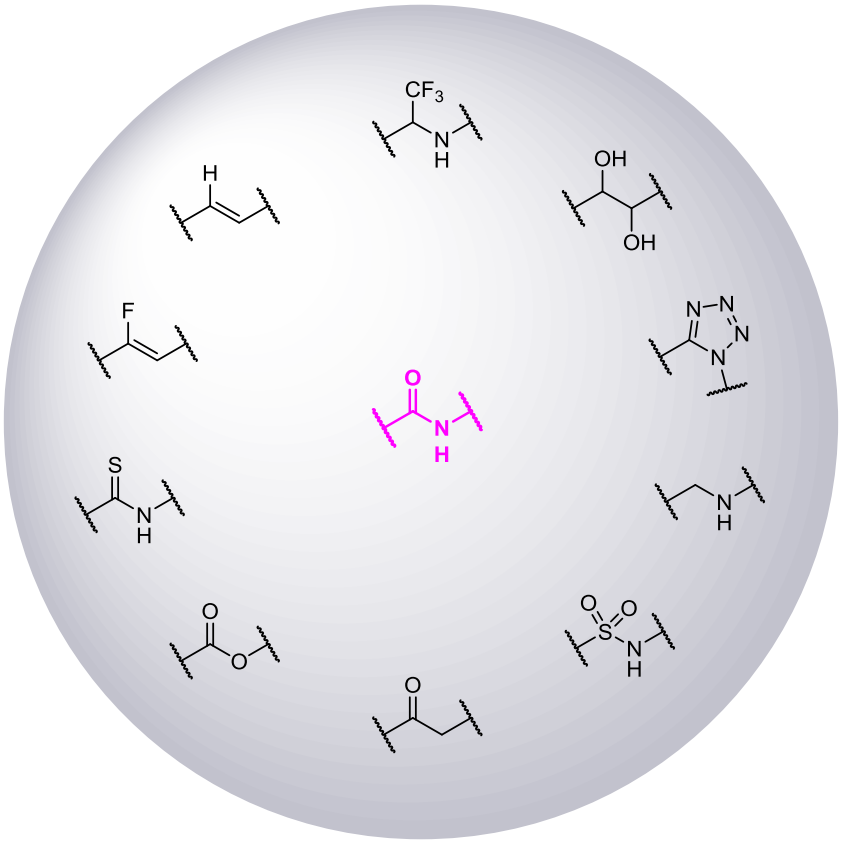


Figure 17. Synopsis of amide isosteres.

Amides feature a planar geometry due to the delocalization of the nitrogen lone pair into the antibonding orbital of the carbonyl moiety. In this rigid structure the carbonyl group and the N–H bond are mostly aligned in a *trans* orientation. The first examples of amide bond bioisosteres, that will be discussed in the following, retain this planar structure due to sp^2 hybridized atoms in the core structure.

Amide surrogates that essentially mimic the geometry of a peptide bond are *E*-alkene and fluoroalkene groups.[95-97] However, there are substantial differences in electronic properties of alkenes compared to amides. The dipole moment of the alkene bond is evanescently small (0.1 D), leading to a low ability of alkenes to form dipolar interactions. In contrast, fluoroalkenes in which a fluorine atom mimics the carbonyl oxygen have a

stronger dipole moment (1.4 D).[97] Nevertheless, both alkenes and fluoroalkenes are poor hydrogen-bond donors and acceptors and additionally hydrophobic. (*Z*)- and (*E*)-fluoroalkenes have been studied as mimics of peptide bonds in peptide nucleic acids (PNAs). The results indicated that both olefinic peptide nucleic acids (OPAs) bound to the DNA forming a duplex.[98-99] However, the formed duplexes were less stable than the corresponding PNA:DNA duplex most presumably due to the missing interaction of the lone pair of the carbonyl oxygen with the aromatic ring of the nucleobases.[100-101]

The substitution of an amide bond with a thioamide presents a classical isosteric replacement with a large overlap in structure. However, there are several properties of this surrogate, which again differ from an amide bond in key aspects. Comparison of bond lengths in the thioamide and amide functionality reveal a shorter C═S and a longer C–N bond length in the thioamide resulting from a pronounced charge separated resonance structure with a double bond between the nitrogen and carbonyl carbon atom.[102] Furthermore, thioamides are weaker hydrogen-bond acceptors and stronger hydrogen-bond donors than amides. The replacement of an amide bond with a thioamide in α-helix peptide scaffolds can therefore result in both an increase and a decrease of helix stability.[103-104]

Depsipeptides, in which one or more amide bonds are substituted by an ester moiety, find applications in drugs with versatile biological activities including anticancer, antibiotic and antiviral drugs or enzyme inhibitors.[105-108] Esters show a comparable geometric structure to amides with regard to the delocalization of the oxygen lone pair into the antibonding orbital of the carbonyl group.[109] In contrast to this structural analogy, esters and also ketones exhibit different hydrogen bonding properties. Both moieties are only weak hydrogen-bond acceptors and cannot donate hydrogen bonds.[110-111] In addition, they are susceptible to hydrolysis, making them poor bioisosteric replacements regarding proteolytic stability.

Tetrazole groups have often proven beneficial and find versatile applications in medicinal research due to their good pharmacokinetic profiles. They exhibit high metabolic stability and broad biological activity in many different modes of action although they are structurally different from amides. Tetrazolyl moieties have been introduced in compounds as 1,5- and 2,5-tetrazole-diyl derivatives replacing a *cis*- or *trans*-amide bond.[112-113]

Sulfonamides play an significant role in medicinal chemistry research and are widely used in the design of new drugs.[114] There are also examples for their incorporation into peptides,[115-118] even though they show crucial discrepancies in hydrogen-bonding properties and geometric structure. Sulfonamides have two hydrogen-bond accepting oxygen atoms as well as a strong hydrogen-donating nitrogen due to the increased acidity of the N–H bond. Regarding the geometric structure, sulfonamides often represent transition state isosteres since they exhibit a dihedral angle in contrast to the planar conformation of the amide backbone.[119] *Sanjayan* and co-workers studied the effect of amide bond replacements with sulfonamides in hetero foldamers (Figure 18). They demonstrated that the difference in the torsion angles of the sulfamide **14** and the amide backbone **15** had substantial impact on hydrogen bonds within the oligomers and hence governs the folding of the helical structures.[120]

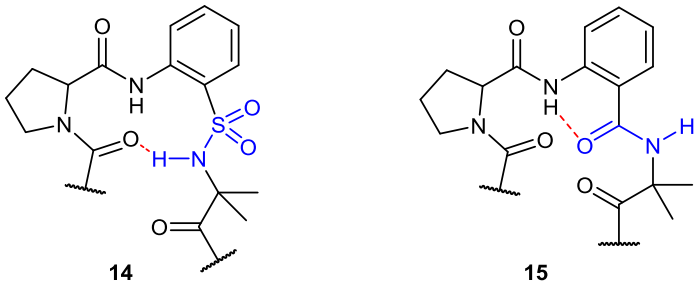


Figure 18. Differences in hydrogen bonding in tripeptide hetero foldamers studied by *Sanjayan* and co-workers.[120]

The introduction of amines as amide replacements bears many disadvantages, making them poor bioisosteric surrogates in many regards. In contrast to an amide bond, amines lack the ability to form hydrogen accepting bonds due to the missing carbonyl oxygen atom. Furthermore, the geometric structure is not planar and is very flexible due to the sp^3 hybridization of the neighboring carbon atoms. However, the main challenge in incorporating amines into drug candidates is the basicity of the amine. Pronounced basicity of amines facilitate protonation under physiological conditions, leading to a reduced lipophilicity and membrane permeability as well as interference with the hERG potassium ion channel.[43-44, 121-122]

Other amide surrogates like hydroxyethylene, dihydroxyethylene or epoxide have been studied, but will not be discussed here in further detail. Most bioisosteres mimic specific properties of the amide but show deficits in other aspects. Alkenes and fluoroalkenes primarily mimic the planar structure of an amide bond, while ester or ketomethylene moieties show similar proton accepting properties. Depending on the position of the functionality in the molecule and its impact on protein interactions, these replacements can nevertheless be useful tools to modify a drugable compound. However, there are only few examples of bioisosteres which mimic the hydrogen-donating character of the amide N–H. Next to sulfamides and amine moieties more recently trifluoroethylamines have attracted attention due to their unique properties.

5. Trifluoroethylamines as Amide Surrogates

Trifluoroethylamines as amide surrogates were first described by *Zanda* and co-workers who replaced a glycine amide bond and a malonamide to synthesize partially-modified ψ[CH(CF_3)NH]- and retro-ψ [NHCH(CF_3)]-peptides (Figure 19). They proposed that the replacement of an amide moiety with a trifluoroethylamine unit should increase the metabolic stability toward proteolytic degradation. Furthermore the stereoelectronically demanding trifluoromethyl moiety might act as a good hydrogen bond acceptor.[123-124]

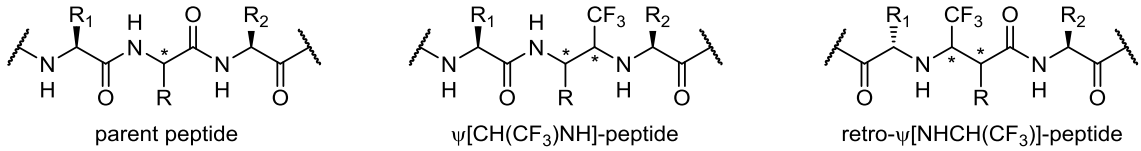


Figure 19. Structure of natural and partially-modified peptides by *Zanda* and co-workers. [123-124]

The C–CF_3 bond is isopolar with the C═O bond and the backbone angle of the CH(CF_3)–NH–CH unit is close to 120° resembling an amide bond. As discussed earlier, amine isosteres with hydrogen donating properties bear the risk of protonation in a biological milieu to form a R_2NH^+ species.[125] *Morgenthaler et al*. stated that the pK_a value of a compound can be decreased upon fluorination, leading to an approximate pK_a of 5.7 in trifluoroethylamines, which eliminates the risk of protonation under physiological conditions.[41] This was confirmed by studies on fluorinated and non-fluorinated piperidine and pyrazine derivatives which represent active 5-HT_{1D} inhibitors (Figure 20). Mono- and difluorination of a propyllinker close to the amine moiety had a profound effect, improving the oral absorption of the drug candidates **16** and **17**, due to a reduction in the pK_a value.[45]

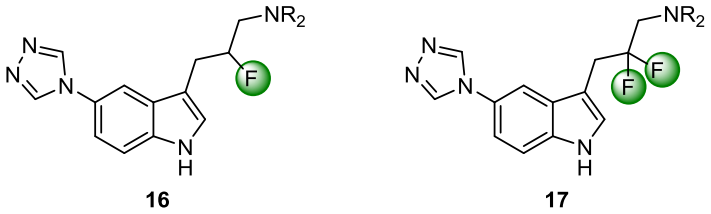


Figure 20. Mono- and Difluorinated 5-HT_{1D} inhibitors.[45]

The trifluoroethylamine moiety preserves the hydrogen-donating character of the parent amide, generating a metabolically stable non-basic amine. A possible restriction of this surrogate may be the bulkiness of the trifluoromethyl moiety which could influence the conformation of a compound, limiting the number of conformational isomers. Depending on the target, these conformational changes may improve or reduce the binding affinity. Furthermore, the trifluoromethyl group is only a weak hydrogen-bond acceptor.[126] Therefore, it was suggested that the trifluoroethylamine should only replace amide bonds where the carbonyl oxygen is not involved in substantial hydrogen-bonding with the receptor.[125]

The development of odanacatib, a very potent and selective cathepsin K inhibitor, is a remarkable example for the application of trifluoroethylamines in lead optimization.[127-128] Cathepsin K (Cat K) is a lysosomal cysteine protease which plays a major role in cells responsible for bone degradation in type I collagen. Type I collagen is the main component of the bone, therefore Cat K is considered a valuable target.[129] It has been shown that

Cat K deficiency results in a higher bone mineral density.[130] Thus, inhibitors of Cat K are urgently needed in treatment of osteoporosis. Previously developed inhibitors of Cat K contained amide bonds and therefore showed peptide-like properties, limiting their applicability for drug use. The initial lead structure L-006235 turned out to be lysomotropic due to the basicity and lipophilicity of the compound (Figure 21). This led to a loss of selectivity in cell-based assays as opposed to the promising results in enzyme assays.[131-132] Thus, drug optimization of the initial compound resulted in the replacement of one amide bond with a trifluoroethylamine group and the removing of the basic substituents. The neutral Cat K inhibitor L-873724 showed a 10- to 20-fold higher potency than the initial compound and more than 800-fold increase in selectivity against other cathepsins.[128, 133] However, the optimized candidate still displayed liabilities as regards its short half-life (2 h) and clearance (Cl = 7.5 mL/min/kg). These concerns resulted in the blocking of metabolic sites to adjust the pharmacokinetic properties by minimizing leucine hydroxylation, amide hydrolysis and lactonization. The final drug candidate odanacatib (MK-0822) is currently being tested in phase III of clinical trials.[127]

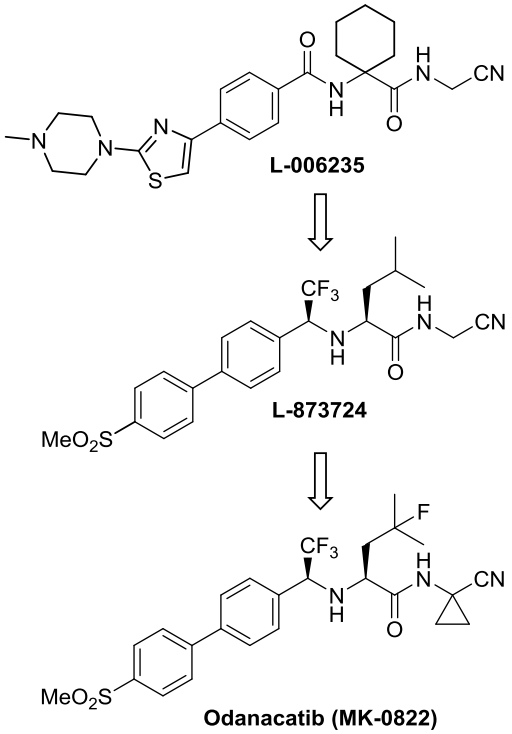
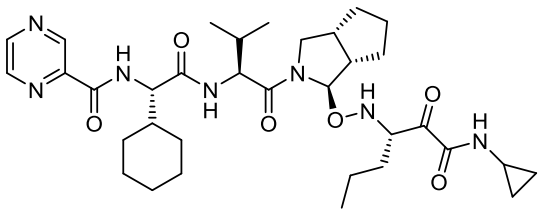
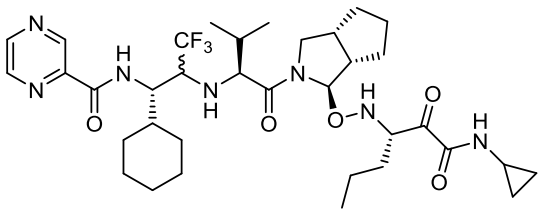


Figure 21. The development of odanacatib, a potent inhibitor of Cathepsin K.[127-128, 133]

The modification of teleprevir, a potent hepatitis C virus (HCV) NS3 protease inhibitor (IC_{50} = 70 nM), points to the impact of amide replacement with trifluoroethylamine moieties concerning the selectivity of the drug toward different targets (Figure 22).[134] Teleprevir can also act as an inhibitor against cysteine proteases like cathepsin B (IC_{50} = 210 nM). Replacing one of the amide moieties by trifluoroethylamine surrogates identified two active inhibitors of cathepsin S (compounds **18a** and **b)** which, in contrast to the unfluorinated parent compound, only exhibited a weak inhibition of HCV NS3. Since cathepsin S activity is connected to Alzheimer´s disease and autoimmune disorders, Cat S inhibitors are potentially useful drugs.[135]



Teleprevir



18a and **b**
α- and β-CF_3 derivative

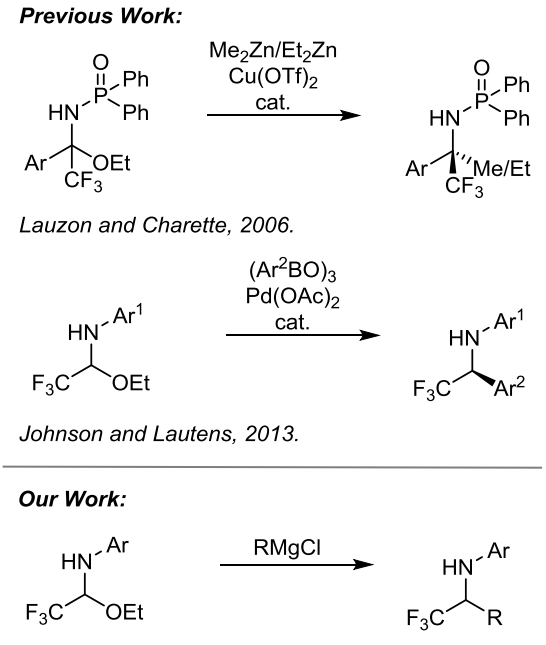
Figure 22. Structure of teleprevir and trifluoromethylated cathepsin S inhibitors **18a** and **b**.[135]

Despite these promising results of amide replacement with trifluoroethylamines, there are only few examples presented in literature. This seems to be due to limited synthetic access toward these compounds, evidencing the need for improved methods with a broad substrate range and variable substitution patterns.

II. OBJECTIVE

The growing importance of fluorinated entities in medicinal chemistry is a result of the exceptional properties of the element fluorine. Fluorination is an instrument to fine-tune lead compounds toward drug candidates, eliminating physicochemical or metabolic liabilities and optimizing target binding.[22, 47, 53, 136-137] Despite a limited number of investigated drugs presented so far,[127, 135] implementation of trifluoroethylamines as carboxamide surrogates in drug candidates is an unique opportunity to develop drug candidates with improved properties. The lack of applications may be a result of the limitations regarding the synthetic access to this structural motif. Most common routes to synthesize trifluoroethylamines are based on addition reactions of nucleophiles to trifluoromethylated imines.[138-143] Alternatively, hydrogenation and aromatic substitution of activated imines have been described.[144-149] These imine-based strategies are hampered by the tendency of fluorinated imines to form hydrates which leads to their subsequent deactivation. Other approaches using trifluoromethylated hemiaminal ethers are often dependent on the use of auxiliary protection of the nitrogen.[150] However, a few examples of *N*-functionalized *N*,*O*-acetals which have been converted into the corresponding trifluoroethylamines using *C*-nucleophiles have been described in the literature.[151-152]

The aim of this work was to establish synthetic routes toward novel trifluoromethylated amine derivatives starting from trifluoromethylated *N*-aryl *N*,*O*-acetals. The focus was set on the synthesis of yet unknown functionalized trifluoroethylamines and trifluoromethylated amine derivatives which might be promising building blocks for drug development. Initially in our first project, we envisioned the development of a practical and readily applicable synthetic strategy based on functionalized *N*-aryl *N*,*O*-acetals and simple alkyl magnesium reagents (Scheme 4). The requisite *N*,*O*-acetals could be obtained by reaction of various (hetero-)arylamines and 1-ethoxy-2,2,2-trifluoroethanol as previously shown by *Gong et al*.[153]



Scheme 4. Previous and targeted approach toward the synthesis of trifluoroethylamines.

After establishing a convenient procedure using commercially available alkyl *Grignard* reagents, we aimed at synthesizing more complex substituted trifluoroethylamines by extending the project to the use of functionalized organomagnesium reagents. Subsequently, we envisaged to implement our synthetic protocol in more complex syntheses for generation of bioisosteric analogs of pharmaceutically active compounds to illustrate its applicability. Finally, we planned to develop a stereoselective synthesis of these compounds by employing copper-catalyzed reactions for which chiral ligands could be screened.

Besides trifluoroethylamines, the synthesis of difluoroethylamines is of interest in the pharmaceutical context. For instance, replacement of a trifluoromethyl moiety with a difluoromethyl group can be used to alter pK_a values of the adjacent amines in cases where an increase in basicity is beneficial. Furthermore, difluoromethyl moieties have been studied as hydroxyl bioisosteres, exhibiting weak hydrogen-bond donating properties. However, a difluoromethyl group usually enhances the lipophilicity compared to hydroxyl or amine moieties which may improve membrane permeability. Therefore, we envisioned to extend our methodology toward difluoromethylated *N*,*O*-acetals in a second project to furnish previously unknown difluoroethylamines as potential scaffolds for pharmaceutical applications.

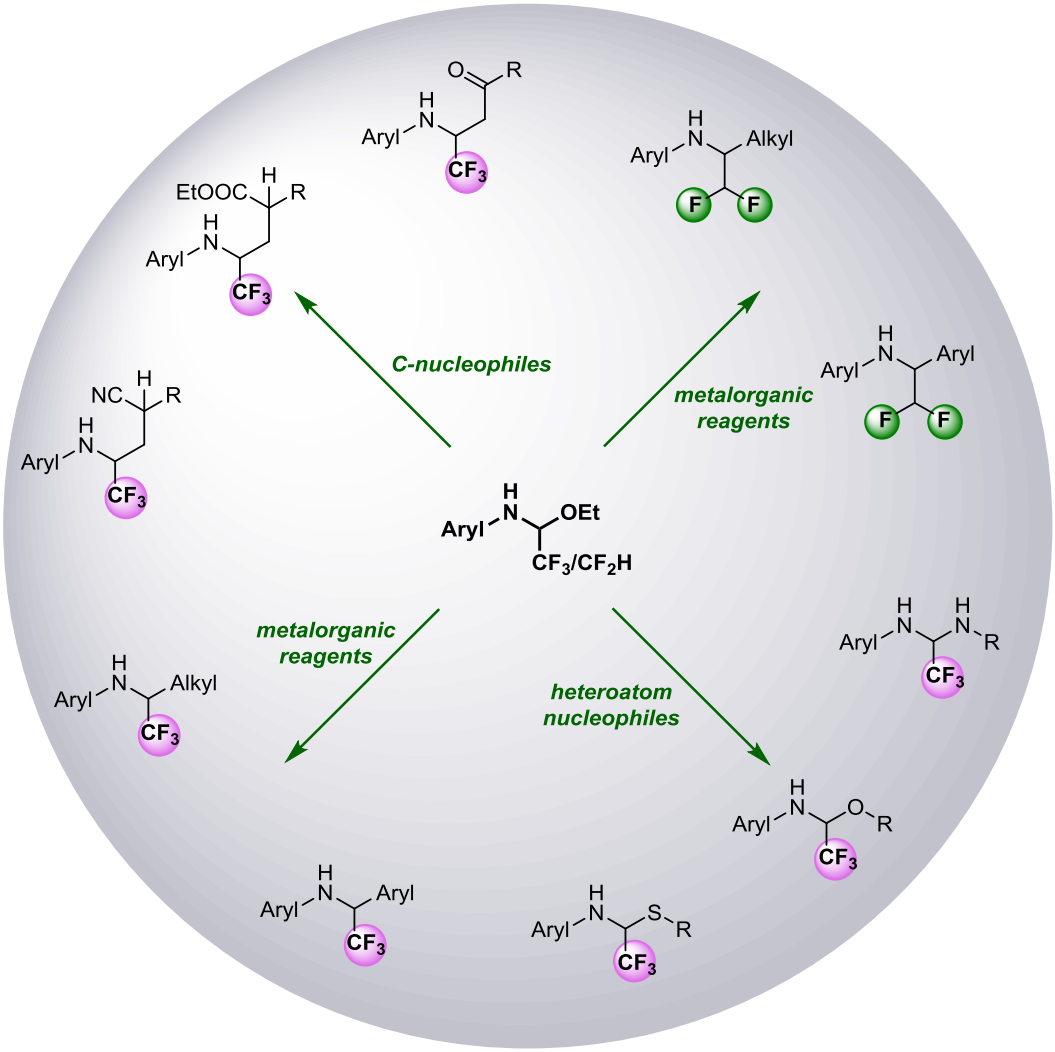


Figure 23. Compounds of interest and synthetic strategies toward their synthesis.

In a further project, we planned to establish a simple methodology to synthesize *β*-amino-*β*-fluoroalkyl carbonyl compounds by converting *N*,*O*-acetals with other nucleophiles such as lithium enolates *via* a *Mannich*-type reaction. These compounds are particularly interesting as peptide surrogates which may be incorporated as building blocks for pharmaceutical and biological application.

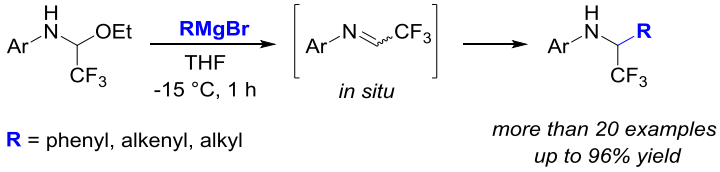
Finally, we envisioned the application of the methods described above to access trifluoromethylated amino acid precursors which should subsequently be integrated in manual or automatic solid-phase peptide synthesis (SPPS). The investigation of such modified peptide derivatives regarding the structural and metabolic deviations from naturally occurring peptides may be of particular interest for future application in medicinal chemistry.

RESULTS AND DISCUSSION

III. Results and Discussion

1. Synthesis of Functionalized α-Trifluoroethylamine Scaffolds *via Grignard* Addition to *N*-Aryl Hemiaminal Ethers

A. Deutsch, H. Glas, A. Hoffmann-Röder* and C. Deutsch*, *RSC Adv.* **2014**, *4*, 9288–9291.



Declaration of Contribution

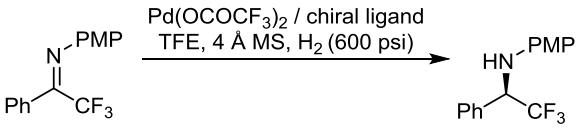
Based on an idea initialized and supervised by *Dr. Carl Deutsch, Herbert Glas* performed first experiments to access trifluoroethylamines in the laboratories of *Merck KGaA* (Darmstadt). In collaboration with *Dr. Carl Deutsch*, I then developed a protocol and optimized the reaction conditions for the synthesis of functionalized *N*-aryl trifluoroethylamines. Additionally, I applied this methodology to synthesize a set of trifluoroethylamines by variation of the trifluoromethylated hemiaminal ethers and the alkyl- and phenylmagnesium reagents.

Background

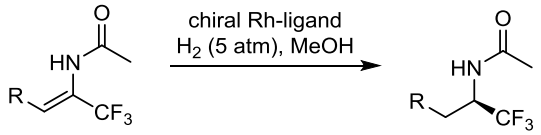
The importance of trifluoroethylamines as bioisosteric replacement for amides has been illustrated in the introductory chapter (see I.5). Even though trifluoroethylamines were used for the optimization of CatK inhibitors quite successfully, only a limited number of lead structures comprising this moiety are described in the literature. This is most likely due to various limitations of the reported synthetic strategies accessing these structures, namely a small substrate scope, hydrolysis of the starting material or the necessity of activating *N*-protecting groups. A brief outline of the current methods and their possible limitations will be highlighted in the following.

Hydrogenation of trifluoromethylated imines is a common synthetic strategy often applied toward the synthesis of trifluoroethylamines (Scheme 5).[144-148] In this context, *Chen et al*. reported the reduction of fluorinated *N*-protected imines into the corresponding amines by enantioselective Pd-catalyzed hydrogenation in good enantiomeric excess (*ee*) of ≥ 84%.[149] Recently, *Zhang* and co-workers presented a Rh-catalyzed asymmetric hydrogenation of *α*-trifluoromethylated enamides to synthesize both aryl- and alkyl-substituted trifluoromethylated amines.[154] However, both synthetic approaches require subsequent *N*-deprotection for further functionalization.

Hydrogenation of trifluoromethylated imines and enamides:



Chen et al., 2010.

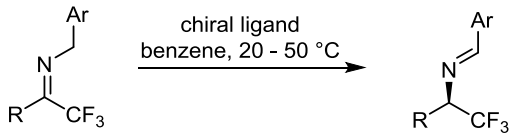


Jiang et al., 2015.

Scheme 5. Synthesis of trifluoroethylamines *via* hydrogenation of imines and enamides.[149, 154]

Furthermore, asymmetric [1,3]-proton shifts of trifluoromethyl ketimines have been described to give enantioenriched aldimines (see Scheme 6 for a selected example by *Liu et al.*), which can be readily converted into the corresponding amines by hydrolyzation. However, this strategy is limited by the necessity of electron-withdrawing benzylic protecting groups to facilitate the [1,3]-proton shift.[155-157]

Catalytic asymmetric [1,3]-proton shift of trifluoromethyl imines:

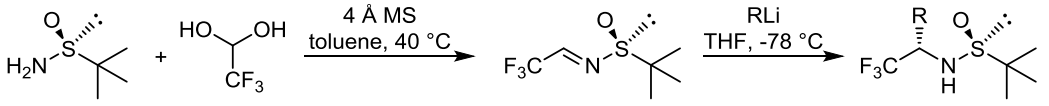


Liu et al., 2013.

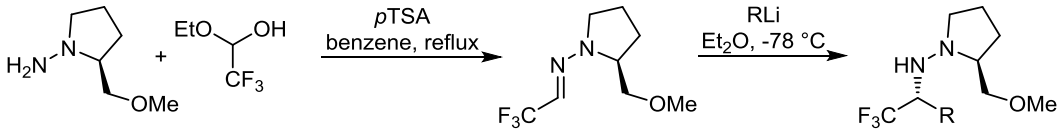
Scheme 6. [1,3]-proton shift of trifluoromethylated imines.[155]

Moreover, trifluoromethylated aldimines can be converted into amines by nucleophilic addition of various organometallic reagents (Scheme 7).[138-142] As described by *Truong et al.*, 2-methyl-*N*-(2,2,2-trifluoroethylidene)propane-2-sulfinamide, accessible by condensation of *N-tert*-butanesulfinamide and trifluoroacetaldehyde hydrate, can be reacted with different aryllithium and arylmagnesium reagents.[143] Similarly, lithium and magnesium organyls were reported to react with trifluoromethylated hydrazone derivatives (see *Enders et al.*, Scheme 7).[158-159]

Addition of organometallic reagents to trifluoromethylated imines and hydrazones:



Truong et al., 2007.

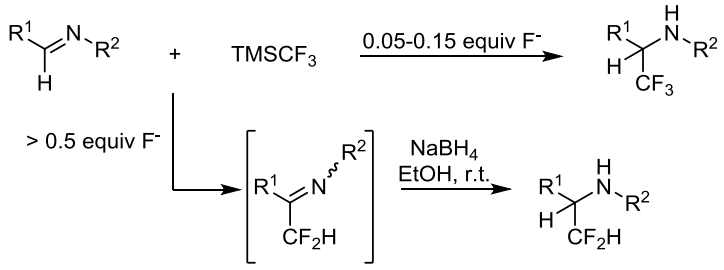


Enders et al., 2001.

Scheme 7. Addition of lithium organyls to trifluoromethylated imines and hydrazones.[143, 158]

A different synthetic approach converts imines with nucleophilic trifluoromethylating agents such as trimethyl(trifluoromethyl)silane ($TMSCF_3$) which itself does not react with an imine but has to be activated using a nucleophilic initiator.[160-162] A prominent example represents the enantioselective trifluoromethylation of *N*-(*tert*-butylsulfinyl)-imines developed by *Prakash et al.* (Scheme 8). The trifluoromethide anion, which is liberated by a tetraalkylammonium fluoride source, was used to introduce the trifluoromethyl group into imines. Interestingly, depending on the type and amount of fluoride source used, difluoromethylated amines can also be accessed from the transient imine species after *in situ* reduction with $NaBH_4$ (Scheme 8).[163]

Di- and trifluorination of aldimines using $TMSCF_3$:

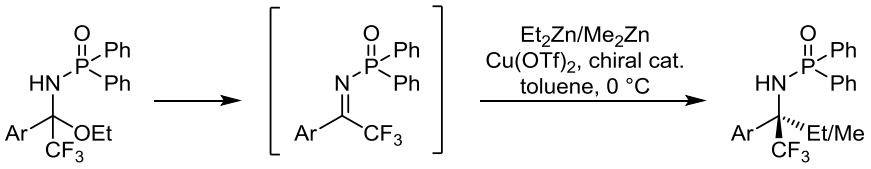


Prakash et al., 2006.

Scheme 8. Synthesis of tri- and difluoroamines using $TMSCF_3$.[163]

Most of the synthetic strategies described so far rely on imines which can be converted into trifluoroethylamines. However, the disadvantage associated with their use is a high tendency to form hydrates. This has led to a search for more stable substrates and the discovery of hemiaminal ethers being synthetically useful and readily available surrogates of imines.[164-165] For instance, *Lauzon* and *Charette* described an asymmetric synthesis of trifluoroethylamines by copper-catalyzed addition of diorgano zinc reagents to *in situ* generated *N*-phosphinoylimines from the corresponding hemiaminal ethers (Scheme 9). Dimethyl and diethyl zinc were successfully reacted to the desired amines with an *ee* above 90% using a chiral diphosphine ligand. However, this conversion is restricted to the introduction of methyl and ethyl substituents and requires cleavage of the *N*-phosphinoyl moiety under relatively harsh reaction conditions to allow further functionalization of the amine.[151]

Synthesis of trifluoromethylated amines from N-phosphinoyl hemiaminal ethers and organozinc reagents:

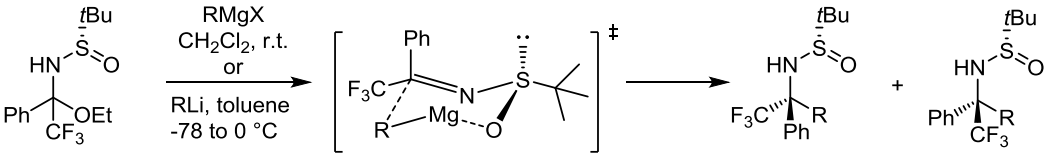


Lauzon and Charette, 2006.

Scheme 9. Synthesis of methyl and ethyl substituted trifluoroethylamines.[151]

Grellepois et al. reported a method using *N-tert*-butanesulfinyl protected hemiaminal ethers, which can be converted into trifluoromethylated amines by addition of simple lithium and magnesium organyls as illustrated in Scheme 10. Thereby a six-membered chair transition state is formed in which the sulfinyl oxygen atom of the intermediate imine coordinates to magnesium. Due to steric hindrance exerted by the trifluoromethyl moiety, the equatorial position in this transition state is preferred, favoring the addition of the organometallic reagent from the *re*-side.[150]

Synthesis of trifluoromethylated amines from N-tert-butanesulfinyl hemiaminal ethers and organometallic reagents:

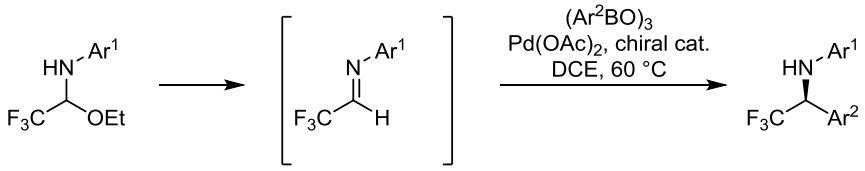


Grellepois et al., 2013.

Scheme 10. Synthesis of *N-tert*-butanesulfinyl trifluoroethylamines.[150]

A further procedure worth mentioning is the Pd-catalyzed addition of arylboroxines to *in situ* generated trifluoromethylacetaldimines by *Johnson* and *Lautens* (Scheme 11). Using chiral pyridine-oxazolidine ligands, a variety of *N,O*-acetals were reacted with electron-neutral or electron-rich arylboroxines, which were accessible by dehydration of boronic acids.[152] In 2016, this method was extended to the use of electron-poor boroxines by addition of an ammonium or silver salt.[166] Despite this important development, the addition reaction is again restricted to the synthesis of α-substituted aryl amines and requires relatively harsh reaction temperatures which may exclude the use of particulary sensitive substrates.

Synthesis of trifluoromethylated amines from hemiaminal ethers and organometallic reagents:



Johnson and Lautens, 2013.

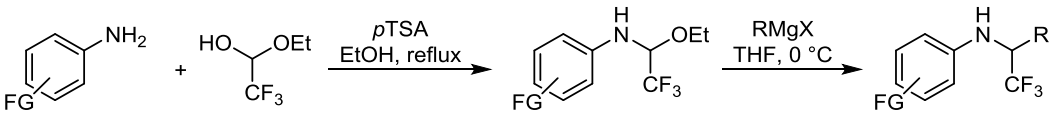
Scheme 11. Synthesis of trifluoroethylamines from hemiaminal ethers.[152]

Despite the large effort put into the development of a convenient synthesis of trifluoroethylamines, the methods presented so far are hampered by several disadvantages. The asymmetric addition reaction to imines or

hemiaminal ethers often rely on *N*-activating protecting or chiral auxiliary groups, which need to be cleaved to enable a further functionalization of the amine moiety. Furthermore, many procedures are limited to a small substrate scope or require harsh reaction conditions.

Based on the methods established in the literature and their limitations mentioned above, we therefore decided to investigate the use of *Grignard* reagents in a direct addition reaction to functionalized, trifluoromethylated *N*,*O*-acetals. Our main objective was to develop a convenient method which allows access to a wide variety of substituted trifluoroethylamines. Moreover, the applicability of the procedure in multistep synthesis should initialize a possible embedment of the strategy in lead structure research and optimization. After initial experiments to determine the basic requirements for a successful formation of the desired trifluoroethylamines, we optimized the reaction conditions toward a high yielding procedure. The *N,O*-acetal substrates used in this synthesis were readily available by condensation of the corresponding arylamines and 1-ethoxy-2,2,2-trifluoroethanol (TFAE) as described by *Gong et al*.[153] Upon treatment of these substrates with organomagnesium halides the corresponding trifluoromethylated aldimines are formed *in situ*. Subsequent addition of a second equivalent of the *Grignard* nucleophile then results in the formation of the desired trifluoroethylamines (Scheme 12). With the optimized reaction conditions in hands, we studied the substrate scope of the reaction by variation of the *N*,*O*-acetals and the *Grignard* reagents. To our delight we found that this efficient procedure can be applied to a broad variety of aromatic and heteroaryl hemiaminal ethers with a large tolerance for functional moieties. Furthermore the application of alkyl, alkenyl and aryl *Grignard* reagents was successfully demonstrated in high yields.[167]

Addition of organometallic reagents to N-aryl N,O-acetals:



Deutsch et al., 2014.

Scheme 12. Synthesis of trifluoromethylated amines.[167]

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Synthesis of functionalized α-trifluoroethyl amine scaffolds *via* Grignard addition to *N*-aryl hemiaminal ethers†

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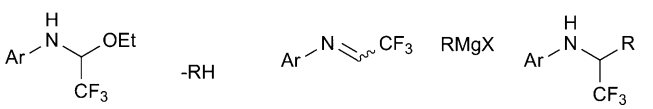
The synthesis of a variety of α-branched trifluoroethyl amines was achieved by reaction of *N*-aryl hemiaminal ethers with organomagnesium reagents.

The design of compounds suitable for drug development is a multi-dimensional process that requires the fine tuning of molecular properties beyond potency. For instance, physical–chemical properties that directly affect hydrolytic stability and bioavailability of the compound must be addressed to avoid side effects *in vivo*. Due to the excellent pharmacological profile of fluorinated drugs, the strategic incorporation of fluorine atoms has nowadays become routine in medicinal chemistry development programs.[1] For instance, incorporation of a trifluoromethyl substituent adjacent to an amine is a means to improve the metabolic stability and to attenuate the basicity of the compound by shifting its pK_a value more towards those of amides.[2] Furthermore the C–CF_3 bond is substantially isopolar with the C=O bond and the trifluoroethyl amine moiety has a structural similarity to the tetrahedral proteolytic transition state.[3] As a consequence, trifluoroethyl amines can be used as versatile hydrolysis-resistant bioisosteres of amides[4] which retain the geometry of the amide bond and, in contrast to other mimetics[5], also preserve the donating properties of the N–H bond. An illustrative example for the successful replacement of the amide functionality by a trifluoroethyl amine is given by Odanacatib, a highly potent drug candidate for the inhibition of Cathepsin K.[6]

Various methods for the synthesis of α-trifluoromethylated amines have been described so far,[7] including hydrogenation[8] and aromatic substitution[9] of activated imines, as well as base-catalyzed asymmetric isomerization reactions of ketoimines.[10] Furthermore, nucleophilic addition reactions of various organometallics to trifluoromethylated imines[11] and hydrazones[12] have been reported. In this context, Lauzon and Charette have shown that trifluoromethyl amine derivatives can be prepared by copper-catalyzed nucleophilic addition of diorganozinc reagents to *N*-phosphinoylimines, using an excess of organozinc reagent.[13] Similarly, trifluoromethylated α,α-dibranched carbinamines can be obtained from *N*-*tert*-butylsulfinyl hemiaminals with organomagnesium or organolithium reagents.[14] However, most of these approaches are either hampered by the high tendency of α,α,α-trifluorethylimines to form hydrates or by the need of additional deprotection steps for further functionalization of the nitrogen atom. In a seminal paper, Mikami and coworkers showed that an excess of Grignard reagents can be used to prepare α-trifluoromethylated amines from stable N,O-acetals of trifluoroacetaldehyd.[15,16] This work was recently extended to the use of arylboroxines for palladium(II)-catalyzed synthesis of α-(trifluoromethyl)arylmethyl amines.[17]

Herein, we report a systematic study on the synthesis of functionalized α-substituted trifluoromethyl amines using Grignard reagents and readily available trifluoromethylated hemiaminal ethers.[18] The latter are shelf-stable compounds derived from 1-ethoxy-2,2,2-trifluoroethanol and aromatic amines and can be converted into trifluoromethylated aldimines *in situ*. Thus, upon treatment with Grignard reagent deprotonation should provide the corresponding imine which would then undergo nucleophilic attack by excess Grignard reagent to furnish the desired trifluoromethyl amine (Scheme 1). Formation of the transient imine species was confirmed by observing the corresponding imine hydrate *via* HPLC-MS after addition of MeMgBr to the reaction mixture.



Scheme 1

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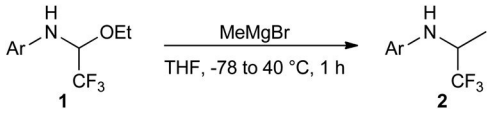
† Electronic supplementary information (ESI) available: See DOI: 10.1039/c3ra47708h

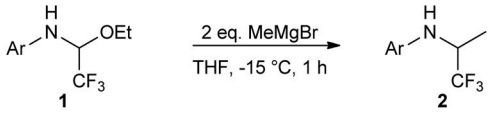
Table 1 Optimization studies

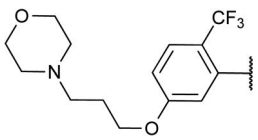
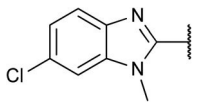
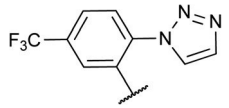
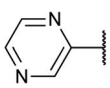
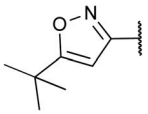


Entry	Ar	Eq. [MeMgBr]	T [°C]	Yield (%)[a]	Product
1	3-ClC_6H_4	2	40	65	**2a**
2	3-ClC_6H_4	2	25	70	**2a**
3	3-ClC_6H_4	2	0	84	**2a**
4	3-ClC_6H_4	2	−15	87	**2a**
5	3-ClC_6H_4	2	−78	74	**2a**
6	3-ClC_6H_4	3	−15	75	**2a**
7	C_6H_5	1	−15	34[b]	**2b**
8	C_6H_5	2	−15	63	**2b**
9	C_6H_5	3	−15	65	**2b**

[a] Yield of isolated product after flash chromatography. [b] Reaction time of 2 h.

Table 2 Addition of MeMgBr to (hetero)aromatic N,O-acetals[a]



Entry	Ar	Yield (%)[b]	Product
1	3-ClC_6H_4	87	**2a**
2	C_6H_5	63	**2b**
3	4-pyridyl	81	**2c**
4	4-$OMeC_6H_4$	40	**2d**
5	4-$COOEtC_6H_4$	94[c]	**2e**
6		57	**2f**
7		69	**2g**
8		96[d]	**2h**
9		80	**2i**
10		74	**2j**

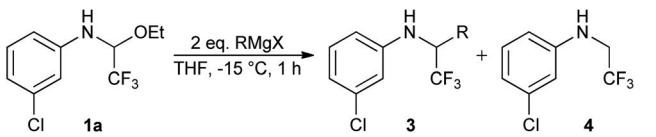
[a] All reactions were performed according to the optimized procedure. [b] After flash chromatography. [c] Use of 3 eq. MeMgBr. [d] Without further purification.

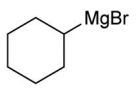
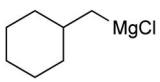
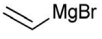
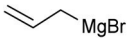
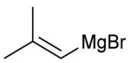
To determine the optimal conditions, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** was treated with MeMgBr in dry THF under argon at different reaction temperatures (Table 1). Thus, the addition proceeded smoothly at −78 °C furnishing the desired trifluoroethyl amine **2a** in 74% yield after one hour. Whereas higher temperatures above 0 °C led to significant formation of side and decomposition products, best yields were obtained at a temperature of −15 °C (Table 1, entries 1–5). For complete conversion of the trifluoromethyl N,O-acetals at least 2 eq. MeMgBr are required. However, larger excess of the nucleophile did not improve the yield significantly. Similar results were obtained with *N*-(1-ethoxy-2,2,2-trifluoroethyl)-aniline **1b** bearing a neutral aryl ring (Table 1, entries 7–9).

With the optimized reaction conditions in hands, the substrate scope of the nucleophilic addition was tested using various functionalized aryl N,O-acetals **1** and MeMgBr (Table 2). We were pleased to find that besides halides also ester, triazole, trifluoromethyl groups and morpholino substituents are well tolerated to provide the desired trifluoroethyl amines **2** in fair to excellent yields (Table 2, entries 1, 5, 6 and 8). However, electron-rich aniline derivatives proceeded more sluggishly and led to formation of the desired product with only diminished yields (Table 2, entry 4). In contrast, both electron-deficient and moderately electron-rich heteroaromatic N,O-acetals **1c** and **1g–j** were readily converted to the corresponding amines **2c**, **2g–j** (Table 2, entries 3, 7–10), thus giving access to compounds with potential applications in drug design.

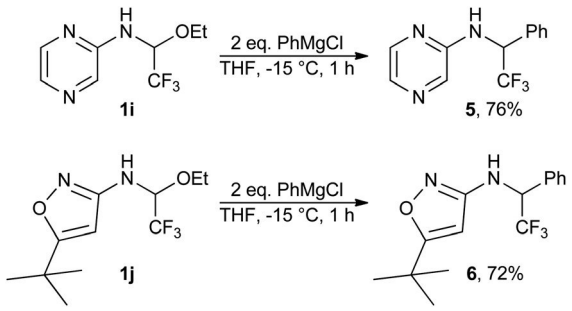
Next, we turned our attention to other Grignard reagents for nucleophilic addition to trifluoromethylated N,O-acetals. Thus,

Table 3 Addition of Grignard reagents to 3-chlorophenyl N,O-acetal[a]



Entry	RMgX	Yield of **3** (%)[b]	Yield of **4** (%)[b]
1	*i*-PrMgCl	**3a**, 70	16
2	*i*-PrMgCl·LiCl	**3a**, 67	30
3	*n*-BuMgBr	**3b**, 94	nd[c]
4	*t*-BuMgCl	**3c**, 57	nd
5		**3d**, 78	nd
6		**3e**, 26	19
7		**3f**, 62	nd
8		**3g**, 84	nd
9		**3h**, 85	nd

[a] All reactions were performed according to the optimized procedure. [b] After flash chromatography. [c] nd = not detected.



Scheme 2

upon treatment of 3-chlorophenyl hemiaminal **1a** with several alkyl Grignard reagents, various α-branched trifluoromethyl *N*-arylamines **3a–e** were obtained in moderate to good yields (Table 3, entries 1–6). Notably, even highly sterically hindered nucleophiles like *t*-BuMgCl or cyclohexylmagnesium bromide can be successfully employed in this reaction (Table 3, entries 4 and 5). Interestingly, by using *i*-PrMgCl, *i*-PrMgCl·LiCl and cyclohexylmethylmagnesium chloride as nucleophiles, also generation of the formal reduction product 3-chloro-*N*-(2,2,2-trifluoroethyl)aniline **4** was observed. It is worth mentioning that the yield of this side-product was substantially higher with *i*-PrMgCl·LiCl (up to 30%) than with *i*-PrMgCl and cyclohexylmethylmagnesium chloride (Table 3, entries 1, 2 and 6). This is presumably due to the higher degree of complexation in the presence of LiCl, which facilitates hydride transfer to the substrate. Furthermore, nucleophilic addition of alkenyl Grignard reagents proceeded smoothly and provided the desired unsaturated trifluoromethyl *N*-arylamines **3f**, **3g** and **3h** in moderate to good yields (Table 3, entries 7–9).

Finally, PhMgCl can be used for conversion of trifluoromethyl N,O-acetals into trifluoromethylated benzylamine derivatives. For instance, treatment of the pyrazine derivative **1i** and the isoxazolyl hemiaminal ether **1j** with 2 eq. PhMgCl afforded amines **5** and **6** in good yields (Scheme 2).

In summary, an efficient procedure for the synthesis of α-branched trifluoromethylated amines has been developed starting from stable *N*-aryl trifluoromethyl hemiaminal ethers. Whereas alkyl amines were incompatible with N,O-acetal formation, a broad range of aromatic and heteroaromatic substrates can be applied successfully to allow for rapid generation of functionalized amine scaffolds for medicinal chemistry purposes after addition of alkyl, alkenyl and aryl Grignard reagents. Moreover and in contrast to other known protocols, protecting group manipulations are not required if the resulting trifluoromethylated amines are to be used as amide bio-isosteres for use in lead optimization. Further investigations in this direction and on the use of functionalized organometallic reagents are ongoing and will be reported in due course.

Acknowledgements

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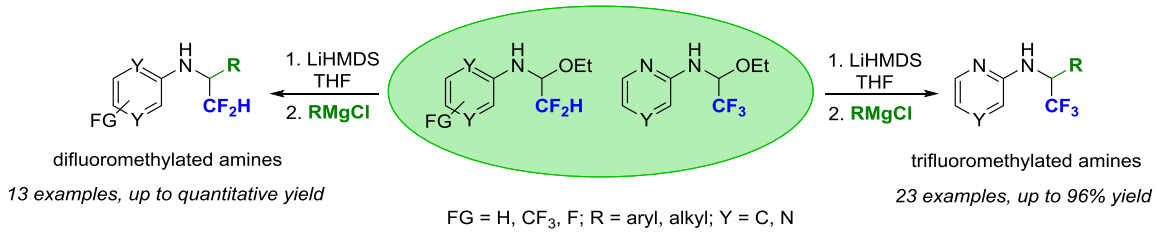
2. Convenient Access to Di- and Trifluoroethylamines for Lead Structure Research

A. Deutsch, C. Wagner, C. Deutsch* and A. Hoffmann-Röder*, *Eur. J. Org. Chem.* **2016**, *5*, 930–945.



Declaration of Contribution

Based on the synthesis described in our earlier protocol, *Christian Wagner* extended the synthesis to the use of an external base under my supervision to decrease the necessary amount of *Grignard* reagent for this conversion.[168] We then synthesized a large number of pyridyl- and pyrazyl-substituted trifluoroethylamines together using functionalized magnesium organyls. Furthermore, I synthesized various difluoroethylamines and developed a method to access novel trifluoromethylated scaffolds *via* addition of heteroatom nucleophiles. To demonstrate the synthetic applicability of the newly modified protocol, I prepared two previously unknown trifluoroethylamine analogs of reported biologically active compounds *via* multistep synthesis.

Synopsis

As a logic extension of our first project, we then aimed at increasing the degree of functionalization of the synthesized trifluoroethylamines. To access trifluoromethylated *N*,*O*-acetals bearing electron withdrawing substituents we initially developed a microwave protocol for the conversion of heteroaryl- and electron-poor arylamines. Subsequently, we modified our previously developed protocol to reduce the amount of organometallic reagent required for the complete conversion of the starting material by addition of an external base. This efficient methodology could then be applied to a wide range of functionalized *Grignard* reagents. Next to the synthesis of these amide surrogates, we focused our attention on the synthesis of difluoroethylamines, since they were so far underrepresented but very promising motifs in medicinal chemistry research. Therefore, we successfully converted difluoromethylated *N*,*O*-acetals which were accessible by condensation of the corresponding amines with 1-ethoxy-2,2-difluoroethanol with functionalized *Grignard* reagents. Finally, we developed a procedure to allow the addition of simple heteroatom nucleophiles to

N,*O*-acetals. To underline the synthetic applicability of the reported protocol for multistep synthesis two potential bioisosteres of 1,2-dihydroquinazolin-4-(1*H*)-thione and the androgen receptor antagonist DIMN were successfully prepared.[169]

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EurJOC European Journal of Organic Chemistry

Full Paper

Fluorinated Amines

Convenient Access to Di- and Trifluoroethylamines for Lead Structure Research

Amrei Deutsch,[a] Christian Wagner,[a] Carl Deutsch,*[b] and Anja Hoffmann-Röder*[a]

Dedicated to Professor Paul Knochel on the occasion of his 60th birthday

Abstract: Much research effort has been devoted to the synthesis of fluorinated organic compounds in medicinal chemistry programs. For instance, incorporation of fluorine substituents and trifluoromethyl groups has become a widespread lead optimization strategy owing to the often favorable influence of such moieties on affinity and physicochemical properties. However, introduction of fluoroalkyl groups into dedicated positions of pharmacophores is synthetically challenging. In particular, efficient syntheses of di- and trifluoroethylamines are needed as they are an interesting, yet underrepresented, class of carboxamide mimics. Thus, a practical and reliable protocol for their preparation is described by using functionalized di- and trifluoromethylated *N*-aryl-substituted *N*,*O*-acetals as synthetic aldimine equivalents. Moreover, previously unknown β-trifluoroethylamine analogs of 1,2-dihydroquinazolin-4(1*H*)-thione and the androgen receptor antagonist DIMN are prepared to demonstrate the method's applicability.

Introduction

One of the major challenges in medicinal chemistry, aside from the identification of new lead structures, is their development into clinical candidates, which requires inter alia optimization of pharmacokinetic properties like absorption, distribution, metabolism, and excretion.[1] For instance, the use of hydrolytically stable and bioisosteric functional entities that block metabolic sites not involved in the enzyme-binding mechanism, has become an important strategy to increase the metabolic resistance of a given compound without reducing its potency.[2]

The development of the drug candidate and cathepsin K inhibitor, Odanacatib (MK-0822), which is currently in clinical trials, is an illustrative example of this approach.[3] Previous amide-containing lead structures showed poor selectivity relative to other cathepsins under physiologically relevant conditions, whereas replacement of the amide bond by a trifluoroethylamine surrogate granted sufficient selectivity and potency towards cathepsin K, and excellent metabolic stability in rat, dog and rhesus monkey hepatocytes.[4] Except for this successful example, further applications of amide-bond substitution by trifluoroethylamine surrogates are scarce, most likely owing to the lack of convenient synthetic methods to access substituted trifluoroethylamine derivatives.[5] So far, most approaches towards these building blocks rely upon the use of trifluoromethylated imines, the preparation of which is often very challenging.[6] In contrast, a recently developed protocol applies to electron-rich and moderately electron-deficient *N*-aryl-trifluoromethyl *N*,*O*-acetals, which after addition of Grignard reagents allows formation of the corresponding functionalized trifluoroethylamines in good yields.[7] The requisite shelf-stable *N*,*O*-acetals are readily accessible by condensation of an amine and trifluoroacetaldehyde ethyl hemiacetal (TFAE) in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*TSA).[8] Because these conditions preclude the use of amines with electron-withdrawing groups or heteroaromatic amines, both of which are common substructures of pharmaceutically relevant scaffolds, a modified version of this reaction is now being reported. This protocol allows preparation of electron-deficient *N*-(hetero)-aryl-trifluoromethyl *N*,*O*-acetals and their difluoromethylated congeners. In addition, the subsequent Grignard addition has successfully been extended to the use of functionalized organomagnesium reagents to provide a broad range of complex substituted α-difluoro- and α-trifluoromethylated amines in good to excellent yields. Such compounds are of particular interest with regard to potential medicinal chemistry applications, e.g. during lead optimization studies and diversifying the family of peptide mimics.[9] Finally, new trifluoromethylated analogs of a 1,2-dihydroquinazolin-4(1*H*)-thione scaffold and the nicotinamide androgen receptor antagonist 6-(3,4-dihydro-1*H*-isoquinolin-2-yl)-

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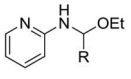
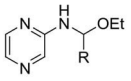
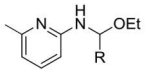
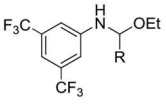
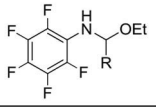
N-(6-methylpyridin-2-yl)nicotinamide (DIMN) are presented, which corroborate the synthetic applicability of the reported protocol.

Results and Discussion

Synthesis of CF_2H- and CF_3-Substituted *N*,*O*-Acetals

Although only a few examples of difluoromethylated *N*,*O*-acetals have been reported,[10] various syntheses of their trifluoromethylated congeners are known. For instance, electron-rich arylamines readily condense with TFAE under acidic conditions by following the procedure by Gong and Kato.[8] However, when applied to electron-deficient amines or heteroaromatic amines, this protocol only furnished the desired products in diminished yields of < 30 %. In particular, the preparation of electron-poor *N*-aryl-substituted *N*,*O*-acetals, such as *N*-(1-ethoxy-2,2,2-trifluoroethyl)-pyridine-2-amine (**1a**), proved difficult and required optimization of the reaction conditions. Therefore, a revised microwave-assisted protocol was developed, which furnished **1a** in a satisfying yield of 82 %. Moreover, electron-poor trifluoromethylated *N*-aryl-substituted *N*,*O*-acetals **1c**–**1e** were easily accessible upon heating the corresponding amines and TFAE in toluene at 180 °C under microwave irradiation (Table 1). In contrast, yields of corresponding difluoromethylated *N*,*O*-acetals **1f** and **1g** were higher under conventional heating, i.e. without the use of microwave irradiation, which is presumably a result of their lower intrinsic stability (vide infra).

Table 1. Synthesis of difluoromethylated and trifluoromethylated *N*,*O*-acetals.

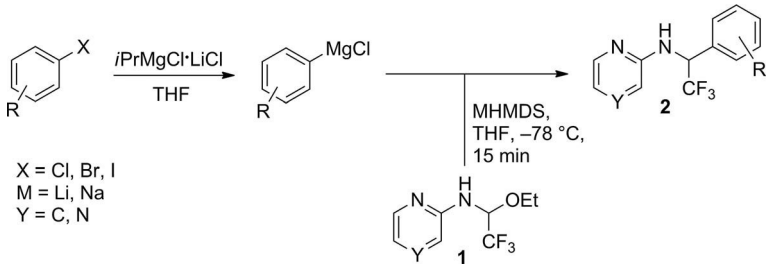
Entry	Hemiaminal ether	Product	R	Yield [%]
1		**1a** **1b**	CF_3 CF_2H	82[a] 39[a]
2		**1c** **1d**	CF_3 CF_2H	78[a] 44[a]
3		**1e**	CF_3	54[a]
4		**1f**	CF_2H	66[b]
5		**1g**	CF_2H	36[b]

[a] Reactions were performed in accordance with the optimized microwave procedure. [b] Reactions were performed by following a literature procedure.[8]

Synthesis of CF_2H- and CF_3-Substituted *N*-Arylethylamines

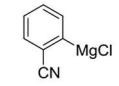
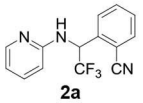
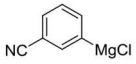
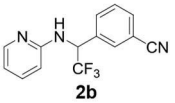
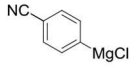
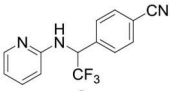
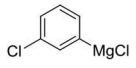
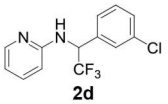
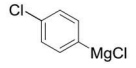
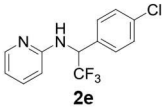
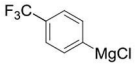
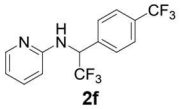
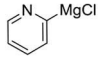
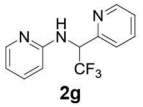
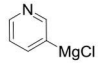
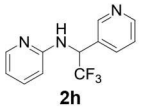
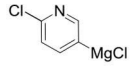
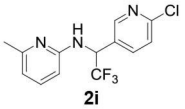
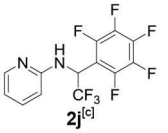
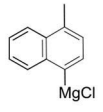
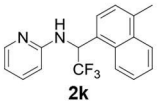
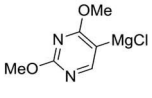
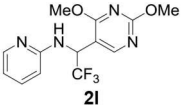
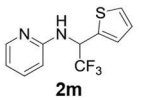
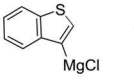
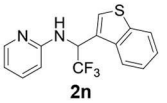
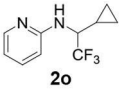
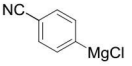
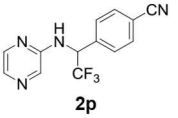
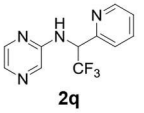
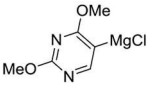
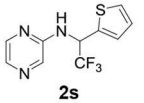
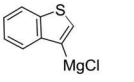
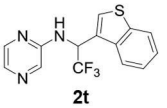
Trifluoromethylated *N*-arylamines can be directly prepared from their corresponding *N*,*O*-acetals, upon addition of a suitable Grignard reagent (2 equiv.), as previously reported.[7a] Unfortunately, this procedure is less beneficial when precious (poly-)functionalized Grignard reagents are used. To reduce the necessary amount of Grignard reagent, the aim was to separate the nucleophilic addition reaction from the initial deprotonation step by using an external non-nucleophilic base. Fortunately, initial deprotonation of hemiaminal ethers **1** with lithium bis(trimethylsilyl)amide (LiHMDS; 1 equiv.) to form the transient imine species and subsequent addition of Grignard reagent (1 equiv.) furnished desired α-trifluoromethylated amines **2** in similar yields to those already achieved (Scheme 1). Because a broad spectrum of functionalized Grignard reagents can readily be obtained from the corresponding aryl and heteroaryl halides by using *i*PrMgCl[11] or *i*PrMgCl·LiCl (Turbo-Grignard),[12] the revised protocol now offers a convenient route towards the synthesis of various complex trifluoroethylamine scaffolds. To illustrate this, a range of new trifluoroethylamines is depicted in Table 2.

Grignard reagents, prepared from 2-, 3-, or 4-bromobenzonitrile and *i*PrMgCl·LiCl in tetrahydrofuran (THF), were added at –78 to –30 °C to a solution of the in situ generated imine of pyridine *N*,*O*-acetal **1a**. In all cases, smooth formation of the nitrile-functionalized trifluoroethylamines was observed to give desired compounds **2a**–**2c** in 75, 71, and 68 % yield, respectively, after column chromatography (Table 2, Entries 1–3). Similarly, addition of the 4-bromobenzonitrile-derived Grignard reagent to pyrazyl *N*,*O*-acetal **1c** furnished corresponding amine **2p**, albeit in slightly lower yield of 56 % (Table 2, Entry 16). Moreover, the use of 1-bromo-3-chlorobenzene and 1-bromo-4-chlorobenzene allowed chemoselective transmetalations to take place to afford the corresponding chlorophenylmagnesium reagents, which after reaction with *N*,*O*-acetal **1a** furnished *N*-[1-(3-chlorophenyl)-2,2,2-trifluoroethyl]pyridin-2-amine (**2d**; 75 %) and *N*-[1-(4-chlorophenyl)-2,2,2-trifluoroethyl]pyridin-2-amine (**2e**; 66 %; Table 2, Entries 4 and 5). The latter compounds are easily further functionalized, e.g. through metal-catalyzed



Scheme 1. Synthesis of functionalized trifluoromethylated amines.

Table 2. Synthesis of trifluoromethylated amines by addition of functionalized Grignard reagents to hemiaminal ethers.[a]

Entry	Grignard reagent	T, t	Substrate	Product	Yield [%][b]
1		–30 °C, 2 h	**1a**	 **2a**	75
2		–30 °C, 2 h	**1a**	 **2b**	71
3		–30 °C, 2 h	**1a**	 **2c**	68
4		–30 °C, 2 h	**1a**	 **2d**	75
5		–30 °C, 2 h	**1a**	 **2e**	66
6		–30 °C, 2 h	**1a**	 **2f**	73
7		–30 °C, 2 h	**1a**	 **2g**	62
8		–30 °C, 2 h	**1a**	 **2h**	69
9		0 °C, 5 h	**1e**	 **2i**	65
10		–30 °C, 2 h	**1a**	 **2j**[c]	85
11		25 °C, 18 h	**1a**	 **2k**	58
12		–30 °C, 2 h	**1a**	 **2l**	85
13		–30 °C, 2 h	**1a**	 **2m**	72
14		–30 °C, 3 h	**1a**	 **2n**	83
15		0 °C, 2 h	**1a**	 **2o**	85
16		–30 °C, 2 h	**1c**	 **2p**	56
17		–30 °C, 2 h	**1c**	 **2q**	56
18		–30 °C, 2 h	**1c**	 **2r**	79
19		–30 °C, 8 h	**1c**	 **2s**	55
20		0 °C, 6 h	**1c**	 **2t**	86
21		–78 °C, 2 h	**1c**	**2u**	96
22		–78 °C, 5 h	**1c**	**2v**[c]	92
23		–20 °C, 2 h	**1c**	**2w**	80

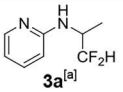
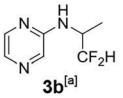
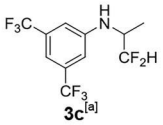
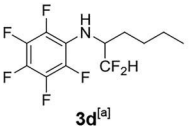
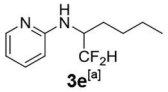
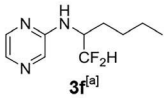
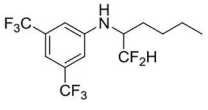
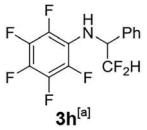
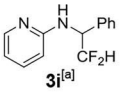
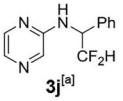
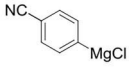
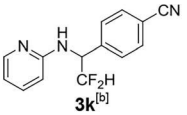
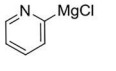
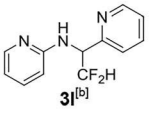
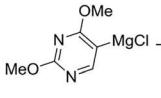
[a] Reactions were performed in accordance with the optimized procedure. [b] Total yield after flash chromatography. [c] The Grignard reagent was prepared from the corresponding aryl bromide and *i*PrMgCl.

cross-coupling reactions to enhance the level of scaffold complexity.

The Grignard reagent derived from 5-bromo-2-chloropyridine reacted analogously with *N*,*O*-acetal **1e** to yield corresponding amine product **2i** in 65 % yield and with an intact C–Cl bond at the pyridine ring (Table 2, Entry 9). Heteroaromatic Grignard reagents, which include pyridine, pyrimidine, thiophene, and benzothiophene derivatives, were also successfully employed. In some cases the yields of the targeted trifluoromethylated amines were somewhat reduced as a result of in-

trinsic low reactivities of the corresponding Grignard species. For instance, addition of 2-thiophenylmagnesium chloride to *N*,*O*-acetal **1c** proceeded sluggishly and resulted in a diminished yield of only 55 % of desired amine **2s** (Table 2, Entry 19). Similarly, reaction of 2-pyridylmagnesium chloride with **1c** was hampered and furnished amine **2q** in 56 % yield with concomitant amounts of unreacted *N*,*O*-acetal **1c** (Table 2, Entry 17). Lastly, trifluoroethylamines with triple bonds are particularly useful synthetic building blocks for larger scaffolds. Hence, *N*-pyrazyl *N*,*O*-acetal **1c** was treated with ethynylmagnesium chloride and ethynylcyclopropylmagnesium chloride to afford corresponding amines **2u** and **2w** in 96 and 80 % yield, respectively (Table 2, Entries 21 and 23). The examples presented so far demonstrate the versatility of the protocol to access functionalized trifluoroethylamines.

Table 3. Synthesis of difluoromethylated amines by addition of Grignard reagents to hemiaminal ethers.

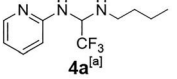
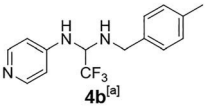
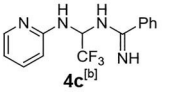
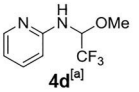
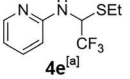
Entry	Grignard reagent	*T*, *t*	Substrate	Product	Yield [%]
1	MeMgBr	0 °C, 2 h	**1b**	 **3a**[a]	72
2	MeMgBr	0 °C, 1.5 h	**1d**	 **3b**[a]	94
3	MeMgBr	0 °C, 3 h	**1f**	 **3c**[a]	71
4	*n*BuMgCl	0 °C, 1.5 h	**1g**	 **3d**[a]	92
5	*n*BuMgCl	0 °C, 2.5 h	**1b**	 **3e**[a]	68
6	*n*BuMgCl	0 °C, 1.5 h	**1d**	 **3f**[a]	quant.
7	*n*BuMgCl	0 °C, 2 h	**1f**	 **3g**[a]	96
8	PhMgBr	0 °C, 4 h	**1g**	 **3h**[a]	50
9	PhMgBr	0 °C, 2 h	**1b**	 **3i**[a]	quant.
10	PhMgBr	0 °C, 1.5 h	**1d**	 **3j**[a]	quant.
11		–30 °C, 4 h	**1b**	 **3k**[b]	56
12		–30 °C, 4 h	**1b**	 **3l**[b]	44
13		–30 °C, 4 h	**1b**	 **3m**[b]	75

[a] Reactions were performed by following the reported procedure.[7a] [b] Reactions were performed in accordance with the optimized procedure.

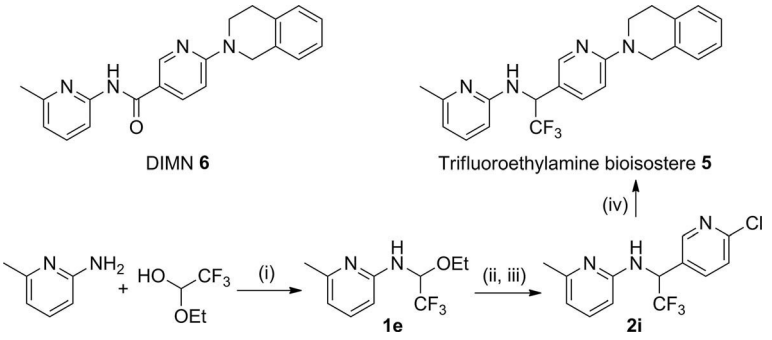
To address the syntheses of related CHF_2-substituted derivatives, Grignard additions with the corresponding difluoromethylated *N*,*O*-acetals were investigated (Table 3). As expected, their conversion with simple commercially available alkyl and aryl Grignard reagents proceeded smoothly and furnished target difluoroethylamines **3a**–**3j** in good yields. Application of functionalized Grignard reagents in combination with LiHMDS provided access to more complex difluoromethylated amine scaffolds (Table 3, Entries 11–13). In some cases, such as amines **3h** and **3l**, reduced stability of the difluoroethylamines was observed, which resulted in significantly lower yields of isolated products.

The addition reactions described above are not restricted to the use of Grignard or organolithium reagents but also allow heteroatom nucleophiles to be employed. Hence, *n*-butylamine was deprotonated and subjected to *N*,*O*-acetal **1a**. In this case, the highest yield of desired product **4a** (75 %) was obtained with *n*-butyllithium in dry *n*-hexane at 0 °C (Table 4, Entry 1). Further transformations with *N*-nucleophiles included the use of 4-methylbenzylamine and benzamidine, both of which fur-

Table 4. Addition of *N*-, *O*-, *S*-nucleophiles to hemiaminal ethers.

Entry	Nu–H	*T*, *t*	Substrate	Product	Yield [%]
1	$C_4H_9NH_2$	0 °C, 2 h	**1a**	 **4a**[a]	75
2	H_2NCH_2-tolyl-*p*	0 °C, 2h	**1h**	 **4b**[a]	87
3	Benz-amidine	160 °C, MW, 1 h	**1a**	 **4c**[b]	86
4	MeOH	25 °C 48 h	**1a**	 **4d**[a]	49
5	EtSH	25 °C, 3 d	**1a**	 **4e**[a]	quant.

[a] Reactions were performed with *n*BuLi as a base and *n*-hexane as solvent. [b] Reaction was performed with microwave irradiation and toluene as a solvent.



Scheme 2. Synthesis of DIMN trifluoroethylamine bioisostere **5**. (i) *p*TSA, MW, 180 °C, 30 min, 54 %; (ii) 3-bromo-6-chloropyridine, *i*PrMgCl•LiCl, –30 °C, 2 h; (iii) NaHMDS, THF, –78 °C, 15 min, then organyl magnesium, –30 °C, 2 h, 65 %; (iv) 1,2,3,4-tetrahydroisoquinoline, 2-propanol, reflux, 48 h, 33 %.

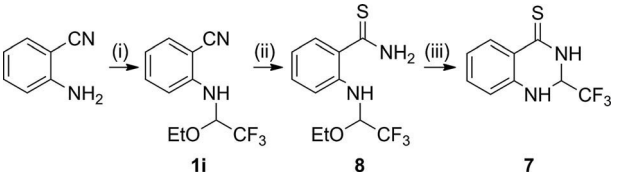
nished desired products **4b** and **4c** in good yields of 87 and 86 %, respectively (Table 4, Entries 2 and 3). Notably, for amine **4c** the best results were obtained under microwave irradiation at 160 °C in toluene and without the use of an external base.

O- and *S*-Nucleophiles can also be successfully employed in addition reactions to *N*,*O*-acetal **1a** (Table 4, Entries 4 and 5), which leads to the formation of corresponding hemiaminal ether **4d** and hemiaminal thioether **4e**, respectively.

Finally, a hitherto unknown trifluoromethylated analog of the non-steroidal androgen receptor (AR) antagonist DIMN[13] has been synthesized to demonstrate the versatility of this protocol to prepare scaffolds for potential pharmaceutical applications (Scheme 2). DIMN (**6**) has been reported recently as a promising new anti-androgenic compound for the treatment of both early-stage androgen-dependent and later-stage androgen-independent prostate cancers.[13,14] In regard to the inefficiencies of many classical AR antagonists in the treatment of advanced prostate cancers, new lead scaffolds for better AR antagonists are still urgently needed. Besides, the development of metabolically more resistant compounds might be particularly rewarding. The synthesis of corresponding β-trifluoroethylamine analog **5** of DIMN commenced with microwave-assisted conversion of commercially available 2-amino-5-methylpyridine into requisite *N*,*O*-acetal **1e**, as described. Subsequent addition of the Grignard reagent prepared from 3-bromo-6-chloropyridine and *i*PrMgCl•LiCl afforded intermediate **2i**, which was successfully coupled to 1,2,3,4-tetrahydroisoquinoline to provide target compound **5** over three steps.

In addition, preparation of trifluoromethylated 1,2-dihydroquinazolin-4(1*H*)-thione **7** was tackled as outlined in Scheme 3. Sulfur analogs of quinazolinone alkaloids are interesting pharmacophores with diverse biological activities, such as antipsychotic and antihypertensive effects.[15]

Based on a recent report from Oschatz et al.[16] and by starting from 2-aminobenzonitrile, target compound **7** was synthesized in three steps. Thus, 2-aminobenzonitrile was converted into *N*,*O*-acetal **1i**, followed by thiolysis of the nitrile group, as described before.[16] Ring closure to the target trifluoromethylated 1,2-dihydroquinazolin-4(1*H*)-thione **7** was accomplished by stirring compound **8** in THF under basic conditions to yield compound **7** in 86 %.



Scheme 3. Synthesis of 1,2-dihydroquinazolin-4(1*H*)-thione **7**. (i) TFAE, *p*TSA, ethanol, reflux, 30 min, 35 %; (ii) $NaSH•H_2O$, $MgCl_2$, DMF, 1.5 h, quant. (iii) KO*t*Bu, THF, molecular sieves 4 Å, room temp., 48 h, 86 %.

Conclusions

In summary, a practical and efficient approach towards preparation of various functionalized difluoromethylated and trifluoromethylated *N*-arylamines was devised. Thereby, the use of fluoroalkylated *N*,*O*-acetals as shelf-stable, easily applicable aldimine equivalents in combination with (poly-)functional Grignard reagents or heteroatom nucleophiles allows access to a broad range of fluoroalkylated *N*-arylamines in synthetically useful yields. The resulting α-difluoro- and α-trifluoromethyl *N*-arylamines belong to an interesting, yet underrepresented, class of carboxamide bioisosteres and are of interest for potential pharmaceutical applications. To illustrate our approach, syntheses of hitherto unknown β-trifluoroethylamine analog to the nicotinamide-derived androgen receptor (AR) antagonist DIMN and 1,2-dihydroquinazolin-4(1*H*)-thione were reported. Further studies on the application of difluoromethylated and trifluoromethylated amine derivatives are currently underway.

Experimental Section

General Remarks: All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes, which were used to transfer anhydrous solvents or reagents, were purged with argon prior to use. Dry THF was freshly distilled from sodium and benzophenone under argon. Commercially available reagents and solvents were used without further purification. Grignard reagents were purchased from Aldrich or synthesized according to the procedures described. All microwave irradiation experiments were carried out in a CEM Explorer™ microwave apparatus, which operated at a frequency of 2.45 GHz with continuous irradiation power from 0 to 200 W, and used the standard absorbance level of 300 W maximum power. The reactions were carried out in 10 mL Pyrex vessels sealed with CEM plastic crimp tops equipped with magnetic stirrers. The

temperature was measured with an infrared sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (1–2 min) to ambient temperature by using a nitrogen jet.

Reactions were monitored by TLC with pre-coated silica gel 60 F_{254} aluminum plates (Merck KGaA, Darmstadt) with UV light as the visualizing agent. The crude products were purified by standard flash chromatography with silica gel (35–70 μm) from Acros Organics. Analytical RP-HPLC was measured on a JASCO system with a Phenomenex Luna C18 column (5 μm, 250 × 4.6 mm). Low resolution (ESI) and high resolution (ESI) mass spectra were recorded with a Thermo Finnigan LTQ FT or with a Bruker maXis equipped with a Waters Acquity UPLC and a Kinetex C18 column (2.6 μ, 100 A) at 40 °C. In all cases, mixtures of water (eluent A) and acetonitrile (eluent B) were used as solvents; if required, formic acid (0.05 %) or trifluoroacetic acid (TFA; 0.1 %) were added. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded with a Varian 300 or 600 MHz spectrometer or with a Bruker Avance II 400 MHz spectrometer in [D_6]DMSO or $CDCl_3$. The chemical shifts are reported relative to the signal of the deuterated solvent. Multiplicities are given as: s (singlet), br. s (broad singlet), d (doublet), t (triplet), and m (multiplet). Melting points were measured with a Melting Point B-540 Büchi.

Typical Procedure for the Microwave Synthesis of Hemiaminal Ethers (TP1): A dry microwave tube equipped with a magnetic stirrer was charged with an arylamine (1 equiv.) and *p*TSA·H_2O (0.05 equiv.). The starting material was dissolved in toluene and TFAE/difluoroacetaldehyde ethyl hemiacetal (1.2 equiv.) was added. The microwave tube was sealed and the reaction mixture was reacted at 180 °C for 30 min (max. 200 W).

The solvent was evaporated and the crude product was purified by flash chromatography (SiO_2).

Typical Procedure for the Synthesis of Hemiaminal Ethers (TP2): A round-bottomed flask equipped with a magnetic stirrer was charged with an arylamine (1 equiv.) and *p*TSA·H_2O (0.05 equiv.). The starting material was dissolved in ethanol and TFAE/difluoroacetaldehyde ethyl hemiacetal (1.2 equiv.) was added. The reaction mixture was heated under reflux (90 °C) until the reaction showed no further conversion.

The solvent was evaporated and the product was purified by flash chromatography (SiO_2).

Typical Procedure for the Magnesium Insertion (TP3):[11] A dry and argon-flushed 10 mL flask equipped with a magnetic stirrer and a septum was charged with *i*PrMgCl·LiCl (1.25 M in THF, 1.1 equiv.). Neat aryl bromide (1 equiv.) was added at the appropriate temperature. The reaction mixture was stirred at the stated temperature, and completion of the Br/Mg exchange was monitored by GC analysis.

Typical Procedure for the Addition of the Functionalized Grignard Reagent to Hemiaminal Ethers (TP4): Hemiaminal ether (0.045 mmol, 1 equiv.) was dissolved in freshly distilled THF (5 mL) in a dry and argon-flushed 10 mL flask equipped with a magnetic stirrer and a septum and cooled to –78 °C. NaHMDS or LiHMDS (1 M in THF, 0.045 mmol, 1 equiv.) was added and the reaction was stirred for 15 min until the deprotonation was complete. The Grignard reagent was added dropwise with a syringe and the solution was warmed to the appropriate temperature. The reaction was stirred until GC analysis showed that conversion was complete. After the reaction was complete satd. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The solvent was evaporated and the product was purified by flash chromatography (SiO_2).

Typical Procedure for the Synthesis of CF_2H-Amines with RMgX (TP5): In a dry, argon-flushed Schlenk flask hemiaminal ether (1 equiv.) was dissolved in dry THF. The solution was cooled to 0 °C, RMgX (2 equiv.) was added dropwise, and the solution was stirred at 0 °C until complete consumption of the starting material (≈ 2 h, TLC control). Then the solution was quenched with saturated NH_4Cl solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (SiO_2) furnished the desired amines.

***N*-(1-Ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (1a):** Hemiaminal ether **1a** was prepared in accordance with **TP1**. 2-Aminopyridine (100 mg, 1.06 mmol), *p*TSA·H_2O (10 mg, 0.05 mmol), and TFAE (0.15 mL, 1.28 mmol) were reacted in a CEM microwave reactor in toluene (2 mL). Flash column chromatography (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **1a** as a white solid (196 mg, 82 %). R_f = 0.45 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1), m.p. 84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (ddd, $J_{H6,H5}$ = 5.0, $J_{H6,H4}$ = 1.9 Hz, J = 0.9 Hz, 1 H, H6), 7.48 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.73 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 1.0 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.3, J = 5.1 Hz, 1 H, H3), 6.01 (dq, $J_{CH,NH}$ = 10.2, $J_{CH,CF3}$ = 5.1 Hz, 1 H, CH), 4.89 (d, $J_{NH,CH}$ = 10.4 Hz, 1 H, NH), 3.86–3.66 (m, 2 H, CH_2), 1.22 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.66 (d, $J_{CF3,CH}$ = 5.0 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.19 (C2), 148.06 (C6), 138.13 (C4), 123.27 (q, $J_{C,F}$ = 282.2 Hz, CF_3), 115.66 (C5), 109.24 (C3), 78.50 (q, $J_{C,F}$ = 33.9 Hz, $CHCF_3$), 65.35 (CH_2), 15.30 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_9H_{12}ON_2F_3^+$ $[M + H]^+$ 221.0902; found 221.0898. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.21 min, λ = 214 nm.

***N*-(1-Ethoxy-2,2-difluoroethyl)pyridine-2-amine (1b):** In accordance with **TP1**, 2-aminopyridine (100 mg, 1.06 mmol), *p*TSA·H_2O (10 mg, 0.05 mmol), and difluoroacetaldehyde ethyl hemiacetal (0.15 mL, 1.28 mmol) were reacted in a CEM microwave reactor in toluene (2.5 mL). Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 100:1:1 → 10:2:0.1) furnished **1b** (84 mg, 39 %) as a white solid. R_f = 0.74 (cyclohexane/ethyl acetate, 1:1), m.p. <40 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (ddd, $J_{H6,H5}$ = 5.0, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.45 (ddd, $J_{H4,H3}$ = 8.4, $J_{H4,H5}$ = 7.3 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.70 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.3, $J_{H3,H6}$ = $J_{H3,H5}$ = 0.9 Hz, 1 H, H3), 5.86 (ddd, $J_{H,F}$ = 55.1, $J_{H,F}$ = 53.3 Hz, $J_{CHF2,CH}$ = 2.3 Hz, 1 H, CHF_2), 5.74–5.70 (m, 1 H, CH), 4.94 (d, $J_{NH,CH}$ = 10.0 Hz, 1 H, NH), 3.71 (ddq, $J_{CH2,CH}$ = 44.3, $J_{CH2,CH2}$ = 9.6 Hz, $J_{CH2,CH3}$ = 7.0 Hz, 1 H, CH_2), 1.21 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –129.66 (ddd, $J_{F,F}$ = 286.6, $J_{F,H}$ = 54.7 Hz, $J_{F,CH}$ = 8.2 Hz, CHF_2), –133.95 (ddt, $J_{F,F}$ = 286.7, $J_{F,H}$ = 55.8 Hz, $J_{F,CH}$ = 12.4 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.84 (C2), 148.00 (C6), 137.89 (C4), 115.09 (C5), 113.74 (dd, $J_{C,F}$ = 246.4, $J_{C,F}$ = 244.7 Hz, CHF_2), 108.90 (C3), 79.35 (dd, $J_{C,F}$ = 26.8, $J_{C,F}$ = 22.7 Hz, CH), 64.36 (CH_2), 15.31 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_9H_{13}F_2N_2O^+$ $[M + H]^+$ 203.0990; found 203.0991. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 7.41 min, λ = 214 nm.

***N*-(1-Ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (1c):** Hemiaminal ether **1c** was prepared in accordance with **TP1**. Aminopyrazine (100 mg, 1.05 mmol), *p*TSA·H_2O (10 mg, 0.05 mmol) and TFAE (0.17 mL, 1.26 mmol) were reacted together in a CEM microwave reactor in toluene (2 mL). Flash column chromatography (cyclohexane/ethyl acetate/NEt_3, 3:1:0.1) furnished **1c** as a white solid (181 mg, 78 %). R_f = 0.55 (cyclohexane/ethyl acetate/NEt_3, 2:1:0.05), m.p. 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (ddd, $J_{H6,H5}$ = 2.7,

$J_{H6,H3}$ = 1.5 Hz, $J_{H6,NH}$ = 0.4 Hz, 1 H, H6), 8.03 (dd, $J_{H3,H6}$ = 1.5, $J_{H3,H5}$ = 0.4 Hz, 1 H, H3), 7.99 (dd, $J_{H5,H6}$ = 2.8, $J_{H5,H3}$ = 0.4 Hz, 1 H, H5), 5.94 (dq, $J_{CH,NH}$ = 10.0, $J_{CH,CF3}$ = 5.0 Hz, 1 H, CH), 5.26 (d, $J_{NH,CH}$ = 10.1 Hz, 1 H, NH), 3.93–3.64 (m, 2 H, CH_2), 1.23 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.71 (d, $J_{CF3,CH}$ = 5.1 Hz, $CHCF_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.56 (C2), 141.73 (C6), 135.68 (C5), 133.17 (C3), 122.87 (q, $J_{C,F}$ = 282.2 Hz, CF_3), 78.01 (q, $J_{C,F}$ = 34.3 Hz, $CHCF_3$), 65.69 (CH_2), 15.11 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_9H_{12}F_3N_3O^+$ [M + H]$^+$ 222.0849; found 222.0848. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 13.99 min, λ = 214 nm.

***N*-(1-Ethoxy-2,2-difluoroethyl)pyrazin-2-amine (1d):** In accordance with **TP1**, aminopyrazine (100 mg, 1.05 mmol), *p*TSA·H_2O (10 mg, 0.05 mmol), and difluoroacetaldehyde ethyl hemiacetal (0.15 mL, 1.28 mmol) were reacted together in a CEM microwave reactor in toluene (2.5 mL). Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 100:2:1 → 10:2:0.1) furnished **1d** (95 mg, 44 %) as a white solid. R_f = 0.55 (cyclohexane/ethyl acetate, 1:1), m.p. 64–65 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.03–8.01 (m, 2 H, H3, H6), 7.95 (dd, $J_{H5,H6}$ = 2.7, $J_{H5,H3}$ = 1.0 Hz, 1 H, H5), 5.87 (dddd, $J_{H,F}$ = 55.7, $J_{H,F}$ = 54.8 Hz, $J_{CHF2,CH}$ = 2.2 Hz, $J_{CHF2,NH}$ = 1.3 Hz, 1 H, CHF_2), 5.75–5.68 (m, 1 H, CH), 5.26 (d, $J_{NH,CH}$ = 9.9 Hz, 1 H, NH), 3.78–3.62 (m, 1 H, CH_2), 1.21 (td, $J_{CH3,CH2}$ = 7.0, $J_{CH3,CH}$ = 1.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –129.03 (ddd, $J_{F,F}$ = 288.0, $J_{F,H}$ = 55.0 Hz, $J_{CHF2,CH}$ = 7.9 Hz, CHF_2), –134.70 (ddt, $J_{F,F}$ = 287.9, $J_{F,H}$ = 55.7 Hz, $J_{CHF2,CH}$ = 12.1 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.27 (C2), 141.73 (C6), 135.17 (C5), 133.10 (C3), 113.41 (t, $J_{C,F}$ = 245.7 Hz, CHF_2), 78.94 (dd, $J_{C,F}$ = 27.6, $J_{C,F}$ = 22.5 Hz, CH), 64.73 (CH_2), 15.20 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_8H_{12}F_2N_3O^+$ [M + H]$^+$ 204.0943; found 204.0943. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 11.43 min, λ = 214 nm.

***N*-(1-Ethoxy-2,2,2-trifluoroethyl)-6-methylpyridin-2-amine (1e):** Hemiaminal ether **1e** was prepared in accordance with **TP1**. 6-Methylpyridinamine (300 mg, 2.77 mmol), *p*TSA·H_2O (26 mg, 0.14 mmol), and TFAE (0.43 mL, 3.32 mmol) were reacted together in a CEM microwave reactor in toluene (4 mL). Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 20:1:0.1 → 10:1:0.1) furnished **1e** as a colorless oil (350 mg, 54 %). R_f = 0.40 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (dd, $J_{H4,H3}$ = 8.1, $J_{H4,H5}$ = 7.4 Hz, 1 H, H4), 6.59 (dq, $J_{H5,H4}$ = 7.3, $J_{H5,CH3}$ = 0.6 Hz, 1 H, H5), 6.31 (dt, $J_{H3,H4}$ = 8.2, J = 0.6 Hz, 1 H, H3), 5.99 (dq, $J_{CH,NH}$ = 10.3, $J_{CH,CF3}$ = 5.1 Hz, 1 H, CH), 4.84 (d, $J_{NH,CH}$ = 10.4 Hz, 1 H, NH), 3.90–3.62 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 1.22 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_2CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.49 (d, $J_{CF3,CH}$ = 4.8 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.53 (C6), 155.96 (C2), 138.69 (C4), 123.72 (q, $J_{C,F}$ = 282.3 Hz, CF_3), 115.18 (C5), 106.04 (C3), 78.88 (q, $J_{C,F}$ = 33.7 Hz, $CHCF_3$), 65.57 (CH_2CH_3), 24.89 (CCH_3), 15.61 (CH_2CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{10}H_{14}F_3N_2O^+$ [M + H]$^+$ 235.1053; found 235.1054. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.79 min, λ = 214 nm.

***N*-(1-Ethoxy-2,2-difluoroethyl)-3,5-bis(trifluoromethyl)aniline (1f):** In accordance with **TP2**, 3,5-*bis*(trifluoromethyl)aniline (0.50 g, 2.18 mmol), difluoroacetaldehyde ethyl hemiacetal (0.32 mL, 2.62 mmol), and *p*TSA·H_2O (21 mg, 0.11 mmol) were dissolved in EtOH (15 mL) and the reaction mixture was heated to reflux for 18 h. After removal of the solvent, flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 100:1:1 → 100:2:1) furnished **1f** (485 mg, 66 %) as a white solid. R_f = 0.66 (cyclohexane/ethyl acetate, 4:1), m.p. 50–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (s, 1 H, H4), 7.14 (s, 2 H, H2, H6), 5.87 (ddd, $J_{H,F}$ = 55.5, $J_{H,F}$ = 54.7 Hz, $J_{CHF2,CH}$ = 2.5 Hz, 1 H, CHF_2), 5.00–4.88 (m, 1 H, CH), 4.69 (d, $J_{NH,CH}$ = 9.3 Hz, 1 H, NH), 3.70 (ddq, $J_{CH2,CH2}$ = 41.2, $J_{CH2,CH}$ = 9.2 Hz, $J_{CH2,CH3}$ = 7.0 Hz, 2 H, CH_2), 1.24 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 63.27 (2 × CF_3), –128.05 (dd, $J_{F,F}$ = 289.6, $J_{F,H}$ = 54.7 Hz, CHF_2), –133.54 (ddd, $J_{F,F}$ = 289.6, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 10.7 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 146.30 (C1), 132.96 (q, $J_{C,F}$ = 33.1 Hz, C3, C5), 123.40 (q, $J_{C,F}$ = 272.7 Hz, 2 × CF_3), 113.81 (C2, C6), 113.34 (t, $J_{C,F}$ = 246.9 Hz, CHF_2), 113.14–112.94 (m, C4), 82.68 (dd, $J_{C,F}$ = 27.8, $J_{C,F}$ = 23.3 Hz, CH), 64.21 (CH_2), 15.21 (CH_3) ppm. HRMS (ESI$^-$): *m/z* calcd. for $C_{12}H_{11}F_8NO^-$ [M – H]$^-$ 336.0640; found 336.0646. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 20.02 min, λ = 214 nm.

***N*-(1-Ethoxy-2,2-difluoroethyl)-2,3,4,5,6-pentafluoroaniline (1g):** In accordance with **TP2**, 2,3,4,5,6-pentafluoroaniline (1.00 g, 5.45 mmol), difluoroacetaldehyde ethyl hemiacetal (0.77 mL, 6.56 mmol), and *p*TSA·H_2O (52 mg, 0.27 mmol) were solved in EtOH (15 mL) and the reaction mixture was heated to reflux for 18 h. After removal of the solvent, flash column chromatography (SiO_2, gradient: cyclohexane/NEt_3, 100:1 → cyclohexane/ethyl acetate/NEt_3, 100:3:1) furnished **1g** (574 mg, 36 %) as a colorless oil. R_f = 0.73 (cyclohexane/ethyl acetate, 7:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.81 (ddd, $J_{H,F}$ = 55.6, $J_{H,F}$ = 54.6 Hz, $J_{CHF2,CH}$ = 2.2 Hz, 1 H, CHF_2), 4.99–4.87 (m, 1 H, CH), 4.13 (d, $J_{NH,CH}$ = 11.1 Hz, 1 H, NH), 3.73 (ddq, $J_{CH2,CH}$ = 67.9, $J_{CH2,CH2}$ = 9.4 Hz, $J_{CH2,CH3}$ = 7.0 Hz, 1 H, CH_2), 1.22 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (377 MHz, $CDCl_3$): δ = –129.19 (ddd, $J_{F,F}$ = 289.8, $J_{F,H}$ = 54.8 Hz, $J_{F,H}$ = 7.1 Hz, CHF_2), –135.38 (ddt, $J_{F,F}$ = 289.2, $J_{F,H}$ = 55.3 Hz, $J_{CHF2,CH}$ = 9.9 Hz, CHF_2), –156.49 – –156.63 (m, 2 F, F2; F6), –163.13 (td, $J_{F5,F4}$ = $J_{F5,F6}$ = $J_{F3,F2}$ = $J_{F3,F4}$ = 22.1, $J_{F5,F3}$ = $J_{F3,F5}$ = 4.8 Hz, 2 F, F3, F5), –167.38 (tt, $J_{F4,F3}$ = $J_{F4,F5}$ = 21.9, $J_{F4,F2}$ = $J_{F4,F6}$ = 4.7 Hz, F4) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.33–137.45 (m), 139.84–137.00 (m), 136.89–133.89 (m), 121.01–120.55 (m), 113.49 (t, $J_{C,F}$ = 246.4 Hz, CHF_2), 84.43 (ddt, $J_{C,F}$ = 27.1, $J_{C,F}$ = 23.1 Hz, $J_{C,F}$ = 3.9 Hz, CH), 65.07 (CH_2), 15.16 (CH_3) ppm. HRMS (ESI$^-$): *m/z* calcd. for $C_{10}H_7F_7NO^-$ [M – H]$^-$ 290.0421; found 290.0422. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 18.81 min, λ = 214 nm.

***N*-(2,2,2-Trifluoro-1-ethoxyethyl)aminopyridine (1h):** In accordance with **TP1**, 4-aminopyridine (200 mg, 2.12 mmol), *p*TSA·H_2O (20 mg, 0.11 mmol), and TFAE (0.33 mL, 2.55 mmol) were reacted in a CEM microwave reactor in toluene (2.5 mL). Flash column chromatography (SiO_2, gradient: ethyl acetate → ethyl acetate/MeOH, 10:1) furnished **1h** as a white solid (258 mg, 55 %). R_f = 0.11 (cyclohexane/ethyl acetate/NEt_3, 1:1:0.01), m.p. 84 °C. ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 8.24–8.05 (m, 2 H, H2, H6), 7.37 (d, $J_{NH,CH}$ = 10.0 Hz, 1 H, NH), 6.97–6.80 (m, 2 H, H3, H5), 5.70 (dq, $J_{CH,NH}$ = 10.3, $J_{CH,CF3}$ = 5.2 Hz, 1 H, CH), 3.82–3.47 (m, 2 H, CH_2), 1.13 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (377 MHz, [D_6]DMSO): δ = –78.80 (d, $J_{CF3,CH}$ = 5.8 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, [D_6]DMSO): δ = 151.94 (C4), 149.84 (C2, C6), 123.06 (q, $J_{C,F}$ = 283.8 Hz, CF_3), 108.31 (C3, C5), 78.89 (q, $J_{C,F}$ = 33.3 Hz, $CHCF_3$), 63.52 (CH_2), 14.86 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_9H_{12}F_3N_2O^+$ [M + H]$^+$ 221.0896; found 221.0898. HPLC-MS (0.1 % formic acid; 0 min: 4 % B → 2.8 min: 100 % B, flow: 2.4 mL/min): t_R = 1.18 min, λ = 220 nm.

2-[2,2,2-Trifluoro-1-(pyridin-2-ylamino)ethyl]benzonitrile (2a): (2-Cyanophenyl)magnesium chloride was prepared in accordance with **TP3** from 2-bromobenzonitrile (91 mg, 0.50 mmol) in 1 h at 0 °C. The addition reaction was performed In accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2a** as a light yellow oil (94 mg, 75 %). R_f = 0.45 (cyclohexane/ethyl acetate/NEt_3,

8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (ddd, $J_{H6',H5'}$ = 4.9, $J_{H6',H4'}$ = 1.9 Hz, $J_{H6',H3'}$ = 0.9 Hz, 1 H, H6′), 8.04 (s, 2 H, NH, H3′), 7.85–7.75 (m, 2 H, H4, H4′), 7.71–7.52 (m, 3 H, H3, H5, H6), 7.11 (ddd, $J_{H5',H4'}$ = 7.3, $J_{H5',H6'}$ = 4.9 Hz, $J_{H5',H3'}$ = 1.0 Hz, 1 H, H5′), 6.59–6.46 (m, 1 H, CH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.06 (dd, $J_{CF3,CH}$ = 5.7, $J_{CF3,NH}$ = 1.2 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.50 (C2′), 148.23 (C6′), 138.11 (C4′), 134.87 (d, $J_{C,F}$ = 1.5 Hz, CF_3), 133.78 (C1), 132.16 (C6), 130.23 (C5), 130.21–118.74 (m, CF_3), 124.49 (d, $J_{C,F}$ = 1.9 Hz, C3), 122.84 (C4), 120.17 (C5′), 117.66 (CN), 61.67 (q, $J_{C,F}$ = 32.7 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{10}F_3N_3^+$ [M + H]$^+$ 278.0905; found 278.0899. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.83 min, λ = 214 nm.

3-[2,2,2-Trifluoro-1-(pyridin-2-ylamino)ethyl]benzonitrile (2b): (3-Cyanophenyl)magnesium chloride was prepared in accordance with **TP3** from 3-bromobenzonitrile (91 mg, 0.50 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2b** as a light yellow oil (89 mg, 71 %). R_f = 0.45 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (ddd, $J_{H6',H5'}$ = 5.1, $J_{H6',H4'}$ = 1.9 Hz, $J_{H6',H3'}$ = 0.9 Hz, 1 H, H6′), 7.80 (td, $J_{H6,H2}$ = $J_{H6,H4}$ = 1.4, $J_{H6,H3}$ = 0.6 Hz, 1 H, H6), 7.74 (dtt, $J_{H4,H3}$ = 7.9, $J_{H4,H2}$ = $J_{H4,H6}$ = 1.3 Hz, $J_{H4,CH}$ = $J_{H4,NH}$ = 0.7 Hz, 1 H, H4), 7.65 (dt, $J_{H2,H3}$ = 7.9, $J_{H2,H4}$ = $J_{H2,H6}$ = 1.4 Hz, 1 H, H2), 7.50 (t, $J_{H3,H2}$ = $J_{H3,H4}$ = 7.5 Hz, 1 H, H3), 7.45 (ddd, $J_{H4',H3'}$ = 8.3, $J_{H4',H5'}$ = 7.1 Hz, $J_{H4',H6'}$ = 1.8 Hz, 1 H, H4′), 6.69 (dddd, $J_{H5',H4'}$ = 7.2, $J_{H5',H6'}$ = 5.0 Hz, $J_{H6',H5'}$ = 0.9 Hz, $J_{H6',NH}$ = 0.3 Hz, 1 H, H5′), 6.53 (ddd, $J_{H3',H4'}$ = 8.4, $J_{H3',H5'}$ = $J_{H3',NH}$ = 0.7 Hz, 1 H, H3′), 6.01 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.0 Hz, 1 H, CH), 5.04 (d, $J_{NH,CH}$ = 8.7 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.60 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.77 (C2′), 148.11 (C6′), 138.02 (C4′), 136.57 (d, $J_{C,F}$ = 1.1 Hz, C5), 132.77 (C4), 132.68 (C2), 132.05–131.64 (m, C6), 129.83 (C3), 124.98 (q, $J_{C,F}$ = 281.7 Hz, CF_3), 118.56 (CN), 115.38 (C5′), 113.31 (C1), 109.22 (C3′), 55.92 (q, $J_{C,F}$ = 30.6 Hz, CH) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{11}N_3F_3^+$ [M + H]$^+$ 278.0905; found 278.0898. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 10.30 min, λ = 214 nm.

4-[2,2,2-Trifluoro-1-(pyridin-2-ylamino)ethyl]benzonitrile (2c): (4-Cyanophenyl)magnesium chloride was prepared in accordance with **TP3** from 4-bromobenzonitrile (91 mg, 0.50 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2c** as a light yellow oil (85 mg, 68 %). R_f = 0.45 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (ddd, $J_{H6',H5'}$ = 5.0, $J_{H6',H4'}$ = 1.9 Hz, $J_{H6',H3'}$ = 0.9 Hz, 1 H, H6′), 7.72–7.65 (m, 2 H, H2, H6), 7.64–7.59 (m, 2 H, H3, H5), 7.44 (ddd, $J_{H4',H3'}$ = 8.3, $J_{H4',H5'}$ = 7.2 Hz, $J_{H4',H6'}$ = 1.9 Hz, 1 H, H4′), 6.68 (ddd, $J_{H5',H4'}$ = 7.2, $J_{H5',H6'}$ = 5.0 Hz, $J_{H6',H5'}$ = 0.9 Hz, 1 H, H5′), 6.51 (dt, $J_{H3',H4'}$ = 8.3, J = 0.9 Hz, 1 H, H3′), 6.01 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.0 Hz, 1 H, CH), 5.06 (d, $J_{NH,CH}$ = 8.9 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.38 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.81 (C2′), 148.09 (C6′), 140.02 (d, $J_{C,F}$ = 0.9 Hz, C4), 138.01 (C4′), 129.07 (q, $J_{C,F}$ = 1.2 Hz, C3, C5), 128.17 (C2, C6), 124.96 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 118.50 (CN), 115.36 (C5′), 113.13 (C1), 109.15 (C3′), 56.23 (q, $J_{C,F}$ = 30.6 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{11}N_3F_3^+$ [M + H]$^+$ 278.0905; found 278.0897. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 7.28 min, λ = 214 nm.

***N*-[1-(3-Chlorophenyl)-2,2,2-trifluoroethyl]pyridin-2-amine (2d):** (3-Chlorophenyl)magnesium chloride was prepared in accordance with **TP3** from 1-bromo-3-chlorobenzene (96 mg, 0.50 mmol) in 3 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 3 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2d** as a light yellow oil (97 mg, 75 %). R_f = 0.40 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, $J_{H6,NH}$ = 0.3 Hz, 1 H, H6), 7.48 (ddt, $J_{H2',H6'/H4'}$ = 1.9, $J_{H2',H6'/H4'}$ = 1.3 Hz, $J_{H2',H5'}$ = $J_{H2',CH}$ = 0.7 Hz, 1 H, H2′), 7.44 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 7.39–7.36 (m, 1 H, H6′), 7.36–7.29 (m, 2 H, H4′, H5′), 6.68 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.0 Hz, $J_{H6,H5}$ = 0.9 Hz, 1 H, H5), 6.49 (dt, $J_{H3,H4}$ = 8.3, $J_{H3,H5}$ = $J_{H3,NH}$ = 0.9 Hz, 1 H, H3), 5.95–5.85 (m, 1 H, CH), 5.00 (d, $J_{NH,CH}$ = 9.4 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.36 (d, $J_{CF3,CH}$ = 4.6 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.19 (C2), 148.25 (C6), 138.05 (C4), 136.57 (d, $J_{C,F}$ = 1.0 Hz, C1′), 135.05 (C3′), 130.39 (C5′), 129.47 (C4′), 128.45 (q, $J_{C,F}$ = 1.2 Hz, C2′), 126.56 (q, $J_{C,F}$ = 1.2 Hz, C6′), 129.59–120.84 (CF_3), 115.24 (C5), 109.04 (C3), 56.13 (q, $J_{C,F}$ = 30.7 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{11}N_3F_3^+$ [M + H]$^+$ 287.0557; found 287.0557. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 11.35 min, λ = 214 nm.

***N*-[1-(4-Chlorophenyl)-2,2,2-trifluoroethyl]pyridin-2-amine (2e):** (4-Chlorophenyl)magnesium chloride was prepared in accordance with **TP3** from 1-bromo-4-chlorobenzene (96 mg, 0.50 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2e** as a light yellow oil (85 mg, 66 %). R_f = 0.40 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (ddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.47–7.38 (m, 3 H, H4, H2′, H6′), 7.38–7.33 (m, 2 H, H3′, H5′), 6.67 (dddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, $J_{H5,NH}$ = 0.3 Hz, 1 H, H5), 6.47 (dt, $J_{H3,H4}$ = 8.3, J = 0.9 Hz, 1 H, H3), 5.87 (dq, $J_{CH,NH}$ = 8.7, $J_{CH,CF3}$ = 7.9 Hz, 1 H, CH), 4.99 (d, $J_{NH,CH}$ = 9.0 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.88 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.20 (C2), 148.16 (C6), 137.93 (C4), 135.16 (C4′), 133.35–133.04 (m, C1′), 129.55 (q, $J_{C,F}$ = 1.2 Hz, C2′, C6′), 129.26 (C3′, C5′), 125.22 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 115.10 (C5), 108.88 (C3), 56.04 (q, $J_{C,F}$ = 30.6 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{13}H_{11}ClN_2F_3^+$ [M + H]$^+$ 287.0563; found 287.0557. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 11.43 min, λ = 214 nm.

***N*-{2,2,2-Trifluoro-1-[4-(trifluoromethyl)phenyl]ethyl}pyridin-2-amine (2f):** [4-(Trifluoromethyl)phenyl]magnesium chloride was prepared in accordance with **TP3** from 1-bromo-4-(trifluoromethyl)benzene (113 mg, 0.50 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2f** as a light yellow oil (105 mg, 73 %). R_f = 0.50 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, $J_{H6,H5}$ = 4.0 Hz, 1 H, H6), 7.66 (d, $J_{H3',H2'}$ = $J_{H5',H6'}$ = 8.9 Hz, 2 H, H3′, H5′), 7.61 (d, $J_{H2',H3'}$ = $J_{H6',H5'}$ = 8.8 Hz, 2 H, H2′, H6′), 7.44 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.68 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.50 (dt, $J_{H3,H4}$ = 8.3, J = 0.9 Hz, 1 H, H3), 6.00 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.0 Hz, 1 H, CH), 5.04 (d, $J_{NH,CH}$ = 8.9 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.84 (s, CCF_3), –73.60 (d, $J_{CF3,CH}$ = 7.9 Hz, $CHCF_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.03 (C2), 148.14 (C6), 138.69 (C1′), 138.00 (C4), 131.38 (q, $J_{C,F}$ = 32.3 Hz, C4′), 128.68 (q, $J_{C,F}$ = 1.2 Hz, C2′, C6′), 126.00 (q, $J_{C,F}$ =

3.8 Hz, C3′, C5′), 125.13 (q, $J_{C,F}$ = 282.3 Hz, $CHCF_3$), 124.09 (q, $J_{C,F}$ = 272.2 Hz, CCF_3), 115.26 (C5), 109.02 (C3), 56.21 (q, $J_{C,F}$ = 30.6 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{11}N_2F_3^+$ [M + H]$^+$ 321.0826; found 321.0820. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 11.98 min, λ = 214 nm.

***N*-[2,2,2-Trifluoro-1-(pyridin-2-yl)ethyl]pyridin-2-amine (2g):** Pyridin-2-ylmagnesium chloride was prepared in accordance with **TP3** from 2-bromopyridine (50 µL, 0.55 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2g** as a light yellow oil (71 mg, 62 %). R_f = 0.35 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, $J_{H6',H5'}$ = 4.9, $J_{H6',H4'}$ = 1.8 Hz, J = 1.0 Hz, 1 H, H6′), 8.12 (ddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.9 Hz, J = 0.9 Hz, 1 H, H6), 7.78–7.67 (m, 1 H, H4′), 7.48–7.39 (m, 2 H, H3′, H4), 7.30 (ddd, $J_{H5',H4'}$ = 7.6, $J_{H5',H6'}$ = 4.9 Hz, $J_{H5',H3'}$ = 1.2 Hz, 1 H, H5′), 6.67–6.59 (m, 2 H, H3, H5), 6.17 (d, $J_{NH,CH}$ = 8.5 Hz, 1 H, NH), 6.08 (p, $J_{CH,NH}$ = $J_{CH,CF3}$ = 7.4 Hz, 1 H, CH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.10 (d, $J_{CF3,CH}$ = 7.2 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.75 (C2), 152.26 (C2′), 149.49 (C6′), 147.76 (C6), 137.59 (C4), 136.89 (C4′), 125.08 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 124.39 (C3′), 124.00 (C5′), 114.56 (C5), 109.77 (C3), 55.83 (q, $J_{C,F}$ = 31.0 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{12}H_{11}F_3N_3^+$ [M + H]$^+$ 254.0900; found 254.0899. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.13 min, λ = 214 nm.

***N*-[2,2,2-Trifluoro-1-(pyridin-3-yl)ethyl] pyridin-2-amine (2h):** Pyridin-3-ylmagnesium chloride was prepared in accordance with **TP3** from 3-bromopyridine (50 µL, 0.55 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2h** as a light yellow oil (79 mg, 69 %). R_f = 0.50 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.75 (d, $J_{H2',H4'}$ = 2.2 Hz, 1 H, H2′), 8.60 (dd, $J_{H6',H5'}$ = 4.8, $J_{H6',H4'}$ = 1.6 Hz, 1 H, H6′), 8.10 (ddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.81 (dt, $J_{H4',H5'}$ = 8.2, $J_{H4',H2'}$ = $J_{H4',H6'}$ = 1.8 Hz, 1 H, H4′), 7.43 (ddd, $J_{H4,H3}$ = 8.8, $J_{H4,H5}$ = 7.3 Hz, $J_{H4,H6}$ = 1.8 Hz, 1 H, H4), 7.32 (ddd, $J_{H5',H4'}$ = 8.0, $J_{H5',H6'}$ = 4.8 Hz, $J_{H5',H2'}$ = 1.0 Hz, 1 H, H5′), 6.68 (ddd, $J_{H5,H4}$ = 7.1, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 1.0 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.4, J = 1.0 Hz, 1 H, H3), 6.02 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.2 Hz, 1 H, CH), 5.14 (d, $J_{NH,CH}$ = 9.0 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.63 (q, J = 8.0 Hz, CF_3) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.74 (C2), 150.14 (C6′), 149.59 (C2′), 147.85 (C6), 137.76 (C4), 135.41 (C4′), 130.51 (C3′), 124.94 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 123.62 (C5′), 115.02 (C5), 108.91 (C3), 54.37 (q, $J_{C,F}$ = 31.0 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{12}H_{11}N_3F_3^+$ [M + H]$^+$ 254.0905; found 254.0899. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 10.33 min, λ = 214 nm.

***N*-[1-(6-Chloropyridin-3-yl)-2,2,2-trifluoroethyl]-6-methylpyridin-2-amine (2i):** (6-Chloropyridin-3-yl)magnesium chloride was prepared in accordance with **TP3** from 5-bromo-3-chloropyridine (218 mg, 1.13 mmol) in 1 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)-6-methylpyridin-2-amine (100 mg, 0.43 mmol) at 0 °C in 5 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 20:1:0.1) furnished **2i** as a white solid (84 mg, 65 %). R_f = 0.40 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1), m.p. 74 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.53 (s, 1 H, H2′), 7.77 (dd, $J_{H4',H5'}$ = 8.4, $J_{H4',CH}$ = 2.4 Hz, 1 H, H4′), 7.35 (d, $J_{H5',H4'}$ = 8.0 Hz, 1 H, H5′), 7.32 (d, $J_{H5,H4}$ = 8.2 Hz, 1 H, H4), 6.60–6.47 (d, $J_{H5,H4}$ = 7.0 Hz, 1 H, H5), 6.29 (d, $J_{H5,H4}$ = 8.2 Hz, 1 H, H3), 5.95 (p, $J_{CH,CF}$ = $J_{CH,NH}$ = 8.1 Hz, 1 H, CH), 4.92 (d, $J_{NH,CH}$ = 8.7 Hz, 1 H, NH), 2.35 (s, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.59 (d, $J_{CF3,CH}$ = 8.1 Hz, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 157.18 (C6), 154.96 (C2), 152.05 (C6′), 149.85 (C2′), 138.23 (C4, C4′), 129.92 (C3′), 124.88 (q, $J_{C,F}$ = 281.3 Hz, CF_3), 124.52 (C5′), 114.56 (C5), 105.54 (C3), 54.22 (q, $J_{C,F}$ = 31.2 Hz, $CHCF_3$), 24.40 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{13}H_{12}ClF_3N_3^+$ [M + H]$^+$ 302.0666; found 302.0664. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 10.50 min, λ = 214 nm.

***N*-[2,2,2-Trifluoro-1-(perfluorophenyl)ethyl]pyridin-2-amine (2j):** (Perfluorophenyl)magnesium chloride was prepared from 1-bromo-2,3,4,5,6-pentafluorobenzene (60 µL, 0.50 mmol) dissolved in THF (0.50 mL). *i*PrMgCl (1.25 M, 0.44 mL, 0.55 mL) was added dropwise at –78 °C and the reaction mixture was stirred for 45 min. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –78 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2j** as a light yellow oil (131 mg, 85 %). R_f = 0.45 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (ddd, $J_{H6,H5}$ = 5.2, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.47 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H3,H6}$ = 1.9 Hz, 1 H, H4), 6.72 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.2 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.72–6.63 (m, 1 H, CH), 6.55 (dt, $J_{H3,H4}$ = 8.3, J = 0.9 Hz, 1 H, H3), 5.21 (d, $J_{NH,CH}$ = 10.6 Hz, 1 H, NH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.63 (q, J = 7.9 Hz, CF_3), –141.29 (s, F2′, F6′), –152.01 (tt, $J_{F4',F3'}$ = $J_{F4',F5'}$ = 20.9, $J_{F4',F2'}$ = $J_{F4',F6'}$ = 2.7 Hz, F4′), –160.80 (td, $J_{F5',F4'}$ = $J_{F5',F6'}$ = $J_{F3',F2'}$ = $J_{F3',F4'}$ = 22.0, $J_{F5',F3'}$ = $J_{F3',F5'}$ = 7.8 Hz, F5′, F3′) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.30 (C2), 148.07 (C6), 147.54–144.58 (m, C2′, C6′), 143.52–140.32 (m, C3′, C5′), 138.12 (C4), 139.48–136.17 (m, C4′), 124.44 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 115.66 (C5), 109.47 (C3), 109.21–108.71 (m, C1′), 48.11 (q, $J_{C,F}$ = 34.3 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{13}H_7N_2F_8^+$ [M + H]$^+$ 343.0481; found 343.0474. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 14.56 min, λ = 214 nm.

***N*-[2,2,2-Trifluoro-1-(4-methylnaphthalen-1-yl)ethyl]pyridin-2-amine (2k):** (4-Methylnaphthalen-1-yl)magnesium chloride was prepared in accordance with **TP3** from 1-bromo-4-methylnaphthalen (158 mg, 0.50 mmol) in 18 h at 25 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at 25 °C in 18 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2k** as a light yellow oil (83 mg, 58 %). R_f = 0.45 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29–8.22 (m, 1 H, H8′), 8.17 (dddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, $J_{H6,NH}$ = 0.3 Hz, 1 H, H6), 8.09–8.03 (m, 1 H, H5′), 7.64 (dd, $J_{H2',H3'}$ = 7.3, $J_{H2',CH}$ = 1.2 Hz, 1 H, H2′), 7.62–7.54 (m, 2 H, H6′, H7′), 7.39 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 7.35 (dd, $J_{H3',H2'}$ = 7.4, $J_{H3',CH3}$ = 0.9 Hz, 1 H, H3′), 6.81 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 7.7 Hz, 1 H, CH), 6.66 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.41 (dt, $J_{H3,H4}$ = 8.3, J = 0.9 Hz, 1 H, H3), 5.04 (d, $J_{NH,CH}$ = 8.8 Hz, 1 H, NH), 2.71 (d, $J_{CH3,C3'}$ = 0.9 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.38 (d, $J_{CF3,CH}$ = 4.7 Hz, $CHCF_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.56 (C2), 148.34 (C6), 137.95 (C4), 136.25 (C8′a), 133.31 (C4′a), 132.02 (C4′), 129.29 (d, $J_{C,F}$ = 1.0 Hz, C1′), 126.93 (C7′), 126.39 (C3′), 126.23 (C6′), 126.11 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 125.31 (C5′), 124.88 (q, $J_{C,F}$ = 1.8 Hz, C2′), 123.94 (d, $J_{C,F}$ = 0.9 Hz, C8′), 114.88 (C5), 108.70 (C3), 51.67 (q, $J_{C,F}$ = 30.6 Hz, CH), 20.04 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{18}H_{16}F_3N_2^+$ [M + H]$^+$ 317.1260; found 317.1262. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 12.09 min, λ = 214 nm.

***N*-[1-(2,4-Dimethoxypyrimidin-5-yl)-2,2,2-trifluoroethyl]pyridin-2-amine (2l):** (2,4-Dimethoxypyrimidin-5-yl)magnesium chloride was prepared in accordance with **TP3** from 5-bromo-2,4-dimethoxypyrimidine (110 mg, 0.50 mmol) in 1 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2l** as a light yellow oil (120 mg, 85 %). R_f = 0.40 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, H6′), 8.11 (ddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.8 Hz, $J_{H6,H3}$ = 0.8 Hz, 1 H, H6), 7.43 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.66 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.49 (dt, $J_{H3,H4}$ = 8.3, J = 0.9 Hz, 1 H, H3), 6.07 (dqd, $J_{CH,NH}$ = 9.7, $J_{CH,CF3}$ = 8.0 Hz, $J_{CH,H5}$ = 0.5 Hz, H, CH), 5.34 (d, $J_{NH,CH}$ = 9.6 Hz, 1 H, NH), 4.07 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.27 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.61 (C4′), 165.72 (C2′), 159.12 (q, $J_{C,F}$ = 1.1 Hz, C6′), 156.22 (C2), 148.20 (C6), 137.99 (*C*4), 125.29 (q, $J_{C,F}$ = 282.6 Hz, CF_3), 115.08 (C5), 109.07 (C3), 108.68 (d, $J_{C,F}$ = 1.2 Hz, C5′), 55.29 (OCH_3), 54.82 (OCH_3), 50.95 (q, $J_{C,F}$ = 32.4 Hz, *C*HCF$_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{11}N_3F_3^+$ [M + H]$^+$ 315.1063; found 315.1064. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.46 min, λ = 214 nm.

***N*-[2,2,2-Trifluoro-1-(thiophen-2-yl)ethyl]pyridin-2-amine (2m):** Thiophen-2-ylmagnesium chloride was prepared in accordance with **TP3** from 2-bromothiophene (0.05 mL, 0.50 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2m** as a colorless oil (84 mg, 72 %). R_f = 0.60 (cyclohexane/ethyl acetate, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (dddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.8 Hz, $J_{H6,H3}$ = 0.8 Hz, $J_{H6,NH}$ = 0.3 Hz, 1 H, H6), 7.45 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 7.30 (dd, $J_{H5′,H4′}$ = 5.1, $J_{H5′,H3′}$ = 1.2 Hz, 1 H, H5′), 7.21 (ddt, $J_{H3′,H4′}$ = 3.6, $J_{H3′,H5′}$ = 1.3 Hz, $J_{H3′,CH}$ = 0.7 Hz, 1 H, H3′), 7.02 (dd, $J_{H4′,H5′}$ = 5.1, $J_{H4′,H3′}$ = 3.6 Hz, 1 H, H4′), 6.70 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.3, J = 0.9 Hz, 1 H, H3), 6.30 (dqd, $J_{CH,NH}$ = 9.5, $J_{CH,CF3}$ = 7.6 Hz, J = 0.8 Hz, 1 H, CH), 4.87 (d, $J_{NH,CH}$ = 9.5 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.72 (d, $J_{CF3,CH}$ = 7.7 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.04 (C2), 148.07 (C6), 137.98 (C4), 137.13–137.08 (m, C2′), 127.43 (C4′), 127.21 (q, $J_{C,F}$ = 1.3 Hz, C3′), 126.15 (C5′), 124.95 (q, $J_{C,F}$ = 281.9 Hz, CF_3), 115.22 (C5), 109.07 (C3), 52.28 (q, $J_{C,F}$ = 32.2 Hz, *C*HCF$_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{11}H_{10}N_2F_3^+$ [M + H]$^+$ 259.0517; found 259.05113. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 10.10 min, λ = 214 nm.

***N*-[1-(Benz[*b*]thiophen-3-yl)-2,2,2-trifluoroethyl]pyridin-2-amine (2n):** Benzo[*b*]thiophen-3-ylmagnesium chloride was prepared in accordance with **TP3** from 3-bromobenz[*b*]thiophene (107 mg, 0.50 mmol) in 3 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at –30 °C in 3 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 50:1:0.1 → 15:1:0.1) furnished **2n** as a yellow oil (115 mg, 83 %). R_f = 0.40 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (ddd, $J_{H6,H5}$ = 5.0, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.86 (dddd, $J_{H4′,H5′}$ = $J_{H7′,H6′}$ = 6.8, $J_{H4′,H6′}$ = $J_{H7′,H5′}$ = 5.4 Hz, $J_{H4′,H7′}$ = $J_{H7′,H4′}$ = 3.3 Hz, $J_{H4′,H2′}$ = $J_{H7′,H2′}$ = 0.7 Hz, 2 H, H4′, H7′), 7.62 (dd, $J_{H2′,CH}$ = 1.5, $J_{H2′,H4′}$ = $J_{H2′,H7′}$ = 0.7 Hz, 1 H, H2′), 7.43 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 7.40–7.35 (m, 2 H, H5′, H6′), 6.71 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.44 (dt, $J_{H3,H4}$ = 8.3, J = 0.9 Hz, 1 H, H3), 6.54 (dqd, $J_{CH,NH}$ = 9.9, $J_{CH,CF3}$ = 7.6 Hz, $J_{CH,H2′}$ = 0.8 Hz, 1 H, CH), 4.79 (d, $J_{NH,CH}$ = 9.3 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.10 (d, $J_{CF3,CH}$ = 7.6, $J_{CF3,NH}$ = 1.1 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.09 (C2), 147.85 (C6), 139.97 (C7′a), 137.90 (C3′a), 137.69 (C4), 129.24 (d, $J_{C,F}$ = 1.1 Hz, C3′), 125.43 (q, $J_{C,F}$ = 282.6 Hz, CF_3), 124.94 (C2′), 124.89 (C5′), 124.61 (C6′), 122.77 (C4′), 121.94 (C7′), 114.73 (C5), 108.62 (C3), 50.20 (q, $J_{C,F}$ = 31.8 Hz, *C*HCF$_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{15}H_{12}F_3N_3S^+$ [M + H]$^+$ 309.0668; found 309.0667. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 11.71 min, λ = 214 nm.

***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)pyridin-2-amine (2o):** The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) and cyclopropylmagnesium bromide (1.0 M, 0.55 mL, 0.55 mmol) at 0 °C in 2 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 50:1:0.1 → 10:1:0.1) furnished **2o** as a white solid (83 mg, 85 %). R_f = 0.45 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1), m.p. 77 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (ddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.42 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.63 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.44 (dt, $J_{H3,H4}$ = 8.4, $J_{H3,H5}$ = $J_{H3,H6}$ = 0.9 Hz, 1 H, H3), 4.47 (d, $J_{NH,CH}$ = 9.5 Hz, 1 H, NH), 4.36–4.17 (m, 1 H, CH), 1.17–1.04 [m, 1 H, *CH*(CH$_2$)$_2$], 0.76–0.63 (m, 1 H, CH$_2$), 0.61–0.49 (m, 2 H, CH$_2$), 0.46–0.32 (m, 1 H, CH$_2$) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –75.58 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.26 (C2), 147.98 (C6), 137.81 (C4), 126.26 (q, $J_{C,F}$ = 283 Hz, CF_3), 114.47 (C5), 108.50 (C3), 55.82 (q, $J_{C,F}$ = 29.3 Hz, *C*HCF$_3$), 10.86 [q, $J_{C,F}$ = 2.3 Hz, *C*H(CH$_2$)$_2$], 3.82 (d, $J_{C,F}$ = 0.9 Hz, CH$_2$), 1.91 (CH$_2$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{10}H_{12}F_3N_2^+$ [M + H]$^+$ 217.0953; found 217.0946. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.14 min, λ = 214 nm.

4-[2,2,2-Trifluoro-1-(pyrazin-2-ylamino)ethyl]benzonitrile (2p): (4-Cyanophenyl)magnesium chloride was prepared in accordance with **TP3** from 4-bromobenzonitrile (91 mg, 0.50 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate, 10:1 → 3:1) furnished **2p** as a light yellow oil (70 mg, 56 %). R_f = 0.37 (cyclohexane/ethyl acetate, 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.07 (d, $J_{H3′,H6′}$ = 1.5 Hz, 1 H, H3′), 8.00 (dd, $J_{H6′,H5′}$ = 2.7, $J_{H6′,H3′}$ = 1.5 Hz, 1 H, H6′), 7.93 (d, $J_{H5′,H6′}$ = 2.7 Hz, 1 H, H5′), 7.72–7.67 (m, 2 H, H3, H5), 7.61 (d, J = 8.1 Hz, 2 H, H2, H6), 5.97 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.0 Hz, 1 H, CH), 5.48 (d, $J_{NH,CH}$ = 8.8 Hz, 1 H, NH) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –73.33 (d, $J_{CF3,CH}$ = 7.7 Hz, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 152.18 (C2′), 141.71 (C6′), 139.01 (C1), 135.19 (C5′), 133.32 (C3′), 132.77 (C3, C5), 128.98 (C2, C6), 124.41 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 118.27 (CN), 113.32 (C4), 55.48 (q, $J_{C,F}$ = 31.0 Hz, *C*HCF$_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{13}H_{10}F_3N_4^+$ [M + H]$^+$ 279.0852; found 279.0852. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 13.16 min, λ = 214 nm.

***N*-[2,2,2-Trifluoro-1-(pyridin-2-yl)ethyl]pyrazin-2-amine (2q):** Pyridin-2-ylmagnesium chloride was prepared in accordance with **TP3** from 2-bromopyridine (50 µL, 0.55 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2q** as a light yellow oil (65 mg, 56 %). R_f = 0.48 (cyclohexane/ethyl acetate, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68–8.62 (m, 1 H, H6′), 8.13–8.10 (m, 1 H, H3), 8.03 (ddd, $J_{H6,H5}$ = 2.8, $J_{H6,H3}$ = 1.5 Hz, J = 0.5 Hz, 1 H, H6), 7.89 (dt, $J_{H5,H6}$ = 2.7, J = 0.5 Hz, 1 H, H5), 7.75 (tdd, $J_{H4′,H3′}$ = $J_{H4′,H5′}$ = 7.7,

J = 1.8 Hz, J = 0.5 Hz, 1 H, H4′), 7.46 (dd, $J_{H3',H4'}$ = 8.1, $J_{H3',H5'}$ = 1.3 Hz, 1 H, H3′), 7.39–7.31 (m, 1 H, H5′), 6.51 (d, $J_{NH,CH}$ = 8.2 Hz, 1 H, NH), 6.00 (m, 1 H, CH) ppm. ^{19}F NMR (280 MHz, $CDCl_3$): δ = –74.15 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.08 (C2), 151.21 (C2′), 149.52 (C6′), 141.53 (C6), 137.08 (C4′), 134.46 (C5), 134.03 (C3), 124.78 (q, $J_{C,F}$ = 283.3 Hz, CF_3), 124.33 (C3′/C5′), 124.29 (C3′/C5′), 55.16 (q, $J_{C,F}$ = 31.1 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): m/z calcd. for $C_{11}H_{10}F_3N_4^+$ $[M + H]^+$ 255.0852; found 255.0852. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 10.98 min, λ = 214 nm.

***N*-[1-(2,4-Dimethoxypyrimidin-5-yl)-2,2,2-trifluoroethyl]pyrazine-2-amine (2r):** (2,4-Dimethoxypyrimidin-5-yl)magnesium chloride was prepared in accordance with **TP3** from 5-bromo-2,4-dimethoxypyrimidine (77 mg, 0.35 mmol) in 1 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (66 mg, 0.3 mmol) at –30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2r** as a light yellow oil (75 mg, 79 %). R_f = 0.24 (cyclohexane/ethyl acetate/NEt_3, 6:4:0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, H6′), 8.05–8.00 (m, 2 H, H3, H5), 7.92 (d, $J_{H6,H5}$ = 2.6 Hz, 1 H, H6), 6.04 (dq, $J_{CH,NH}$ = 9.6, $J_{CH,CF3}$ = 7.9 Hz, 1 H, CH), 5.60 (d, $J_{NH,CH}$ = 9.6 Hz, 1 H, NH), 4.09 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.21 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.38 (C4′), 165.71 (C2′), 159.08 (C6′), 152.39 (C2), 141.69 (C6), 134.94 (C5), 133.29 (C3), 124.84 (q, $J_{C,F}$ = 282.6 Hz, CF_3), 107.71 (C5′), 55.28 (OCH_3), 54.74 (OCH_3), 50.41 (q, $J_{C,F}$ = 33.0 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): m/z calcd. for $C_{12}H_{13}F_3N_5O_2^+$ $[M + H]^+$ 316.1016; found 316.1014.

***N*-[2,2,2-Trifluoro-1-(thiophen-2-yl)ethyl]pyrazin-2-amine (2s):** Thiophen-2-ylmagnesium chloride was prepared in accordance with **TP3** from 2-bromothiophene (0.07 mL, 0.70 mmol) in 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazine-2-amine (100 mg, 0.45 mmol) at –30 °C in 8 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 8:1:0.1) furnished **2s** as a light red oil (64 mg, 55 %). R_f = 0.38 (cyclohexane/ethyl acetate/NEt_3, 4:2:0.1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (ddd, $J_{H6,H5}$ = 2.8, $J_{H6,H3}$ = 1.5 Hz, J = 0.4 Hz, 1 H, H6), 8.03 (dd, $J_{H3,H6}$ = 1.5, J = 0.4 Hz, 1 H, H3), 7.95 (dd, $J_{H5,H6}$ = 2.8, J = 0.4 Hz, 1 H, H5), 7.33 (dd, $J_{H5',H4'}$ = 5.1, $J_{H5',H3'}$ = 1.2 Hz, 1 H, H5′), 7.22 (ddt, $J_{H3',H4'}$ = 3.6, $J_{H3',H5'}$ = 1.3 Hz, $J_{H3',CH}$ = 0.7 Hz, 1 H, H3′), 7.04 (dd, $J_{H4',H5'}$ = 5.1, $J_{H4',H3'}$ = 3.6 Hz, 1 H, H4′), 6.27 (dqd, $J_{CH,NH}$ = 9.4, $J_{CH,CF3}$ = 7.4 Hz, $J_{CH,H3'}$ = 0.8 Hz, 1 H, CH), 5.11 (d, $J_{NH,CH}$ = 9.4 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.67 (d, $J_{CF3,CH}$ = 7.6 Hz, CF_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.28 (C2), 141.73 (C6), 135.84 (C2′), 135.12 (C5), 133.21 (C3), 127.51 (q, $J_{C,F}$ = 1.3 Hz, C3′), 127.45 (C4′), 126.44 (C5′), 124.58 (q, $J_{C,F}$ = 281.9 Hz, CF_3), 51.60 (q, $J_{C,F}$ = 32.7 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): m/z calcd. for $C_{11}H_{10}N_2F_3^+$ $[M + H]^+$ 260.0464; found 260.0463. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 13.50 min, λ = 214 nm.

***N*-[1-(Benz[*b*]thiophen-3-yl)-2,2,2-trifluoroethyl]pyrazine-2-amine (2t):** Benzo[*b*]thiophen-3-ylmagnesium chloride was prepared in accordance with **TP3** from 3-bromobenz[*b*]thiophene (192 mg, 0.90 mmol) in 3 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) at 0 °C in 6 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 20:1:0.1 → 8:1:0.1) furnished **2t** as a yellow oil (120 mg, 86 %). R_f = 0.38 (cyclohexane/ethyl acetate/NEt_3, 2:1:0.05). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (dd, $J_{H6,H5}$ = 2.8, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.96 (d, $J_{H5,H6}$ = 2.8 Hz, 2 H, H3, H5), 7.92–7.85 (m, 1 H, H5′), 7.82–7.75 (m, 1 H, H8′), 7.67–7.62 (m, 1 H, H2′), 7.46–7.32 (m, 2 H, H6′, H7′), 6.59–6.42 (m, 1 H, CH), 5.02 (d, $J_{NH,CH}$ = 9.1 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.06 (dd, $J_{CF3,CH}$ = 7.5, $J_{CF3,NH}$ = 1.2 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.58 (C2), 141.76 (C6), 140.14 (C4′, C9′), 137.84 (C3′), 134.94 (C5), 133.13 (C3), 125.53 (C2′), 125.32 (q, $J_{C,F}$ = 282.5 Hz, CF_3), 125.24 (C6′/C7′), 124.93 (C6′/C7′), 123.07 (C5′), 121.76, 49.69 (q, $J_{C,F}$ = 32.3 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): m/z calcd. for $C_{11}H_{10}N_2F_3^+$ $[M + H]^+$ 310.0620; found 310.0619, HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 15.13 min, λ = 214 nm.

***N*-(1,1,1-Trifluoro-but-3-yn-2-yl)pyrazin-2-amine (2u):** The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) and ethynylmagnesium bromide (0.5 M, 1.4 mL, 0.67 mmol) at –78 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 10:1:0.1) furnished **2u** as a light yellow oil (88 mg, 96 %). R_f = 0.46 (cyclohexane/ethyl acetate/NEt_3, 8:1:0.1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.07 (dd, $J_{H6,H5}$ = 2.8, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 8.04 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 7.99 (d, $J_{H5,H6}$ = 2.7 Hz, 1 H, H5), 5.82 (dqd, $J_{CH,NH}$ = 9.1, $J_{CH,CF3}$ = 6.6 Hz, $J_{CH,C\equiv CH}$ = 2.5 Hz, 1 H, CH), 4.93 (d, $J_{NH,CH}$ = 9.2 Hz, 1 H, NH), 2.46 (d, $J_{C\equiv CH,CH}$ = 2.5 Hz, 1 H, C≡CH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –76.14 (d, $J_{CF3,CH}$ = 6.5 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.74 (C2), 141.62 (C6), 135.60 (C5), 133.34 (C3), 123.36 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 75.30 (C≡CH), 74.45 (C≡CH), 44.83 (q, $J_{C,F}$ = 35.8 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): m/z calcd. for $C_8H_7F_3N_3^+$ $[M + H]^+$ 202.0587; found 202.0586. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 11.99 min, λ = 214 nm.

***N*-[2,2,2-Trifluoro-1-(perfluorophenyl)ethyl]pyrazin-2-amine (2v):** (Perfluorophenyl)magnesium chloride was prepared from 1-bromo-2,3,4,5,6-pentafluorobenzene (90 µL, 0.70 mmol) dissolved in THF (0.50 mL). *i*PrMgCl (2 M, 0.39 mL, 0.77 mL) was added dropwise at –78 °C and the reaction mixture was stirred for 45 min. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) at –78 °C in 5 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate, 30:1 → 8:1) furnished **2v** as a colorless oil (143 mg, 92 %). R_f = 0.58 (cyclohexane/ethyl acetate/NEt_3, 2:1:0.05). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 8.06 (dd, $J_{H6,H5}$ = 2.8, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.99 (d, $J_{H5,H6}$ = 2.7 Hz, 1 H, H5), 6.56 (dq, $J_{CH,NH}$ = 10.2, $J_{CH,CF3}$ = 7.8 Hz, 1 H, CH), 5.48 (d, $J_{NH,CH}$ = 10.4 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.56 (d, $J_{CF3,CH}$ = 7.8 Hz, CF_3), –141.10 (s, F2′, F6′), –151.01 (tt, $J_{F4',F3'}$ = $J_{F4',F5'}$ = 20.9, $J_{F4',F2'}$ = $J_{F4',F6'}$ = 2.9 Hz, F4′), –159.73 to –160.77 (m, F5′, F3′) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.71 (C2), 147.95–144.10 (m, C2′, C6′), 143.95–140.22 (m, C3′, C5′), 141.66 (C6), 139.91–135.96 (m, C4′), 135.71 (C5), 133.45 (C3), 124.04 (q, $J_{C,F}$ = 281.9 Hz, CF_3), 108.30–107.72 (m, C1′), 47.60 (q, $J_{C,F}$ = 34.3 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): m/z calcd. for $C_{11}H_{10}N_2F_3^+$ $[M + H]^+$ 344.0428; found 344.0427. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 15.72 min, λ = 214 nm.

***N*-(4-Cyclopropyl-1,1,1-trifluorobut-3-yn-2-yl)pyrazin-2-amine (2w):** (Cyclopropylethynyl)magnesium chloride was prepared from ethynylcyclopropane (45 µL, 0.54 mmol) in THF (1 mL), which was treated with *n*BuMgBr (2.0 M in Et_2O, 0.27 mL, 0.54 mmol) for 2 h at 0 °C. The addition reaction was performed in accordance with **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) and (cyclopropylethynyl)magnesium chloride at –20 °C in 2 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 10:1:0.1 → 4:1:0.05) furnished **2w** as a colorless oil (87 mg, 80 %). R_f = 0.38 (cyclohexane/ethyl acetate/NEt_3, 2:1:0.05). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (ddd, $J_{H6,H5}$ = 2.8,

$J_{H6,H3}$ = 1.5 Hz, J = 0.4 Hz, 1 H, H6), 8.00 (dd, $J_{H3,H6}$ = 1.5, J = 0.4 Hz, 1 H, H3), 7.95 (dd, $J_{H5,H6}$ = 2.8, J = 0.4 Hz, 1 H, H5), 5.74–5.62 (m, 1 H, NHC*H*), 4.81 (d, $J_{NH,CH}$ = 9.2 Hz, 1 H, NH), 1.32–1.20 (m, 1 H, CH), 0.85–0.77 (m, 2 H, CH_2), 0.75–0.69 (m, 2 H, CH_2) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –76.45 (d, $J_{CF3,CH}$ = 6.6 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.04 (C2), 141.65 (C6), 135.10 (C5), 133.20 (C3), 123.66 (q, $J_{C,F}$ = 281.7 Hz, CF_3), 90.12 [C≡*C*-CH(CH_2)$_2$], 66.43 [C≡C-*C*H(CH_2)$_2$], 45.15 (q, $J_{C,F}$ = 35.4 Hz, *C*HCF$_3$), 8.42 (2 × CH_2), –0.58 [C≡C-*C*H(CH_2)$_2$] ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{11}H_{11}F_3N_3^+$ [M + H]$^+$ 242.0900; found 242.0898. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 13.83 min, λ = 214 nm.

***N*-(1,1-Difluoropropan-2-yl)pyridine-2-amine (3a):** In accordance with **TP5**, hemiaminal ether **1b** (100 mg, 0.50 mmol) was treated with MeMgBr (1.4 M in toluene/THF, 3:1, 0.78 mL, 1.09 mmol) in dry THF (5 mL) for 2 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 100:10:1) to give desired amine **3a** (61 mg, 72 %) as an orange, amorphous solid. R_f = 0.70 (cyclohexane/ethyl acetate, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (ddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.41 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.61 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.42 (dt, $J_{H3,H4}$ = 8.4, $J_{H3,H6}$ = $J_{H3,H5}$ = 0.9 Hz, 1 H, H3), 5.90 (ddd, $J_{F,H}$ = 57.7, $J_{F,H}$ = 55.7 Hz, $J_{CHF2,CH}$ = 2.0 Hz, 1 H, CHF_2), 4.54–4.36 (m, 1 H, CH), 4.32 (br. s, 1 H, NH), 1.30 (dt, $J_{CH3,CH}$ = 6.7, J = 1.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –125.78 (ddd, $J_{F,F}$ = 280.1, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 6.8 Hz, CHF_2), –134.19 (ddt, $J_{F,F}$ = 280.2, $J_{F,H}$ = 57.9 Hz, $J_{CHF2,CH}$ = 20.4 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.28 (C2), 148.10 (C6), 137.57 (C4), 115.65 (dd, $J_{C,F}$ = 245.4, $J_{C,F}$ = 244.2 Hz, CHF_2), 113.92 (C5) 108.47 (C3), 48.23 (dd, $J_{C,F}$ = 26.1, $J_{C,F}$ = 21.7 Hz, CH), 12.79 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_8H_{11}F_2N_2^+$ [M + H]$^+$ 173.0885; found 173.0885. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 3.55 min, λ = 214 nm.

***N*-(1,1-difluoropropan-2-yl)pyrazin-2-amine (3b):** In accordance with **TP5**, hemiaminal ether **1d** (100 mg, 0.49 mmol) was treated with MeMgBr (1.4 M in toluene/THF, 3:1, 0.77 mL, 1.08 mmol) in dry THF (5 mL) for 1.5 h at 0 °C. The crude product was purified by preparative HPLC [0.1 % TFA; 0 min: 4 % MeCN (B) → 15 min: 100 % B, flow: 20 mL/min, t_R = 16.51 min] to give desired amine **3b** (80 mg, 94 %) as a colorless oil. R_f = 0.36 (cyclohexane/ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.91 (m, 2 H, H3, H6), 7.85 (d, $J_{H5,H6}$ = 2.8 Hz, 1 H, H5), 5.89 (ddd, $J_{H,F}$ = 57.4, $J_{H,F}$ = 55.4 Hz, $J_{CHF2,CH}$ = 2.0 Hz, 1 H, CHF_2), 4.61 (br. s, 1 H, NH), 4.55–4.39 (m, 1 H, CH), 1.32 (d, $J_{CH3,CH2}$ = 6.9 Hz, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –126.59 (ddd, $J_{F,F}$ = 281.4, $J_{F,H}$ = 55.4 Hz, $J_{CHF2,CH}$ = 7.8 Hz, CHF_2), –133.24 (ddd, $J_{F,F}$ = 281.5, $J_{F,H}$ = 57.4 Hz, $J_{CHF2,CH}$ = 19.3 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.52 (C2), 141.78 (C6), 133.82 (C5), 133.13 (C3), 115.17 (t, $J_{C,F}$ = 244.8 Hz, CHF_2), 47.83 (dd, $J_{C,F}$ = 26.2, $J_{C,F}$ = 21.8 Hz, CH), 12.84 (dd, $J_{C,F}$ = 5.7, $J_{C,F}$ = 2.1 Hz, CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_7H_{10}F_2N_3^+$ [M + H]$^+$ 174.0837; found 174.0837. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 10.16 min, λ = 214 nm.

***N*-(1,1-Difluoropropan-2-yl)-3,5-*bis*(trifluoromethyl)aniline (3c):** In accordance with **TP5**, hemiaminal ether **1f** (101 mg, 0.30 mmol) was treated with MeMgBr (1.4 M in toluene/THF, 3:1, 0.47 mL, 0.69 mmol) in dry THF (5 mL) for 3 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 100:5:1) to give desired amine **3c** (65 mg, 71 %) as a colorless oil. R_f = 0.64 (cyclohexane/ethyl acetate, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 1 H, H4), 7.00 (s, 2 H, H2, H6), 5.79 (ddd, $J_{H,F}$ = 56.2, $J_{H,F}$ = 55.5 Hz, $J_{CHF2,CH}$ = 2.6 Hz, 1 H, CHF_2), 4.06 (d, $J_{NH,CH}$ = 9.0 Hz, 1 H, NH), 3.98–3.79 (m, 1 H, CH), 1.34 (dt, $J_{CH3,CH2}$ = 6.7, $J_{CH3,CH}$ = 1.1 Hz, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = 63.30 (2 × CF_3), –127.08 (ddd, $J_{F,F}$ = 282.9, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 9.9 Hz, CHF_2), –128.03 (ddd, $J_{F,F}$ = 282.9, $J_{F,H}$ = 56.2 Hz, $J_{CHF2,CH}$ = 14.0 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.31 (C1), 132.87 (q, $J_{C,F}$ = 33.0 Hz, C3, C5), 123.53 (q, $J_{C,F}$ = 272.7 Hz, 2 × CF_3), 115.69 (t, $J_{C,F}$ = 245.8 Hz, CHF_2), 112.62 (m, C2, C6), 111.57 (dq, J = 3.9 Hz, C4), 50.63 (dd, $J_{C,F}$ = 24.0, $J_{C,F}$ = 22.6 Hz, CH), 13.81 (CH_3) ppm. HRMS (ESI$^-$): *m/z* calcd. for $C_{11}H_8F_8N^-$ [M – H]$^-$ 306.0534; found 306.0538. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 19.89 min, λ = 214 nm.

***N*-(1,1-Difluorohexan-2-yl)-2,3,4,5,6-pentafluoroaniline (3d):** In accordance with **TP5**, hemiaminal ether **1g** (113 mg, 0.39 mmol) was treated with *n*BuMgBr (2.0 M in Et_2O, 0.43 mL, 0.85 mmol) in dry THF (5 mL) for 1.5 h at 0 °C. Desired amine **3d** (108 mg, 92 %) was isolated after workup as a yellow liquid without further purification. R_f = 0.80 (cyclohexane/ethyl acetate, 7:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.79 (td, $J_{H,F}$ = 55.7, $J_{CHF2,CH}$ = 2.1 Hz, 1 H, CHF_2), 3.88–3.70 (m, 1 H, CH), 3.46 (d, $J_{NH,CH}$ = 10.7 Hz, 1 H, NH), 1.82–1.68 (m, 1 H, CH_2), 1.60–1.45 (m, 2 H, CH_2), 1.42–1.33 (m, 2 H, CH_2), 0.93 (t, $J_{CH3,CH2}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –127.32 (ddd, $J_{F,F}$ = 282.6, $J_{F,H}$ = 55.8 Hz, $J_{CHF2,CH}$ = 13.0 Hz, CHF_2), –129.96 (ddt, $J_{F,F}$ = 282.6, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 13.0 Hz, CHF_2), –158.23 (d, $J_{F2,F3}$ = $J_{F6,F5}$ = 21.8 Hz, F2, F6), –163.86 (td, $J_{F5,F4}$ = $J_{F5,F6}$ = $J_{F3,F2}$ = $J_{F3,F4}$ = 21.8, $J_{F5,F3}$ = $J_{F3,F5}$ = 6.4 Hz, F3, F5), –169.88 (td, $J_{F4,F3}$ = $J_{F4,F5}$ = 21.9, J = 6.0 Hz, F4) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.07–137.12 (m), 136.10–132.99 (m), 123.47–122.92 (m), 116.28 (t, $J_{C,F}$ = 245.1 Hz, CHF_2), 57.35 (ddt, $J_{C,F}$ = 24.0, $J_{C,F}$ = 20.4 Hz, $J_{C,F}$ = 3.6 Hz, CH), 29.21 (CH_2), 27.79 (CH_2), 22.55 (CH_2), 13.99 (CH_3) ppm. HRMS (ESI$^-$): *m/z* calcd. for $C_{12}H_{11}F_7N^-$ [M – H]$^-$ 302.0785; found 302.0787. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 21.58 min, λ = 214 nm.

***N*-(1,1-Difluorohexan-2-yl)pyridine-2-amine (3e):** In accordance with **TP5**, hemiaminal ether **1b** (100 mg, 0.50 mmol) was treated with *n*BuMgBr (2.0 M in Et_2O, 0.54 mL, 1.08 mmol) in dry THF (5 mL) for 2.5 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 100:10:1) to give desired amine **3e** (72 mg, 68 %) as a white solid. R_f = 0.88 (cyclohexane/ethyl acetate, 1:1), m.p. 30 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (ddd, $J_{H6,H5}$ = 5.1, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.40 (ddd, $J_{H4,H3}$ = 8.4, $J_{H4,H5}$ = 7.1 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.60 (ddd, $J_{H5,H4}$ = 7.1, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.43 (dt, $J_{H3,H4}$ = 8.4, $J_{H3,H6}$ = $J_{H3,H5}$ = 1.0 Hz, 1 H, H3), 5.87 (ddd, $J_{H,F}$ = 57.3, $J_{H,F}$ = 55.9 Hz, $J_{CHF2,CH}$ = 1.9 Hz, 1 H, CHF_2), 4.42–4.19 (m, 2 H, CH, NH), 1.92–1.75 (m, 1 H, CH_2), 1.58–1.40 (m, 2 H, CH_2), 1.42–1.28 (m, 3 H, CH_2), 0.89 (t, $J_{CH3,CH}$ = 7.2 Hz, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –126.07 (ddd, $J_{F,F}$ = 279.8, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 8.6 Hz, CHF_2), –131.59 (ddt, $J_{F,F}$ = 280.0, $J_{F,H}$ = 57.2 Hz, $J_{CHF2,CH}$ = 18.4 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.87 (C2), 148.07 (C6), 137.58 (C4), 115.86 (t, $J_{C,F}$ = 244.6 Hz, CHF_2), 113.74 (C5) 108.16 (C3), 52.45 (dd, $J_{C,F}$ = 24.4, $J_{C,F}$ = 21.1 Hz, CH), 27.91 (CH_2), 27.48 (CH_2), 22.70 (CH_2), 14.02 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{11}H_{17}F_2N_2^+$ [M + H]$^+$ 215.1354; found 215.1354. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.96 min, λ = 214 nm.

***N*-(1,1-Difluorohexan-2-yl)pyrazin-2-amine (3f):** In accordance with **TP5**, hemiaminal ether **1d** (100 mg, 0.49 mmol) was treated with *n*BuMgBr (2.0 M in Et_2O, 0.54 mL, 1.08 mmol) in dry THF (5 mL) for 1.5 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 100:10:1 → 100:15:1) to give desired amine **3f** (112 mg, quant.) as a yellow oil. R_f = 0.61 (cyclohexane/ethyl acetate, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (dd, $J_{H6,H5}$ = 2.8, $J_{H6,H3}$ = 1.5 Hz, 1 H,

H6), 7.94 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 7.84 (d, $J_{H5,H6}$ = 2.8 Hz, 1 H, H5), 5.86 (ddd, $J_{H,F}$ = 56.9, $J_{H,F}$ = 55.6 Hz, $J_{CHF2,CH}$ = 2.0 Hz, $J_{CHF2,NH}$ = 1.3 Hz, 1 H, CHF_2), 4.56 (d, $J_{NH,CH}$ = 8.9 Hz, 1 H, NH), 4.48–4.30 (m, 1 H, CH), 1.90–1.77 (m, 2 H, CH_2), 1.62–1.24 (m, 4 H, 2 × CH_2), 0.89 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –126.96 (ddd, $J_{F,F}$ = 281.2, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 10.6 Hz, CHF_2), –130.63 (ddt, $J_{F,F}$ = 281.1, $J_{F,H}$ = 56.9 Hz, $J_{CHF2,CH}$ = 17.4 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.14 (C2), 141.78 (C6), 133.69 (C5), 132.93 (C3), 115.43 (t, $J_{C,F}$ = 244.8 Hz, CHF_2), 51.93 (dd, $J_{C,F}$ = 24.1, $J_{C,F}$ = 21.0 Hz, CH), 27.82 (CH_2), 27.45 (CH_2), 22.59 (CH_2), 13.97 (CH_3) ppm. HRMS (ESI^+): *m/z* calcd. for $C_{10}H_{16}F_2N_3^+$ $[M + H]^+$ 216.1307; found 216.1307. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 14.57 min, λ = 214 nm.

***N*-(1,1-Difluorohexan-2-yl)-3,5-bis(trifluoromethyl)aniline (3 g):** In accordance with **TP5**, hemiaminal ether **1f** (100 mg, 0.30 mmol) was treated with *n*BuMgBr (2.0 M in Et_2O, 0.33 mL, 0.65 mmol) in dry THF (5 mL) for 2 h at 0 °C. Desired amine **3g** (100 mg, 96 %) was isolated after workup as an orange liquid without further purification. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.20 (s, 1 H, H4), 7.00 (s, 2 H, H2, H6), 5.79 (td, $J_{H,F}$ = 55.7, $J_{CHF2,CH}$ = 2.5 Hz, 1 H, CHF_2), 3.99 (d, $J_{NH,CH}$ = 9.3 Hz, 1 H, NH), 3.78–3.66 (m, 1 H, CH), 1.86–1.77 (m, 1 H, CH_2), 1.58–1.46 (m, 2 H, CH_2), 1.43–1.30 (m, 3 H, CH_2), 0.96–0.89 (m, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.33 (2 × CF_3), –126.33 (ddd, $J_{F,F}$ = 282.7, $J_{F,H}$ = 55.8 Hz, $J_{CHF2,CH}$ = 12.3 Hz, CHF_2), –128.03 (ddd, $J_{F,F}$ = 282.7, $J_{F,H}$ = 55.7 Hz, $J_{CHF2,CH}$ = 12.3 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 148.08 (C1), 132.83 (q, $J_{C,F}$ = 32.9 Hz, C3, C5), 123.56 (q, $J_{C,F}$ = 272.6 Hz, 2 × CF_3), 115.80 (t, $J_{C,F}$ = 245.7 Hz, CHF_2), 112.40 (m, C2, C6), 111.35 (C4), 55.12 (t, $J_{C,F}$ = 21.8 Hz, CH), 28.76 (CH_2), 27.86 (CH_2), 22.65 (CH_2), 13.94 (CH_3) ppm. HRMS (ESI^-): *m/z* calcd. for $C_{14}H_{14}F_8N^-$ $[M - H]^-$ 348.1004; found 348.1010. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 21.70 min, λ = 214 nm.

***N*-(1,1-Difluoro-1-phenylethyl)-2,3,4,5,6-pentafluoroaniline (3h):** In accordance with **TP5**, hemiaminal ether **1g** (91 mg, 0.31 mmol) was treated with PhMgBr (3 M in Et_2O, 0.23 mL, 0.69 mmol) in dry THF (5 mL) for 4 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/NEt_3, 100:1) to give desired amine **3h** (51 mg, 50 %) as a yellow oil. R_f = 0.56 (cyclohexane/ethyl acetate, 7:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.31 (m, 5 H, 5 × H_{Phenyl}), 6.07 (ddd, $J_{H,F}$ = 55.8, $J_{H,F}$ = 55.0 Hz, $J_{CHF2,CH}$ = 2.3 Hz, 1 H, CHF_2), 4.96 (tdd, $J_{CH,F}$ = 13.5, $J_{CH,NH}$ = 10.6 Hz, $J_{CH,CHF2}$ = 2.2 Hz, 1 H, CH), 4.33 (d, $J_{NH,CH}$ = 10.5 Hz, 1 H, NH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –125.23 (ddd, $J_{F,F}$ = 282.4, $J_{F,H}$ = 55.9 Hz, $J_{CHF2,CH}$ = 14.0 Hz, CHF_2), –129.32 (ddt, $J_{F,F}$ = 282.2, $J_{F,H}$ = 55.0 Hz, $J_{CHF2,CH}$ = 13.6 Hz, CHF_2), –157.21 (dd, $J_{F2,F3}$ = $J_{F6,F5}$ = 21.0, $J_{F2,F4}$ = $J_{F6,F4}$ = 4.0 Hz, F2, F6), –163.40 (td, $J_{F5,F4}$ = $J_{F5,F6}$ = $J_{F3,F2}$ = $J_{F3,F4}$ = 21.6, $J_{F5,F3}$ = $J_{F3,F5}$ = 4.4 Hz, 2 F, F3, F5), –168.14 (td, $J_{F4,F3}$ = $J_{F4,F5}$ = 21.9, J = 4.8 Hz, F4) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.06–137.38 (m), 139.48–136.64 (m), 136.26–133.48 (m), 134.41 ($C1_{Phenyl}$), 129.08 (C_{Phenyl}), 129.02 (C_{Phenyl}), 127.48 (C_{Phenyl}), 121.68–121.40 (m, C_{Phenyl}), 115.22 (dd, $J_{C,F}$ = 248.1, $J_{C,F}$ = 246.1 Hz, CHF_2), 61.17 (tt, $J_{C,F}$ = 21.5, $J_{C,F}$ = 4.1 Hz, CH) ppm. HRMS (ESI^-): *m/z* calcd. for $C_{14}H_7F_7N^-$ $[M - H]^-$ 322.0472; found 322.0474. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 19.82 min, λ = 214 nm.

***N*-(1,1-Difluoro-1-phenylethyl)pyridine-2-amine (3i):** In accordance with **TP5**, hemiaminal ether **1b** (100 mg, 0.49 mmol) was treated with PhMgBr (3 M in Et_2O, 0.36 mL, 1.07 mmol) in dry THF (5 mL) for 2 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 100:10:1) to give desired amine **3i** (118 mg, quant.) as a colorless oil. R_f = 0.83 (cyclohexane/ethyl acetate, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10 (ddd, $J_{H6,H5}$ = 5.0, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.47–7.43 (m, 2 H, 2 × H_{Phenyl}), 7.43–7.32 (m, 4 H, 3 × H_{Phenyl}, H4), 6.63 (ddd, $J_{H5,H4}$ = 7.1, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.43 (dt, $J_{H3,H4}$ = 8.4, $J_{H3,H6}$ = $J_{H3,H5}$ = 1.0 Hz, 1 H, H3), 6.12 (td, $J_{H,F}$ = 55.9, $J_{CHF2,CH}$ = 2.4 Hz, 1 H, CHF_2), 5.48–5.33 (m, 1 H, CH), 5.07 (d, $J_{NH,CH}$ = 7.9 Hz, 1 H, NH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –126.42 (ddd, $J_{F,H}$ = 56.0, $J_{F,H}$ = 33.8 Hz, $J_{CHF2,CH}$ = 14.7 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.13 (C2), 148.17 (C6), 137.66 (C4), 135.43 ($C1_{Phenyl}$), 128.91 (C_{Phenyl}), 128.61 (C_{Phenyl}), 128.06 (C_{Phenyl}), 115.51 (t, $J_{C,F}$ = 246.6 Hz, CHF_2), 114.34 (C5) 108.43 (C3), 57.15 (t, $J_{C,F}$ = 22.1 Hz, CH) ppm. HRMS (ESI^+): *m/z* calcd. for $C_{13}H_{13}F_2N_2^+$ $[M + H]^+$ 235.1041; found 235.1041. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 8.77 min, λ = 214 nm.

***N*-(1,1-difluoro-1-phenylethyl)pyrazin-2-amine (3j):** In accordance with **TP5**, hemiaminal ether **1d** (100 mg, 0.49 mmol) was treated with PhMgBr (3 M in Et_2O, 0.39 mL, 1.08 mmol) in dry THF (5 mL) for 1.5 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 100:6:1 → 100:25:1) to give desired slightly impure amine **3j** (145 mg, quant.). A fraction of the product was further purified by preparative HPLC [0.1 % TFA; 0 min: 4 % MeCN (B) → 30 min: 100 % B, flow: 20 mL/min, t_R = 19.37 min] to give desired amine **3j** as a colorless oil. R_f = 0.55 (cyclohexane/ethyl acetate, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (dd, $J_{H6,H5}$ = 2.8, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.98 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 7.86 (d, $J_{H5,H6}$ = 2.7 Hz, 1 H, H5), 7.45–7.33 (m, 5 H, 5 × H_{Phenyl}), 6.11 (ddd, $J_{H,F}$ = 56.0, $J_{H,F}$ = 55.2 Hz, $J_{CHF2,CH}$ = 2.3 Hz, 1 H, CHF_2), 5.52–5.42 (m, 1 H, CH), 5.35 (d, $J_{NH,CH}$ = 8.2 Hz, 1 H, NH) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –125.38 (ddd, $J_{F,F}$ = 280.3, $J_{F,H}$ = 56.1 Hz, $J_{CHF2,CH}$ = 15.3 Hz, CHF_2), –127.47 (ddd, $J_{F,F}$ = 280.3, $J_{F,H}$ = 55.2 Hz, $J_{CHF2,CH}$ = 13.7 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.21 (C2), 141.73 (C6), 134.68 ($C1_{Phenyl}$) 134.12 (C5), 132.90 (C3), 128.90 (C_{Phenyl}), 128.72 (C_{Phenyl}), 127.80 (C_{Phenyl}), 115.08 (t, $J_{C,F}$ = 246.2 Hz, CHF_2), 56.35 (dd, $J_{C,F}$ = 22.6, $J_{C,F}$ = 21.3 Hz, CH) ppm. HRMS (ESI^+): *m/z* calcd. for $C_{12}H_{12}F_2N_3^+$ $[M + H]^+$ 236.0994; found 236.0994. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 13.59 min, λ = 214 nm.

4-[2,2-Difluoro-1-(pyridin-2-ylamino)ethyl]benzonitrile (3k): (4-Cyanophenyl)magnesium chloride was prepared from 4-bromobenzonitrile (82 mg, 0.45 mmol) and *i*PrMgCl•LiCl (1.25 M in THF, 0.36 mL, 0.45 mmol) in accordance with **TP3** within 3 h at 0 °C. In accordance with **TP4**, a solution of *N*-(1-ethoxy-2,2-difluoroethyl)pyridine-2-amine **1b** (76 mg, 0.38 mmol) in dry THF (5 mL) was treated with LiHMDS (1 M in THF, 0.38 mL, 0.38 mmol) at –78 °C. The Grignard reagent was added after 15 min and the reaction mixture was stirred at –30 °C for 4 h. After workup and flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate, 20:1 → 5:1) desired amine **3k** (60 mg, 56 %) was furnished as a light yellow oil. R_f = 0.47 (cyclohexane/ethyl acetate, 2:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, $J_{H6',H5'}$ = 5.1 Hz, 1 H, H6'), 7.74–7.63 (d, $J_{H3,H2}$ = $J_{H5,H6}$ = 8.4 Hz, 2 H, H3, H5), 7.58 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 7.9 Hz, 2 H, H2, H6), 7.48–7.38 (t, $J_{H4',H3'}$ = $J_{H4',H5'}$ = 7.7 Hz, 1 H, H4'), 6.66 (dd, $J_{H5',H4'}$ = 7.2, $J_{H5',H6'}$ = 5.2 Hz, 1 H, H5'), 6.48 (d, $J_{H3',H4'}$ = 8.3 Hz, 1 H, H3'), 6.12 (td, $J_{H,F}$ = 55.7, $J_{CHF2,CH}$ = 2.4 Hz, 1 H, CHF_2), 5.67–5.48 (m, 1 H, CH), 5.11 (d, $J_{NH,CH}$ = 8.2 Hz, 1 H, NH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –124.67 (ddd, $J_{F,F}$ = 282.9, $J_{F,H}$ = 55.1 Hz, $J_{CHF2,CH}$ = 11.2 Hz, CHF_2), –127.41 (ddd, $J_{F,F}$ = 282.8, $J_{F,H}$ = 56.2 Hz, $J_{CHF2,CH}$ = 18.2 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 156.39 (C2'), 148.05 (C6'), 140.97 (C1), 137.85 (C4'), 132.54 (C3, C5), 129.00 (C2, C6), 118.60 (CN), 114.96 (t, $J_{C,F}$ = 247.0 Hz, CHF_2), 114.85 (C5'), 112.51 (C4), 108.86 (C3'), 56.61 (dd, $J_{C,F}$ = 23.7, $J_{C,F}$ = 21.1 Hz, CH) ppm. HRMS (ESI^+): *m/z* calcd. for $C_{14}H_{12}F_2N_3^+$ $[M + H]^+$

260.0994; found 260.0996. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.56 min, λ = 214 nm.

***N*-[2,2-Difluoro-1-(pyridin-2-yl)ethyl]pyridin-2-amine (3l):** Pyridin-2-ylmagnesium chloride was prepared from 2-bromopyridine (43 μL, 0.45 mmol) and *i*PrMgCl·LiCl (1.25 M in THF, 0.36 mL, 0.45 mmol) in accordance with **TP3** within 2 h at 0 °C. In accordance with **TP4**, a solution of *N*-(1-ethoxy-2,2-difluoroethyl)pyridine-2-amine (**1b**; 76 mg, 0.38 mmol) in dry THF (5 mL) was treated with LiHMDS (1 M in THF, 0.38 mL, 0.38 mmol) at –78 °C. The Grignard reagent was added after 15 min and the reaction mixture was stirred at –30 °C for 4 h. After workup and flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate, 10:1 → 5:1) desired amine **3l** (39 mg, 44 %) was furnished as a light yellow oil. R_f = 0.26 (cyclohexane/ethyl acetate, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, $J_{H6',H5'}$ = 4.7 Hz, 1 H, H6′), 8.04 (d, $J_{H6,H5}$ = 4.9 Hz, 1 H, H6), 7.63 (td, $J_{H4',H3'}$ = $J_{H4',H5'}$ = 7.7, $J_{H4',H6'}$ = 1.7 Hz, 1 H, H4′), 7.35 (m, 2 H, H4, H3′), 7.24–7.19 (m, 1 H, H5′), 6.56 (dd, $J_{H5,H4}$ = 7.1, $J_{H5,H6}$ = 5.1 Hz, 1 H, H5), 6.51 (d, $J_{H3,H4}$ = 8.3 Hz, 1 H, H3), 6.34–6.00 (m, 1 H, CHF_2), 5.96 (d, $J_{NH,CH}$ = 7.3 Hz, 1 H, NH), 5.61–5.48 (m, 1 H, CH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –124.85 (ddd, $J_{F,F}$ = 278.5, $J_{F,H}$ = 55.5 Hz, $J_{CHF2,CH}$ = 9.6 Hz, CHF_2), –129.09 (ddd, $J_{F,F}$ = 278.6, $J_{F,H}$ = 56.6 Hz, $J_{CHF2,CH}$ = 17.3 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 157.24 (C2), 153.85 (C2′), 149.31 (C6′), 147.96 (C6), 137.54 (C4), 136.76 (C4′), 123.86 (C3′), 123.41 (C5′), 115.43 (t, $J_{C,F}$ = 246.8 Hz, CHF_2), 114.03 (C5), 109.28 (C3), 56.93 (dd, $J_{C,F}$ = 24.1, $J_{C,F}$ = 22.7 Hz, CH) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{12}H_{12}F_2N_3^+$ [M + H]$^+$ 236.0994; found 236.0997. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 7.48 min, λ = 214 nm.

***N*-[1-(2,4-Dimethoxypyrimidin-5-yl)-2,2-difluoroethyl]pyridin-2-amine (3m):** (2,4-Dimethoxypyrimidin-5-yl)magnesium chloride was prepared from 5-bromo-2,4-dimethoxypyrimidine (99 mg, 0.45 mmol) and *i*PrMgCl·LiCl (1.25 M in THF, 0.36 mL, 0.45 mmol) in accordance with **TP3** within 3 h at 0 °C. In accordance with **TP4**, a solution of *N*-(1-ethoxy-2,2-difluoroethyl)pyridine-2-amine (**1b**; 76 mg, 0.38 mmol) in dry THF (5 mL) was treated with LiHMDS (1 M in THF, 0.38 mL, 0.38 mmol) at –78 °C. The Grignard reagent was added after 15 min and the solution was stirred at –30 °C for 4 h. After workup and flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate, 10:1 → 5:1) desired amine **3m** (85 mg, 75 %) was furnished as a light yellow oil. R_f = 0.36 (cyclohexane/ethyl acetate, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (s, 1 H, H6′), 8.11–8.03 (d, $J_{H6,H5}$ = 4.0 Hz, 1 H, H6), 7.39 (ddd, $J_{H4,H3}$ = 8.6, $J_{H4,H5}$ = 7.2 Hz, J = 1.9 Hz, 1 H, H4), 6.61 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.0 Hz, J = 0.9 Hz, 1 H, H5), 6.46 (dt, $J_{H3,H4}$ = 8.3, J = 1.0 Hz, 1 H, H3), 6.09 (td, $J_{H,F}$ = 56.1, $J_{CHF2,CH}$ = 3.1 Hz, 1 H, CHF_2), 5.68–5.52 (m, 1 H, CH), 5.26 (d, $J_{NH,CH}$ = 9.1 Hz, 1 H, NH), 4.04 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –125.00 (ddd, $J_{F,F}$ = 279.0, $J_{F,H}$ = 56.1 Hz, $J_{CHF2,CH}$ = 13.8 Hz, CHF_2), –126.88 (ddd, $J_{F,F}$ = 279.0, $J_{F,H}$ = 56.0 Hz, $J_{CHF2,CH}$ = 13.8 Hz, CHF_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.13 (C4′), 165.33 (C2′), 158.45 (C6′), 156.70 (C2), 148.01 (C6), 137.65 (C4), 114.47 (t, $J_{C,F}$ = 246.0 Hz, CHF_2), 114.40 (C5), 109.28 (C5′), 108.63 (C3), 55.02 (OCH_3), 54.42 (OCH_3), 51.16 (t, $J_{C,F}$ = 23.6 Hz, CH) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{13}H_{15}F_2N_4O_2^+$ [M + H]$^+$ 297.1158; found 297.1160. HPLC (0.1 % TFA; 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 8.61 min, λ = 214 nm.

***N*-Butyl-2,2,2-trifluoro-*N*′-phenylethan-1,1-diamine (4a):** In a dry, argon-flushed Schlenk-flask *n*BuLi (2.48 M in hexane, 0.36 mL, 0.90 mmol) was slowly added to a solution of *n*-butylamine (0.10 mL, 0.90 mmol) in dry *n*-hexane (3 mL) at 0 °C. The suspension was stirred at 0 °C for 30 min. A solution of *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine (**1a**; 100 mg, 0.45 mmol) in dry THF (3 mL) was added to the reaction mixture. After stirring the reaction mixture for 2 h, the reaction was quenched with satd. NH_4Cl solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3, 100:20:1 → 100:50:1) furnished desired diamine **4a** (84 mg, 75 %) as a light yellow oil. R_f = 0.56(cyclohexane/ethyl acetate/NEt_3, 2:1:0.05). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.13–8.08 (d, $J_{H6,H5}$ = 5.0 Hz, 1 H, H6), 7.45 (dddd, $J_{H4,H3}$ = 8.2, $J_{H4,H5}$ = 7.2 Hz, J = 1.9 Hz, J = 1.0 Hz, 1 H, H4), 6.68 (ddt, $J_{H5,H4}$ = 7.0, $J_{H5,H6}$ = 4.9 Hz, J = 0.9 Hz, 1 H, H5), 6.47 (dt, $J_{H3,H4}$ = 8.4, J = 1.0 Hz, 1 H, H3), 5.49 (m, 1 H, CH), 4.57 (d, $J_{NH,CH}$ = 9.4 Hz, 1 H, NH), 2.72 (m, 2 H, CH_2), 1.53–1.40 (m, 2 H, CH_2), 1.37–1.24 (m, 2 H, CH_2), 0.88 (td, $J_{CH3,CH2}$ = 7.3, J = 1.1 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –78.80 (d, $J_{CF3,CH}$ = 6.1 Hz, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 156.90 (C2), 148.04 (C6), 137.81 (C4), 124.61 (q, $J_{C,F}$ = 282.6 Hz, CF_3), 114.76 (C5), 108.54 (C3), 65.57 (q, $J_{C,F}$ = 31.4 Hz, $CHCF_3$), 45.29 (CH_2), 32.21 (CH_2), 20.33 (CH_2), 14.00 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{11}H_{18}F_3N_3^+$ [M + H]$^+$ 248.1369; found 248.1368. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 3.82 min, λ = 214 nm.

2,2,2-Trifluoro-*N*-(4-methylbenzyl)-*N*′-(pyridin-4-yl)ethane-1,1-diamine (4b): In a dry, argon-flushed Schlenk-flask *n*BuLi (1.7 M in hexane, 0.53 mL, 0.90 mmol) was slowly added to a solution of 4-methylbenzylamine (0.12 mL, 0.90 mmol) in dry *n*-hexane (4 mL) at 0 °C. The white suspension was stirred at 0 °C for 3 h. A solution of *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-4-amine (**1h**; 100 mg, 0.45 mmol) in dry THF (2 mL) was added to the reaction mixture. After stirring the reaction mixture for 2 h at 0 °C, the solution was quenched with satd. NH_4Cl solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. Purification by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate, 10:1 → 5:1) furnished desired diamine **4b** (116 mg, 87 %) as a light yellow oil. R_f = 0.12 (ethyl acetate/MeOH, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 5.5 Hz, 2 H, H2, H6), 7.13 (m, 4 H, H2′, H3′, H5′, H6′), 6.47–6.39 (m, 2 H, H3, H5), 4.67 (dq, $J_{CH,NH}$ = 10.0, $J_{CH,CF3}$ = 5.1 Hz, 1 H, CH), 4.29 (d, $J_{NH,CH}$ = 9.3 Hz, 1 H, NH), 3.98–3.78 (m, 2 H, CH_2), 2.35 (s, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –78.91 (d, $J_{CF3,CH}$ = 5.1 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.39 (C4), 150.37 (C2, C6), 137.48 (C4′), 134.97 (C1′), 129.40 (C3′, C5′), 128.19 (C2′, C6′), 108.40 (C3, C5), 66.22 (q, $J_{C,F}$ = 32.1 Hz, $CHCF_3$), 48.92 (CH_2), 21.11 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{15}H_{17}F_3N_3^+$ [M + H]$^+$ 296.1369; found 296.13696.

***N*-[2,2,2-Trifluoro-1-(pyridin-2-ylamino)ethyl]benzimidamide (4c):** A dry microwave vial equipped with a magnetic stirrer was charged with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine (**1a**; 50 mg, 0.23 mmol) and benzamidine (27 mg, 0.23 mmol) in toluene (2 mL). The reaction mixture was stirred at 160 °C in a CEM microwave reactor that operated at 200 W (maximum power) for 1 h. After removal of the solvent under reduced pressure, purification by flash column chromatography (SiO_2, cyclohexane/ethyl acetate, 4:1 → 1:1) afforded desired product **4c** (58 mg, 86 %) as a white solid. R_f = 0.18 (cyclohexane/ethyl acetate, 4:1), m.p. 99 – 105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (dd, $J_{H6',H5'}$ = 5.2, $J_{H6',H4'}$ = 1.8 Hz, 1 H, H6′), 7.75 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 7.4 Hz,. 2 H, H2, H6), 7.48–7.31 (m, 4 H, H4′, H3, H4, H5), 6.68 (ddd, $J_{H5',H4'}$ = 7.2, $J_{H5',H6'}$ = 5.1 Hz, $J_{H5',H3'}$ = 1.0 Hz, 1 H, H5′), 6.49 (d, $J_{H3',H4'}$ = 8.3 Hz, 1 H, H3′), 6.20 (s, 2 H, NH) 6.12 (dq, $J_{CH,NH}$ = 10.0, $J_{CH,CF3}$ = 6.2 Hz, 1 H, CH), 5.05 (d, $J_{NH,CH}$ = 10.0 Hz, 1 H, NH) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –79.59 (d, $J_{CF3,CH}$ = 6.2 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 160.68 (C=NH), 156.73 (C2′), 147.24 (C6′), 138.28 (C4′), 136.54 (C1), 130.69 (C4), 128.59 (C3, C5), 127.07 (C2, C6), 124.79 (q, $J_{C,F}$ =

280.8 Hz, CF_3), 114.64 (C5′), 110.06 (C3′), 63.82 (q, $J_{C,F}$ = 31.9 Hz, $CHCF_3$) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{14}F_3N_4^+$ [M + H]$^+$ 295.1165; found 295.11646. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 9.78 min, λ = 214 nm.

***N*-(2,2,2-Trifluoro-1-methoxyethyl)pyridin-2-amine (4d):** In a dry, argon-flushed Schlenk-flask *n*BuLi (2.48 M in hexane, 2.00 mL, 5.00 mmol) was slowly added to a solution of MeOH (0.20 mL, 5.00 mmol) in dry *n*-hexane (5 mL) at 0 °C. The suspension was stirred at 0 °C for 1 h. *N*-(1-Ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine (**1a**; 220 mg, 1.00 mmol) was added and the reaction mixture was warmed to room temperature. After stirring the reaction mixture for 48 h the solvent was evaporated in vacuo. Purification by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate, 10:1 → 2:1) furnished desired hemiaminal ether **4d** (100 mg, 49 %) as a yellow solid. R_f = 0.51 (cyclohexane/ethyl acetate/NEt_3, 2:1:0.05), m.p. 63–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, $J_{H6,H5}$ = 5.1 Hz, 1 H, H6), 7.55–7.46 (m, 1 H, H4), 6.76 (ddd, $J_{H5,H4}$ = 7.3, $J_{H5,H6}$ = 5.1 Hz, J = 0.9 Hz, 1 H, H5), 6.59–6.51 (m, 1 H, H3), 5.87 (dq, $J_{CH,NH}$ = 10.1, $J_{CH,CF3}$ = 5.0 Hz, 1 H, CH), 5.08 (d, $J_{NH,CH}$ = 7.6 Hz, 1 H, NH), 3.52 (s, 3 H, OCH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –80.37 (d, $J_{CF3,CH}$ = 5.0 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.14 (C2), 147.91 (C6), 138.34 (C4), 123.06 (q, $J_{C,F}$ = 282.5 Hz, CF_3), 115.76 (C5), 109.18 (C3), 79.97 (q, $J_{C,F}$ = 33.9 Hz, $CHCF_3$), 56.85 (OCH_3) ppm. HRMS (EI): *m/z* calcd. for $C_8H_9F_3N_2O^*$ [M*] 206.0667; found 206.0661. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 8.25 min, λ = 214 nm.

***N*-[1-(Ethylthio)-2,2,2-trifluoroethyl]pyridin-2-amine (4e):** In a dry, argon-flushed Schlenk-flask *n*BuLi (1.7 M in hexane, 1.32 mL, 2.25 mmol) was slowly added to a solution of EtSH (0.17 mL, 2.25 mmol) in dry *n*-hexane (6 mL) at 0 °C. The white suspension was stirred at 0 °C for 1 h. *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine (**1a**; 100 mg, 0.45 mmol) was added to the reaction mixture and the reaction was warmed to room temperature. After stirring for 3 d, the reaction was quenched with satd. NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered, and the solvent was evaporated in vacuo. Desired product **4e** (160 mg, quant.) was obtained as a light yellow solid without further purification. R_f = 0.60 (cyclohexane/ethyl acetate, 3:1), m.p. 54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (ddd, $J_{H6,H5}$ = 5.0, $J_{H6,H4}$ = 1.9 Hz, J = 0.9 Hz, 1 H, H6), 7.47 (ddd, $J_{H4,H3}$ = 8.3, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.72 (ddd, $J_{H5,H4}$ = 7.2, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.3, J = 0.9 Hz, 1 H, H3), 6.03 (dq, $J_{CH,NH}$ = 10.3, $J_{CH,CF3}$ = 7.4 Hz, 1 H, CH), 4.63 (d, $J_{NH,CH}$ = 10.4 Hz, 1 H, NH), 2.74 (tdd, $J_{CH2,CH3}$ = 7.7, $J_{CH2,CH3}$ = 6.9, J = 1.7 Hz, 2 H, CH_2), 1.29 (t, $J_{CH3,CH2}$ = 7.4 Hz, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.24 (d, $J_{CF3,CH}$ = 7.5 Hz, CF_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.62 (C2), 148.04 (C6), 137.94 (C4), 115.37 (C5), 109.22 (C3), 56.55 (q, $J_{C,F}$ = 33.0 Hz, $CHCF_3$), 25.38 (CH_2), 14.97 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_9H_{12}F_3N_2S^+$ [M + H]$^+$ 237.0668; found 237.06672. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 10.33 min, λ = 214 nm.

***N*-(1-{6-[3,4-Dihydroisoquinolin-2(1*H*)-yl]pyridin-3-yl}-2,2,2-trifluoroethyl)-6-methylpyridin-2-amine (5):** *N*-[1-(6-Chloropyridin-3-yl)-2,2,2-trifluoroethyl]-6-methylpyridin-2-amine (**2i**; 1.01 g, 3.35 mmol) and tetrahydroisoquinoline (1.76 g, 13.2 mol) were heated to reflux in 2-propanol (40 mL) for 48 h. After removal of the solvent the crude product was purified by preparative HPLC [0 min: 4 % MeCN (B) → 30 min: 100 % B, flow: 20 mL/min, t_R = 26.28 min] to give desired DIMN bioisostere **5** (438 mg, 33 %) as a colorless oil. R_f = 0.35 (cyclohexane/ethyl acetate/NEt_3, 4:1:0.1). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.29 (d, $J_{H2'',H4''}$ = 2.4 Hz, 1 H, H2″), 7.59 (dd, $J_{H4'',H5''}$ = 8.9, $J_{H4'',H2''}$ = 2.3 Hz, 1 H, H4″), 7.31 (t, $J_{H4,H3,H5}$ = 7.7 Hz, 1 H, H4), 7.22–7.14 (m, 4 H, H5′, H6′, H7′, H8′), 6.66 (d, $J_{H5'',H4''}$ = 8.9 Hz, 1 H, H5″), 6.52 (d, $J_{H5,H4}$ = 7.3 Hz, 1 H, H5), 6.25 (d, $J_{H3,H4}$ = 8.3 Hz, 1 H, H3), 5.59 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.1 Hz, 1 H, CH), 5.12 (s, 1 H, NH), 4.70 (s, 2 H, 2 × H1′), 3.84 (t, $J_{H3',H4'}$ = 5.9 Hz, 2 H, 2 × H3′), 2.96 (t, $J_{H4',H3'}$ = 6.0 Hz, 2 H, 2 × H4′), 2.38 (s, 3 H, CH_3) ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –74.15 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 158.82 (C6″), 157.02 (C6), 155.82 (C2), 148.12 (C2″), 138.26 (C4), 136.71 (C4″), 135.43 (C5a′/C8a′), 134.21 (C5a′/C8a′), 128.48 (C5′/C6′/C7′/C8′), 126.66 (C5′/C6′/C7′/C8′), 126.41 (C5′/C6′/C7′/C8′), 125.37 (q, $J_{C,F}$ = 281.6 Hz, CF_3), 118.23 (H3″), 114.06 (H5), 106.49 (H5″), 104.85 (H3), 54.83 (q, $J_{C,F}$ = 30.9 Hz, $CHCF_3$), 47.15 (C1′), 42.59 (C3′), 29.10 (C4′), 24.30 (CH_3) ppm. HRMS (ESI$^+$): *m/z* calcd. for $C_{22}H_{22}F_3N_4^+$ [M + H]$^+$ 399.1791; found 399.1787. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 10.06 min, λ = 214 nm.

2-[(1-Ethoxy-2,2,2-trifluoroethyl)amino]benzonitrile (1i): In accordance with **TP2**, 2-aminobenzonitrile (2.00 g, 17.0 mmol), TFAE (2.58 mL, 22.0 mmol), and *p*TSA·H_2O (160 mg, 0.86 mmol) were solved in EtOH (20 mL) and the reaction mixture was heated to reflux for 6 h until no further conversion was observed. After removal of the solvent under reduced pressure, flash column chromatography (SiO_2, cyclohexane/ethyl acetate, 20:1) furnished hemiaminal ether **1i** (1.46 g, 35 %) as a colorless solid. R_f = 0.29 (cyclohexane/ethyl acetate, 10:1), m.p. 31 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.43 (m, 2 H, H4, H6), 6.90 (m, 2 H, H3, H6), 5.16–5.06 (m, 1 H, CH), 4.99 (d, $J_{NH,CH}$ = 9.5 Hz, 1 H, NH), 3.85–3.59 (m, 2 H, CH_2), 1.25 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.14 (d, $J_{CF3,CH}$ = 4.2 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.13 (C2), 134.53 (C4), 133.25 (C6), 122.60 (q, $J_{C,F}$ = 283.7 Hz, CF_3), 120.01 (C5), 116.90 (C≡N), 112.93 (C3), 98.68 (C1), 81.76 (q, $J_{C,F}$ = 34.4 Hz, $CHCF_3$), 64.93 (CH_2), 15.03 (CH_3) ppm. HRMS (ESI$^-$): *m/z* calcd. for $C_{11}H_{10}F_3N_2O^-$ [M – H]$^-$ 243.0751; found 243.07511. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 17.69 min, λ = 214 nm.

2-[(1-Ethoxy-2,2,2-trifluoroethyl)amino]benzothioamide (8): By following a literature procedure,[15] 2-[(1-ethoxy-2,2,2-trifluoroethyl)amino]benzonitrile (**1i**; 448 mg, 2.00 mmol), $MgCl_2$ (190 mg, 2.00 mmol), and NaHS·H_2O (296 mg, 4.00 mmol) were solved in dry dimethylformamide (DMF; 8 mL). The reaction mixture was stirred at room temperature for 1.5 h. After complete conversion, the reaction was quenched with distilled water and extracted with ethyl acetate (3 × 30 mL). The aqueous phase was acidified (pH 6.5) with an aqueous solution of HCl (1 N) and extracted with ethyl acetate (3 × 30 mL) again. The combined organic phases were dried with $MgSO_4$. After filtration and removal of the solvent desired thioamide **8** (570 mg, quant.) was obtained as a yellow oil without further purification. R_f = 0.34 (cyclohexane/ethyl acetate, 3:1). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 9.83 (d, J = 158.6 Hz, 2 H, NH_2), 7.71 (d, $J_{NH,CH}$ = 10.1 Hz, 1 H, NH), 7.30 (t, $J_{H4,H3}$ = $J_{H4,H5}$ = 7.8 Hz, 1 H, H4), 7.24 (d, $J_{H6,H5}$ = 7.7 Hz, 1 H, H6), 7.10 (d, $J_{H3,H4}$ = 8.3 Hz, 1 H, H3), 6.80 (t, $J_{H5,H4}$ = $J_{H5,H6}$ = 7.5 Hz, 1 H, H5), 5.73 (dq, $J_{CH,NH}$ = 10.0, $J_{CH,CF3}$ = 4.8 Hz, 1 H, CH), 3.78–3.55 (m, 2 H, CH_2), 1.11 (t, $J_{CH2,CH3}$ = 7.0 Hz, 3 H, CH_3) ppm. ^{19}F NMR (376 MHz, [D$_6$]DMSO): δ = –79.31 (d, $J_{CF3,CH}$ = 4.8 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 199.51 (C=S), 143.21 (C2), 131.09 (C4), 127.12 (C6), 126.49 (C1), 123.38 (q, $J_{C,F}$ = 283.8 Hz, CF_3), 118.20 (C5), 113.59 (C3), 80.12 (q, $J_{C,F}$ = 32.3 Hz, $CHCF_3$), 63.51 (CH_2), 15.08 (CH_3) ppm. HRMS (ESI$^-$): *m/z* calcd. for $C_{11}H_{12}F_3N_2OS^-$ [M – H]$^-$ 277.0628; found 277.06283. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 16.29 min, λ = 214 nm.

2-(Trifluoromethyl)-2,3-dihydroquinazoline-4(1*H*)-thione (7): 2-[(1-Ethoxy-2,2,2-trifluoroethyl)amino]benzothioamide (**8**; 40 mg,

0.14 mmol) was solved in dry THF (2 mL) with molecular sieves (4 Å) and cooled to 0 °C. KO*t*Bu (16 mg, 0.14 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. After complete conversion of the starting material, the reaction was quenched with distilled water, extracted with diethyl ether (3 × 20 mL) and dried with $MgSO_4$. After filtration and removal of the solvent desired dihydroquinazoline thione **7** (28 mg, 86 %) was furnished by crystallization from CH_2Cl_2/cyclohexane as yellow crystals. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.67 (d, $J_{NH,CH}$ = 5.0 Hz, 1 H, NH), 8.07 (dd, $J_{H5,H6}$ = 8.1, $J_{H5,H7}$ = 1.6 Hz, 1 H, H5), 7.81 (d, $J_{NH,CH}$ = 4.0 Hz, 1 H, NH), 7.33 (ddd, $J_{H7,H8}$ = 8.5, $J_{H7,H6}$ = 7.2 Hz, $J_{H7,H5}$ = 1.6 Hz, 1 H, H7), 6.82 (dd, $J_{H8,H7}$ = 8.2, $J_{H8,H6}$ = 1.1 Hz, 1 H, H8), 6.73 (ddd, $J_{H6,H5}$ = 8.1, $J_{H6,H7}$ = 7.2 Hz, $J_{H6,H8}$ = 1.1 Hz, 1 H, H6), 5.43 (dt, $J_{CH,CF3}$ = 6.7, $J_{CH,NH}$ = 4.7 Hz, 1 H, CH) ppm. ^{19}F NMR (376 MHz, [D$_6$]DMSO): δ = –80.74 (d, $J_{CF3,CH}$ = 6.6 Hz, CF_3) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO): δ = 190.73 (C=S), 141.12 (C8a), 134.53 (C7), 131.24 (C5), 123.33 (q, $J_{C,F}$ = 291.7 Hz, CF_3), 118.77 (C4a), 118.02 (C6), 114.51 (C8), 61.55 (q, $J_{C,F}$ = 33.4 Hz, *C*HCF$_3$) ppm. HRMS (ESI$^+$): *m*/*z* calcd. for $C_9H_8F_3N_2S^+$ [M + H]$^+$ 233.0355; found 233.03556. HPLC (0.1 % TFA, 0 min: 4 % B → 15 min: 100 % B, flow: 1 mL/min): t_R = 14.43 min, λ = 214 nm.

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Keywords: Synthetic methods · Medicinal chemistry · Grignard reaction · Amines · Fluorine

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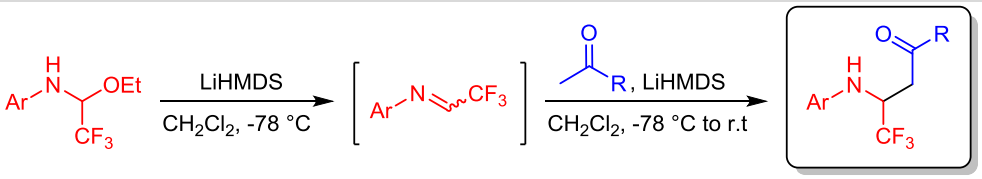
3. One-Pot Synthesis of Functionalized β-Fluoroalkylated Mannich-Type Products from *N*-Aryl *N*,*O*-Acetals

S. Wunder, A. Deutsch, C. Deutsch* and A. Hoffmann-Röder*, *Synthesis* **2016**, *48*, A–J.



24 examples, up to 92% yield

Declaration of Contribution

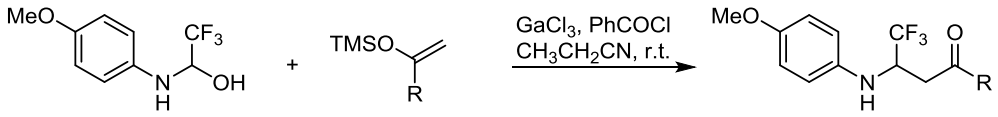
Based on our synthesis of trifluoroethylamines starting from *N*-aryl *N*,*O*-acetals and *Grignard* reagents and literature reports, *Swetlana Wunder* developed and optimized a protocol toward a one-pot synthesis of β-amino-β-fluoroalkyl carbonyl compounds during her internship at *Merck KGaA* (Darmstadt). We then studied the scope of this method using acetophenone and a variety of fluorinated *N*,*O*-acetals together. Therefore, I synthesized fluoroalkylated *N*,*O*-acetals and subsequently converted these substrates into the corresponding fluorinated carbonyl compounds using benzophenone. Furthermore, *Swetlana Wunder* extended the method to other *C*-nucleophiles to access a larger number of *Mannich*-type products for possible pharmaceutical applications.

Background

After the successful application of our developed method for the synthesis of functionalized di- and trifluoroethylamines, we aimed at extending the scope of nucleophiles suitable for addition reactions to trifluoromethylated *N*,*O*-acetals. As *Mannich*-type reactions are particularly significant carbon-carbon bond-forming processes allowing access to a wide range of potential pharmacophores, we focused our attention on developing a procedure to react trifluoromethylated *N*,*O*-acetals as imine precursors under *Mannich*-type conditions. The application of trifluoromethylated imines in *Mannich*-type reactions facilitates the synthesis of fluorinated β-amino carbonyl precursors of trifluoromethylated peptidic building blocks.

In 2000, *Akiyama* and co-workers reported the conversion of silyl enol ethers with trifluoromethylated *N*,*O*-hemiacetals in the presence of $GaCl_3$ and benzoyl chloride (Scheme 13). Under these conditions smooth formation of the corresponding *α*-amino-*α*-trifluoromethyl carbonyl compounds was observed. However, the trifluoromethylated substrates were restricted to *N*-protected *N*,*O*-hemiacetals, requiring subsequent deprotection of the *para*-methoxyphenyl (PMP) moiety under oxidative reaction conditions, which restricts the application of this useful method.[170]

Mannich-type reaction of N,O-hemiacetals and silyl enolates:

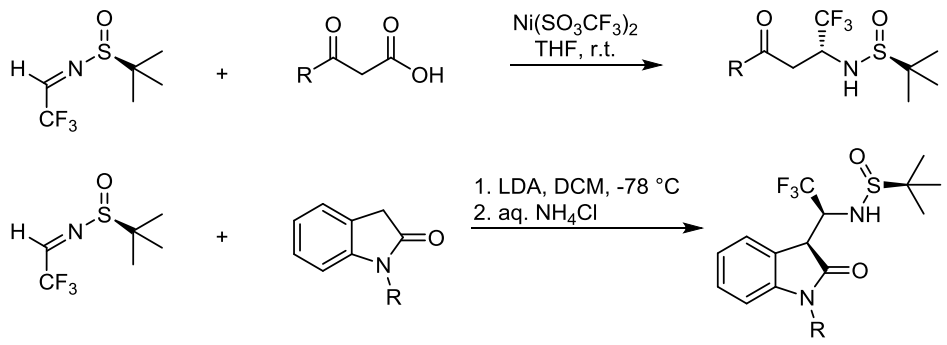


Takaya et al., 2000.

Scheme 13. Synthesis of *α*-amino-*α*-trifluoromethyl carbonyl compounds from *N*,*O*-hemiacetals and silyl enol ethers.[170]

Sonoshonok and co-workers also contributed to this field by describing various reactions of (S)-*N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimines with *β*-keto-acids, imines, indoles and other carbon nucleophiles to synthesize fluoromethylated scaffolds (Scheme 14).[171-180] Among those examples chiral imines were converted into *β*-trifluoromethyl-*β*-amino ketones by application of an asymmetric Ni-catalyzed decarboxylative *Mannich*-reaction.[178] Moreover, imines were reacted with enolates derived from various substituted indolin-2-ones furnishing the corresponding trifluoromethylated heterocyclic structures with three chiral centers.[173] Despite a pleasingly broad substrate scope regarding the carbon nucleophiles applicable to this reaction, the use of the expensive *Ellman´*s auxiliary is mandatory.

Mannich-type reaction of (S)-N-tert-butylsulfinyl-3,3,3-trifluoroacetaldimines:



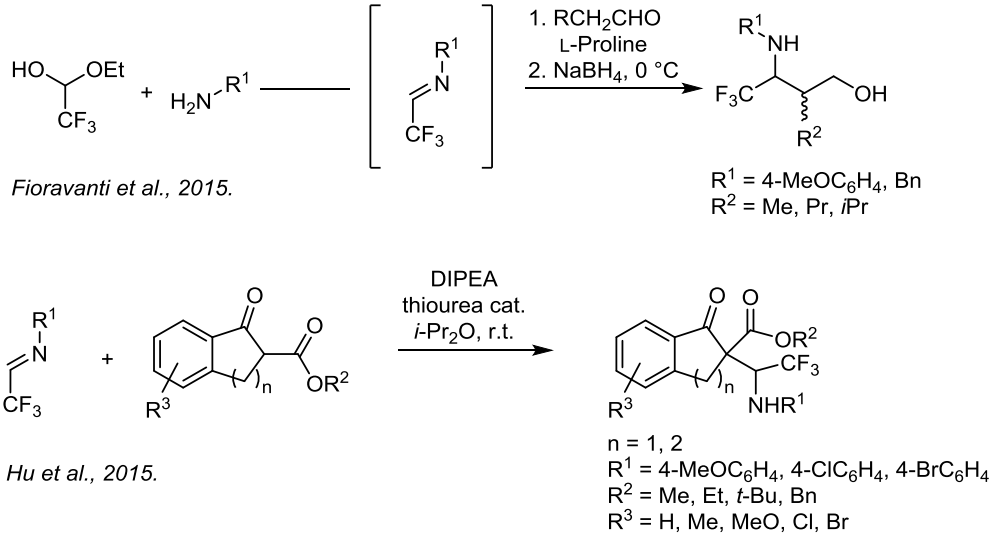
Soloshonok and co-workers, 2014 and 2015.

Scheme 14. Conversion of (S)-*N*-*tert*-butylsulfinyl-3,3,3-trifluoroacetaldimines with *C*-nucleophiles.[173, 178]

Apart from *N*-sulfinyl imines, further *N*-protected trifluoromethylated imines have been used as substrates in *Mannich*-type reactions (Scheme 15). For instance, *Fioravanti et al.* highlighted a L-proline catalyzed conversion of *in situ* formed benzyl-protected imines with aldehydes to furnish *γ*-amino alcohols. The ratio of *syn* and *anti*-diastereomeres was strongly dependent on the reaction conditions, i.e. temperature and time.[181] Moreover, *Hu* and co-workers employed trifluoromethylated *N*-aryl imines in a thiourea catalyzed asymmetric

reaction with *β*-keto esters. The resulting products with two vicinal chiral centers were obtained with good yield and diastereoselectivity, albeit low to moderate enantioselectivity.[182]

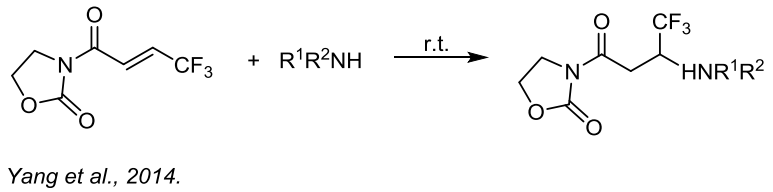
Mannich-type reaction of N-protected trifluoromethylated imines:



Scheme 15. Conversion of trifluoromethylated imines with carbonyl compounds.[181-182]

Recently, *Yang et al.* demonstrated an *aza-Michael* addition of *N*-aryl amines to *β*-fluoroalkylated acrylates providing various fluoroalkylated *β*-amino acid derivatives (Scheme 16). Here, the substrates have to be reacted under solvent- and catalyst-free reaction conditions to furnish the desired fluorinated products in high yields.[183]

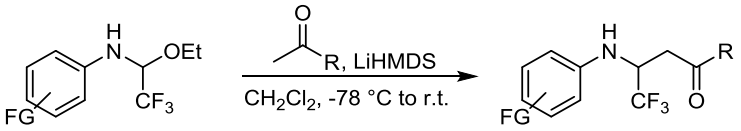
aza-Michael-type reaction of fluoroalkylated acrylates:



Scheme 16. Synthesis of trifluoromethylated carbonyl compounds from amines and trifluoromethylated acrylates.[183]

The procedures toward preparation of trifluoromethylated carbonyl compounds in *Mannich*-type reactions described above are either limited using *N*-protecting groups or a small substrate scope. We therefore decided to investigate the conversion of trifluoromethylated *N*,*O*-acetals under *Mannich* reaction conditions. Based on the advantageous use of *N*,*O*-acetals for the generation of trifluoroethylamines, we converted these imine surrogates with the lithium enolate formed *in situ* by treating acetophenone with LiHMDS. After establishing an efficient protocol which allows a high yielding synthesis of *β*-fluoroalkylated *Mannich*-type products, we demonstrate its applicability and scope by reacting a variety of *N*-aryl *N*,*O*-acetals with lithium enolates of ketones, esters and nitriles (Scheme 17). This simple one-pot procedure allows a large variety in substitution patterns of *Mannich*-type products, most ideally, without the restriction of protecting groups.[184]

Mannich-type reaction of fluoroalkylated N,O-acetals:



Wunder et al., 2016.

Scheme 17. Synthesis of *β*-fluoroalkylated *Mannich*-type products.[184]

One-Pot Synthesis of Functionalized β-Fluoroalkylated Mannich-Type Products from *N*-Aryl *N,O*-Acetals

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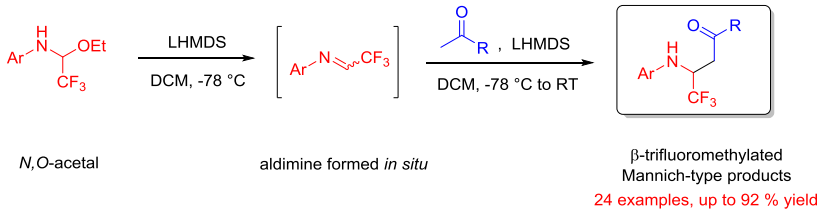
Dedicated to Professor Dr. Rolf Huisgen on the occasion of his 95th birthday.



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Abstract A variety of functionalized β-amino-β-fluoroalkyl carbonyl compounds are accessible *via* a novel one-pot Mannich-type reaction of CF_2- and CF_3-containing *N*-aryl *N,O*-acetals with lithium enolates of ketones, esters and nitriles. The resulting β-fluoroalkylated β-amino carbonyl compounds are promising peptide surrogates to be used in drug development and for biological applications.

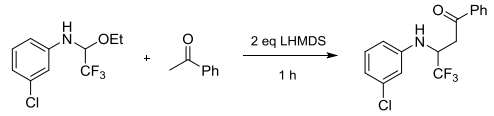
Key words fluoroalkylated compounds, *N,O*-acetals, trifluoroethylamine, difluoroethylamines, Mannich-type reaction.

Drug-development based on a multidimensional optimization (MDO) approach is a great challenge and includes the fine-tuning of physicochemical properties and ADME (absorption, distribution, metabolism and excretion).[1] In particular nitrogen-containing compounds mostly require modulation of their basicity, as this affects properties such as lipophilicity, membrane permeability, binding potency including side effects like hERG inhibition[2] and metabolic stability, all of which will be addressed in the course of the MDO process. In recent years the strategic placement of fluorine atoms in close proximity to nitrogen has become a common tool to fine-tune the molecular properties of biologically active amines by affecting their absorption and distribution behavior.[3] In general, the incorporation of fluorinated groups leads to a lower basicity of neighboring amines, due to the high electrophilicity of fluorine atoms. Lead optimization studies have shown that introduction of a trifluoromethyl group adjacent to an amine enhances the metabolic stability of the compound significantly. Moreover, this transformation leads to a decrease in the pK_a value of approximately 5.7 units, thus matching the pK_a values of amides.[1,4] However, despite structural similarities and isopolarities between C–CF_3 and C=O entities, as well as their increased metabolic stability, α-trifluoromethylated amines have remained an underrepresented, yet interesting class of amide bioisosteres.[5] Thus, only a few examples of pharmaceuticals featuring –NH–CH(CF_3) or –N=C(CF_3) motifs are currently available.[6] The cathepsin K inhibitor Odanacatib[7] is a prominent example for compounds featuring a –NH–CH(CF_3) group, whereas the corresponding imine derivatives are represented by the small-molecule systemic inhibitor of enteroviruses and rhinoviruses Pleconaril.[8]

Mannich bases (β-amino ketones) are particularly useful building blocks[9] for the preparation of nitrogen containing biologically active compounds.[10] Their chemistry has been intensively studied and they can be easily converted into other multifunctional compounds (e.g. β-amino esters, γ-amino alcohols or 1,3-diamines).[11] Likewise, the corresponding β-trifluoromethylated β-amino ketones are promising units for bioorganic and medicinal chemistry applications and various approaches towards their syntheses have been reported. Mannich-type nucleophilic addition reaction represents an established methodology for synthesis of β-amino-β-trifluoromethyl carbonyl compounds whereby efficient asymmetric syntheses can be achieved through the application of chiral auxiliaries.[12] In most of these methods preformed *N*-*tert*-butanesulfinyl (3,3,3)-trifluoro-acetaldimines[13] or other trifluoromethyl aldimines[14] are used, whereas only a few reactions based on trifluoroacetaldehyde ethyl hemiacetal[15] or *N,O*-acetals[16] derived from trifluoroacetaldehyde are known. Since this latter approach does not require expensive chiral *N*-sulfinyl amides and controlled reaction conditions, it would be particularly useful for initial biological testing and lead optimization studies, for which enantiomerically pure compounds are not necessarily required. Thus, the development of a simple and economical one-pot protocol for the synthesis of β-amino-β-trifluoromethyl carbonyl compounds *via* Mannich-type nucleophilic addition reaction to various *N*-aryl *N,O*-acetals is highly desirable and presented herein.

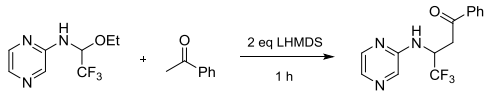
In contrast to the corresponding aldimines, trifluoromethylated *N*,*O*-acetals derived from 1-ethoxy-2,2,2-trifluoroethanol are readily available and shelf-stable compounds.[17,18] Upon base treatment a transient aldimine intermediate is formed, which subsequently can be attacked by *C*-nucleophiles to furnish the desired β-amino-β-trifluoromethyl carbonyl compounds. In our studies we focused on ketones, but also other C–H acidic compounds (esters, nitriles) can be employed as nucleophiles. Hence, by using 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoro-ethyl)-aniline **1a** as a model compound and LHMDS for deprotonation, the corresponding imine species was generated and reacted with an *in situ* forming lithium enolate of acetophenone. Low to moderate yields of the desired product **2a** were obtained in various solvents at 55 °C (Table 1, entries 1–4). However, the yield of **2a** was significantly improved when the reaction was performed at a temperature of -78 °C to RT using dichloromethane as solvent (Table 1, entry 7). Even higher yields were achieved by using *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** as substrate under the same conditions (Table 1, entry 8). The application of tetrahydrofuran, which is usually the solvent of choice in Mannich-type reactions, and diethyl ether at -78 °C to RT resulted in slightly lower yields of the desired product **2b** (Table 1, entries 9 and 10). The employment of alternative non-nucleophilic bases such as DBU, NaHMDS, KHMDS or LDA was found detrimental (data not shown).

Table 1 Optimization studies



1a **2a**

Entry	solvent	T [°C]	Yield [%][a]
1	Toluene	55	38
2	THF	55	26
3	DCM	55	46
4	Acetonitrile	55	8
5	CH_2Cl_2	RT	61
6	CH_2Cl_2	0	38
7	CH_2Cl_2	−78 to RT	71



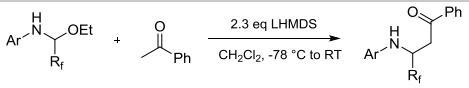
1b **2b**

Entry	solvent	T [°C]	Yield [%][a]
8	DCM	−78 to RT	92
9	THF	−78 to RT	89
10	Et_2O	−78 to RT	91

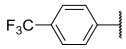
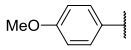
[a] Yield of isolated product after flash chromatography.

Having identified suitable conditions for the Mannich-type reaction, we briefly looked at its scope by varying the substitution pattern of the aromatic ring within the hemiaminal ether (Table 2). Thus it was found that electron-poor *N*,*O*-acetals comprising pyrazine and quinoline groups are particularly well suited for this reaction and provide the target β-trifluoromethylated β-amino ketones **2b** and **2d** in high yields (Table 2, entries 2 and 4). Interestingly, the corresponding *N*,*O*-acetal featuring a (4-trifluoromethyl)phenyl substituent only afforded the desired reaction product **2e** with a moderate yield of 52% (Table 2, entry 5), most presumably due to difficulties during the purification step. In contrast, difluoromethylated and pentafluoroethylated β-amino ketones are accessible in almost quantitative yields by subjecting the corresponding *N*,*O*-acetals **1h** and **1i** to the reaction conditions described above (Table 2, entries 8 and 9).

Table 2 Reaction of acetophenone with aromatic *N*,*O*-acetals



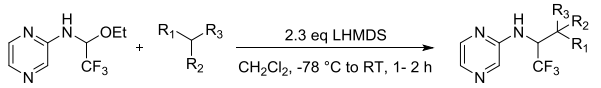
1 **2**

Entry	Ar	R_f	t [h]	Yield [%][a]	product
1[b]		CF_3	1	71	**2a**
2		CF_3	1	92	**2b**
3		CF_3	1	72	**2c**
4		CF_3	0.3	92	**2d**
5		CF_3	1	52	**2e**
6		CF_3	2	64	**2f**
7		CF_3	1	78	**2g**
8		CF_2H	2	quant.	**2h**
9		CF_2CF_3	1	quant.	**2i**

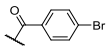
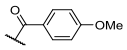
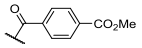
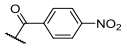
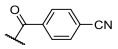
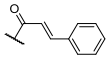
[a] Yield of isolated product after flash chromatography.
[b] Use of 2 equiv LHMDS.

With regard to the scope of *C*-nucleophiles applicable to this Mannich-type reaction, we examined at first acetophenone-derived ketones with both electron-withdrawing and electron-donating substituents on the aromatic ring. To our delight, halogen, methoxy and nitro groups, as well as nitrile and ester-functionalities are tolerated by the reaction conditions to furnish the desired β-trifluoromethylated β-amino ketones **3a**–**f** in reasonable yields (Table 3, entries 2–7). Moreover, ketones carrying furan or indole residues, as well as (*E*)-4-phenylbut-3-en-2-one reacted smoothly to give the corresponding Mannich-type products **3h**–**j** (Table 3, entries 9–11), whereas 2',3',4',5',6'-pentafluoroacetophenone only afforded low yields of β-amino ketone **3g** (Table 3, entry 8), due to the formation of significant amounts of side products. A more sluggishly proceeding reaction was also observed for sterically hindered substrates such as 2-methyl-1-phenylpropan-1-one, as expected (Table 3 entry 13). Last but not least, successful applications of diethyl malonate, ethyl acetate as well as 2,6-dichlorophenylacetonitrile as substrates demonstrated once more the synthetic versatility of this approach to readily access functionalized β-trifluoromethylated β-amino carbonyl compounds **3m**–**o** (Table 3, entries 14–16).

Table 3 Reaction of pyrazyl *N,O*-acetals with various nucleophiles



1b **3**

Entry	R_1	R_2	R_3	Yield [%][a]	product
1	H	H		92	**2b**
2	H	H		62	**3a**
3	H	H		90	**3b**
4	H	H		88	**3c**
5	H	H		82	**3d**
6	H	H		75	**3e**
7	H	H		91	**3f**
8	H	H		35	**3g**
9	H	H		58	**3h**
10	H	H		67	**3i**
11	H	H		64	**3j**
12	H	CH_3		68	**3k**
13	CH_3	CH_3		22	**3l**
14	H	CN		60	**3m**
15	H	CO_2Et	CO_2Et	59	**3n**
16	H	H	CO_2Et	25	**3o**

[a] Yield of isolated product after flash chromatography

In summary, we devise an efficient one-pot procedure for the synthesis of a broad range of functionalized β-amino-β-trifluoromethyl carbonyl derivatives using readily accessible, shelf-stable *N*-aryl *N,O*-acetals and lithium enolates derived from ketones, esters, as well as nitriles. The reaction is easy to perform and allows rapid formation of novel trifluoromethylated Mannich-type products, which are useful potential building blocks for pharmaceutical and biological applications. Moreover, the reaction protocol can be successfully applied to the synthesis of functionalized β-difluoromethylated and β-pentafluoroethylated Mannich-type products.

All reactions were carried out under an argon atmosphere using dried glassware. Commercially available reagents and solvents were used without further purification. Dry CH_2Cl_2 (SeccoSolv®) was purchased from *Merck KGaA*. *N,O*-acetal substrates were synthesized according to standard procedures from 1-ethoxy-2,2,2-trifluoroethanol and the corresponding amines using *p*TSA in EtOH.[17] Purification was performed by flash chromatography and *N,O*-acetal substrates were dried under reduced pressure prior to use. Reactions were monitored by TLC with pre-coated silica gel 60 F254 aluminium plates (*Merck KGaA*) using UV light as the visualizing agent. The crude β-amino-β-trifluoromethyl carbonyl compounds were purified by MPLC with a *CombiFlash Rf Teledyne ISCO* or by standard flash chromatography using silica gel (35–70 µm) from *Acros Organics*. Analytical RP-HPLC was measured on a *JASCO* system with a *Phenomenex Luna* C18 column (5 µm, 250 × 4.6 mm). HR-EI-mass spectra were recorded on a *Finnigan MAT95Q* or on a *Finnigan MAT90*. HR-ESI-mass spectra were recorded on a *Thermo Finnigan LTQ FT* or on a *Bruker maXis* equipped with a *Waters Acquity UPLC* using a *Kinetex* C18 column (2.6 µ, 100 A) at 40 °C and HPLC-MS was performed on *Agilent 1100* and *Agilent 1200* systems using *Chromolith Speed ROD* RP-18e columns. In all cases, mixtures of water (eluent A) and acetonitrile (eluent B) were used as solvents; if required, 0.05 % formic acid or 0.1 % TFA were added. ^1H, ^{13}C, and ^{19}F spectra were recorded on a *Varian* 400 MHz, 600 MHz and 800 MHz spectrometer or on a *Bruker Avance II* 300 MHz, 400 MHz and 500 MHz spectrometer in DMSO-d_6 or $CDCl_3$. The chemical shifts are reported in ppm relative to the signal of the deuterated solvent. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Melting points were measured on a *Melting Point B-540 Büchi*.

Addition of Ketones to *N*-Aryl *N,O*-Acetals 1a-l; General Procedure

N-aryl hemiaminal ether **1** was placed in a dry Schlenk flask equipped with a magnetic stirrer and a septum, and dissolved in dry CH_2Cl_2 (ca. 0.06 M). The solution was flushed with argon and cooled to −78 °C before lithium bis(trimethylsilylamide) (LHMDS, 1.0 M solution in toluene, 2.0–3.3 eq.) was added dropwise. Stirring was continued at −78 °C for 10 min, the ketone (1.5–2.5 eq.) was added, the reaction mixture was allowed to warm up to room temperature and stirred for 1–2 h (TLC and LC-MS control). After complete consumption of the starting material the solution was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash- or column chromatography and optional subsequent crystallization from ^{c}hex/EtOAc furnished the desired β-amino β-fluoroalkylated carbonyl compounds **2a**–**2i** and **3a**–**3o**.

3-((3-Chlorophenyl)amino)-4,4,4-trifluoro-1-phenylbutan-1-one (2a)

According to the general procedure, 3-Chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (150 mg, 0.59 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.18 mL, 1.18 mmol) and reacted with acetophenone (0.10 mL, 0.89 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc 9/1) and recrystallization (^{c}hex) the β-amino ketone **2a** (138 mg, 0.42 mmol, 71 %) was obtained as a colorless crystalline solid. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.07 – 7.93 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.73 – 7.62 (m, 1H, $H4_{ph}$), 7.55 (m, 2H, $H3_{ph}$, $H5_{ph}$), 7.11 (t, $J_{H5,H4/H6}$ = 8.1 Hz, 1H, H5), 6.77 (br s, 1H, H2), 6.65 (m, 2H, H4, H6), 6.30 (d, $J_{NH,CH}$ = 8.4 Hz, 1H, NH), 4.87 – 4.76 (m, 1H, CH), 3.62 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 10.0 Hz, 1H, CH_2), 3.44 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 2.5 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.97 (C=O), 148.96 (C1), 136.13($C1_{ph}$), 133.55 (C3), 133.52 ($C4_{ph}$) 130.34 (C5), 128.73 ($C3_{ph}$, $C5_{ph}$), 128.09 ($C2_{ph}$, $C6_{ph}$), 126.58 (q, $^1J_{C,F}$ = 283.8 Hz, CF_3), 116.47 (C4), 111.93 (C2), 111.35 (C6), 50.16 (q, $^2J_{C,F}$ = 29.7 Hz, CH), 37.54 (CH_2) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = − 74.25 (d, $J_{CF3,CH}$ = 7.4 Hz, CF_3) ppm. HR-EI-MS (m/z) calc. for $C_{16}H_{13}ClF_3NO^+$ $[M]^+$ 327.0638; found 327.0641. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.98 min, λ = 220 nm. m.p.: 98 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.61.

4,4,4-Trifluoro-1-phenyl-3-(pyrazin-2-ylamino)butan-1-one (2b)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with acetophenone (0.08 mL, 0.68 mmol). After

stirring at rt (1h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) and recrystallization (^{c}hex) the β-amino ketone **2b** (123 mg, 0.42 mmol, 92 %) was obtained as a colorless crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 8.01 – 7.94 (m, 3H, H3, $H2_{ph}$, $H6_{ph}$), 7.82 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.70 – 7.63 (m, 1H, $H4_{ph}$), 7.58 – 7.51 (m, 2H, $H3_{ph}$, $H5_{ph}$), 7.48 (d, $J_{NH,CH}$ = 8.2 Hz, 1H, NH), 5.50 – 5.38 (m, 1H, CH), 3.65 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 9.8 Hz, 1H, CH_2), 3.52 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 3.3 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 195.03 (C=O), 153.90 (C2), 141.26 (C6), 136.08 ($C1_{ph}$), 133.55 (C5), 133.02 ($C4_{ph}$), 132.91 (C3), 128.74 ($C3_{ph}$, $C5_{ph}$), 128.07 ($C2_{ph}$, $C6_{ph}$), 126.22 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3) 47.17 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 37.12 (CH_2) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.37 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. HR-EI-MS (m/z) calc. for $C_{14}H_{12}F_3N_3O^+$ $[M]^+$ 295.0932; found 295.0931. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.59 min, λ = 220 nm. m.p.: 128 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.20.

4,4,4-Trifluoro-3-(4-methylpyrimidin-2-ylamino)-1-phenylbutan-1-one (2c)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-methylpyrimidin-2-amine **1c** (100 mg, 0.43 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.98 mL, 0.98 mmol) and reacted with acetophenone (0.08 mL, 0.64 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) and recrystallization (^{c}hex) the β-amino ketone **2c** (97 mg, 0.31 mmol, 72 %) was obtained as a colorless crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19 (br s, 1H, H6), 8.00 – 7.91 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.65 (tt, $J_{H4ph,H3ph/H5ph}$ = 7.4 Hz, $J_{H4ph,H2ph/H6ph}$ = 1.1 Hz, $H4_{ph}$), 7.53 (m, 3H, NH, $H3_{ph}$, $H5_{ph}$), 6.60 (d, $J_{H5,H6}$ = 5.0 Hz, 1H, H5), 5.54 – 5.39 (m, 1H), 3.74 (dd, $J_{CH2,CH2}$ = 17.7 Hz, $J_{CH2,CH}$ = 10.3 Hz, 1H, CH_2), 3.39 (dd, $J_{CH2,CH2}$ = 17.6 Hz, $J_{CH2,CH}$ = 2.9 Hz, 1H, CH_2), 2.25 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 195.89 (C=O), 167.89 (C4), 162.05 (C2), 157.85 (C6), 136.70 ($C1_{ph}$), 134.02 ($C4_{ph}$), 129.24 ($C2_{ph}$, $C6_{ph}$), 128.19 ($C3_{ph}$, $C5_{ph}$), 126.78 (q, $^1J_{C,F}$ = 283.1 Hz, CF_3), 111.53 (C5), 48.51 (q, $^2J_{C,F}$ = 30.2 Hz, CH), 37.21 (CH_2), 24.00 (CH_3) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.48 (br s, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{15}H_{15}F_3N_3O^+$ $[M+H]^+$ 310.1162; found 310.1162. HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 13.93 min, λ = 214 nm. m.p.: 109 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.35.

4,4,4-Trifluoro-1-phenyl-3-(quinolin-8-ylamino)butan-1-one (2d)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)quinolin-8-amine **1d** (100 mg, 0.37 mmol) was dissolved in 5 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.85 mL, 0.85 mmol) and reacted with acetophenone (0.65 mL, 0.56 mmol). After stirring at rt (20 min), aqueous workup and flash chromatography (^{c}hex → ^{c}hex/EtOAc 9/1) the β-amino ketone **2d** (117 mg, 0.34 mmol, 92 %) was obtained as a light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.68 (dd, $J_{H2,H3}$ = 4.2 Hz, $J_{H2,H4}$ = 1.7 Hz, 1H, H2), 8.06 (dd, $J_{H4,H3}$ = 8.2 Hz, $J_{H4,H2}$ = 1.7 Hz, 1H, H4), 7.99 – 7.93 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.62 – 7.54 (m, 1H, $H4_{ph}$), 7.51 – 7.40 (m, 3H, H6, $H3_{ph}$, $H5_{ph}$), 7.36 (dd, $J_{H3,H4}$ = 8.2 Hz, $J_{H3,H2}$ = 4.2 Hz, 1H, H3), 7.16 (dd, $J_{H5,H6}$ = 8.2 Hz, $J_{H5,H7}$ = 1.1 Hz, 1H, H5), 7.07 (d, $J_{H7,H6}$ = 7.6 Hz, 1H, H7), 6.44 (d, $J_{NH,CH}$ = 9.9 Hz, 1H, NH), 5.10 (dtd, $J_{CH,NH}$ = 9.9 Hz, $J_{CH,CF3}$ = 7.2 Hz, $J_{CH,CH2}$ = 4.7 Hz, 1H, CH), 3.63 – 3.49 (m, 2H, CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.05 (C=O), 147.32 (C2), 142.75 (C4a), 138.16 (C8a), 136.42 ($C1_{ph}$), 136.20 (C4), 133.82 ($C4_{ph}$), 128.91 ($C3_{ph}$, $C5_{ph}$), 128.73 (C8), 128.34 ($C2_{ph}$, $C6_{ph}$), 127.71 (C6), 126.40 (q, $^1J_{C,F}$ = 283.3 Hz, CF_3), 121.61 (C3), 116.12 (C5), 106.54 (C7), 51.40 (q, $^2J_{C,F}$ = 30.5 Hz, CCF_3), 39.06 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = – 75.63 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{19}H_{16}F_3N_2O^+$ $[M+H]^+$ 345.1209; found 345.1210. HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 18.93 min, λ = 214 nm. R_f (^{c}Hex/EtOAc = 3:1) = 0.50.

4,4,4-Trifluoro-1-phenyl-3-((4-(trifluoromethyl)phenyl)amino)butan-1-one (2e)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline **1e** (50 mg, 0.17 mmol) was dissolved in 5 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.40 mL, 0.40 mmol) and reacted with acetophenone (0.03 mL, 0.26 mmol). After stirring at rt (1 h), aqueous workup and flash chromatography (^{c}hex → ^{c}hex/EtOAc 5/1) the β-amino ketone **2e** (33 mg, 0.09 mmol, 52 %) was obtained as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.92 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.65 – 7.59 (m, 1H, $H4_{ph}$), 7.50 (dd, *J* = 8.3 Hz, *J* = 7.1 Hz, 2H, $H3_{ph}$, $H5_{ph}$), 7.44 (d, $J_{H3,H2}$ = $J_{H5,H6}$ = 8.5 Hz, 2H, H3, H5), 6.79 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 8.4 Hz, 2H, H2, H6), 4.87 (dtd, $J_{CH,NH}$ = 9.6 Hz, $J_{CH,CF3}$ = 7.2 Hz, $J_{CH,CH2}$ = 4.3 Hz, 1H, CH), 4.14 (d, $J_{NH,CH}$ = 9.9 Hz, 1H, NH), 3.45 – 3.37 (m, 2H, CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.90 (C=O), 148.67 (C1), 136.16 ($C1_{ph}$), 134.14 ($C4_{ph}$), 129.05 ($C3_{ph}$, $C5_{ph}$), 128.31 ($C2_{ph}$, $C6_{ph}$), 126.92 (q, $^3J_{C,F}$ = 3.8 Hz, C3, C5), 125.97 (q, $^1J_{C,F}$ = 283.2 Hz, CF_3), 124.77 (d, $^1J_{C,F}$ = 270.6 Hz, CF_3), 121.15 (q, $^2J_{C,F}$ = 32.8 Hz, C4), 113.19 (C2, C6), 51.80 (q, $^2J_{C,F}$ = 30.7 Hz, CCF_3), 38.34 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = – 61.40 (CF_3), – 75.66 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. HR-ESI-MS (negative, m/z) calc. for $C_{17}H_{12}F_6NO^-$ $[M-H]^-$ 360.0828; found 360.0835. HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 19.85 min, λ = 214 nm. m.p.: 127 °C. R_f (^{c}Hex/EtOAc = 3:1) = 0.46.

4,4,4-Trifluoro-3-((4-methoxyphenyl)amino)-1-phenylbutan-1-one (2f)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-methoxyaniline **1f** (170 mg, 0.68 mmol) was dissolved in 10 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with acetophenone (0.12 mL, 1.02 mmol). After stirring at rt (2 h), aqueous workup and flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) and recrystallization (^{c}hex) the β-amino ketone **2f** (140 mg, 0.43 mmol, 64 %) was obtained as a colorless crystalline solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.95 (m, 1H, $H2_{ph}$/$H6_{ph}$), 7.94 (m, 1H, $H2_{ph}$/$H6_{ph}$), 7.60 (m, 1H, $H4_{ph}$), 7.51 – 7.46 (m, 2H, $H3_{ph}$, $H5_{ph}$), 6.80 – 6.76 (m, 2H, H2, H6), 6.76 – 6.72 (m, 2H, H3, H5), 4.69 (m, 1H, CH), 3.74 (s, 3H, OMe), 3.40 – 3.29 (m, 2H, CH_2) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.53 (C=O), 153.58 (C4), 139.93 (C1), 136.48 ($C1_{ph}$), 133.85 ($C4_{ph}$), 129.94 ($C2_{ph}$, $C6_{ph}$), 128.29 ($C3_{ph}$, $C5_{ph}$), 126.34 (q, $^1J_{C,F}$ = 283.5 Hz, CF_3), 116.13 ($C3_{ph}$, $C5_{ph}$), 114.98 ($C2_{ph,}$ $C1_{ph}$), 55.79 (OMe), 53.97 (q, $^2J_{C,F}$ = 29.5 Hz, CCF_3), 38.47 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = – 75.48 (CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{17}H_{17}F_3NO_2^+$ $[M+H]^+$ 324.1206; found 324.1210. HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 18.43 min, λ = 214 nm. m.p.: 90 °C. R_f (^{c}Hex/EtOAc = 4:1) = 0.53.

4,4,4-Trifluoro-1-phenyl-3-(pyridin-2-ylamino)butan-1-one (2g)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine **1g** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL,

1.04 mmol) and reacted with acetophenone (0.08 mL, 0.68 mmol). After stirring at rt (1 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) and recrystallization (^{c}hex) the β-amino ketone **2g** (104 mg, 0.35 mmol, 78 %) was obtained as a colorless crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (dd, $J_{H6,H5}$ = 5.0 Hz, $J_{H6,H4}$ = 1.2 Hz, 1H, H6), 8.00 – 7.95 (m, 2H, H2$_{ph}$, H6$_{ph}$), 7.69 – 7.63 (m, 1H, H4$_{ph}$), 7.56 – 7.51 (m, 2H, H3$_{ph}$, H5$_{ph}$), 7.41 (ddd, $J_{H4,H3}$ = 8.8 Hz, $J_{H4,H5}$ = 7.1 Hz, $J_{H4,H6}$ = 1.9 Hz, 1H, H4), 6.94 (d, $J_{NH,CH}$ = 8.4 Hz, 1H, NH), 6.59 (ddd, $J_{H5,H4}$ = 7.0 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.8 Hz, 1 H, H5), 6.51 (d, $J_{H3,H4}$ = 8.4 Hz, 1H, H3), 5.60 – 5.44 (m, 1H, CH), 3.60 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 9.6 Hz, 1H, CH_2), 3.43 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 3.5 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 195.50 (C=O), 157.47 (C1), 147.33 (C6), 137.18 (C4), 136.34 (C1$_{ph}$), 133.67 (C4$_{ph}$), 128.92 (C3$_{ph}$, C5$_{ph}$), 128.21 (C2$_{ph}$, C6$_{ph}$), 126.59 (q, $^1J_{C,F}$ = 283.8 Hz, CF_3), 113.32 (C5), 108.74 (C3), 47.56 (q, $^2J_{C,F}$ = 30.0 Hz, CH), 37.55 (CH_2) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.34 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. HR-EI-MS (m/z) calc. for $C_{15}H_{13}F_3N_2O^+$ $[M]^+$ 294.0980; found 294.0977. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.25 min, λ = 220 nm. m.p.: 124 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.46.

4,4-Difluoro-1-phenyl-3-(pyridin-2-ylamino)butan-1-one (2h)

According to the general procedure, *N*-(1-ethoxy-2,2-difluoroethyl)pyridin-2-amine **1h** (100 mg, 0.49 mmol) was dissolved in 5 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.13 mL, 1.13 mmol) and reacted with acetophenone (0.09 mL, 0.74 mmol). After stirring at rt (2 h), aqueous workup and flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) the β-amino ketone **2h** (136 mg, 0.49 mmol, quant.) was obtained as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1H, H6), 8.00 – 7.92 (m, 2H, H2$_{ph}$, H6$_{ph}$), 7.65 – 7.54 (m, 1H, H4$_{ph}$), 7.53 – 7.44 (m, 2H, H3$_{ph}$, H5$_{ph}$), 7.40 (ddd, $J_{H4,H3}$ = 8.4 Hz, $J_{H4,H5}$ = 7.1 Hz, $J_{H4,H6}$ = 1.9 Hz, 1H, H4), 6.62 (ddd, $J_{H5,H4}$ = 7.1 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1H, H5), 6.48 (dt, $J_{H3,H4}$ = 8.3 Hz, $J_{H3,H5}$ = 0.9 Hz, 1H, H3), 6.20 (td, $J_{CHF2,CHF2}$ = 56.7 Hz, $J_{CHF2,CH}$ = 3.1 Hz, 1H, CHF_2), 5.08 – 4.91 (m, 1H, CH), 4.89 (d, $J_{NH,CH}$ = 9.0 Hz, 1H, NH), 3.46 – 3.38 (m, 2H, CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.85 (C=O), 157.16 (C2), 147.97 (C6) , 137.61 (C4), 136.58 (C1$_{ph}$), 133.76 (C4$_{ph}$), 128.89 (C3$_{ph}$, C5$_{ph}$), 128.34 (C2$_{ph}$, C6$_{ph}$), 115.45 (t, $^1J_{CHF2,CHF2}$ = 244.9 Hz, CHF_2), 113.02 (C5), 108.87 (C3), 49.94 (dd, $^2J_{CH,CHF2}$ = 24.5 Hz, $^2J_{CH,CHF2}$ = 22.8 Hz, CH), 36.73 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = – 125.78 (ddd, $J_{CHF2,CHF2}$ = 281.1 Hz, $J_{CHF2,CHF2}$ = 56.4 Hz, $J_{CHF2,CH}$ = 10.4 Hz, CHF_2), – 128.96 (ddd, $J_{CHF2,CHF2}$ = 281.1 Hz, $J_{CHF2,CHF2}$ = 56.9 Hz, $J_{CHF2,CH}$ = 16.0 Hz, CHF_2) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{15}H_{15}F_2N_2O^+$ $[M+H]^+$ 277.1147; found 277.1146. HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 10.23 min, λ = 214 nm. m.p.: 115 °C. R_f (^{c}Hex/EtOAc = 3:1) = 0.24.

4,4,5,5,5-Pentafluoro-1-phenyl-3-(pyrazin-2-ylamino)pentan-1-one (2i)

Following the general procedure, *N*-(1-ethoxy-2,2,3,3,3-pentafluoropropyl)pyrazin-2-amine **1i** (100 mg, 0.37 mmol) was dissolved in 5 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.85 mL, 0.85 mmol) and reacted with acetophenone (0.07 mL, 0.55 mmol). After stirring at rt (1 h), aqueous workup and flash chromatography (^{c}hex → ^{c}hex/EtOAc 2/1) the β-amino ketone **2i** (130 mg, 0.37 mmol, quant.) was obtained as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.99 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 7.95 – 7.91 (m, 2 H, H2$_{ph}$; H6$_{ph}$), 7.90 (m, 1 H, H5), 7.60 (m, 1 H, H4$_{ph}$), 7.48 (m, 2 H, H3$_{ph}$; H5$_{ph}$), 5.73 (m, 1 H, CH), 5.06 (d, $J_{NH,CH}$ = 10.0 Hz, 1 H, NH), 3.51 – 3.46 (m, 2 H, CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.68 (C=O), 152.61 (C2), 141.68 (C6), 136.31 (C1$_{ph}$), 134.84 (C5), 134.01 (C4$_{ph}$), 132.96 (C3), 129.01 (C3$_{ph;}$ C5$_{ph}$), 128.27 (C2$_{ph;}$ C6$_{ph}$), 46.94 (dd, $^2J_{CH,CF2}$ = 27.1 Hz, $^2J_{CH,CF2}$ = 21.4 Hz, CH), 37.07 (CH_2) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = – 81.84 (CF_3), – 118.54 (dd, $J_{CF2,CF2}$ = 273.6 Hz, $J_{CF2,CF3}$ = 7.3 Hz, CF_2), – 124.82 (dd, $J_{CF2,CF2}$ = 273.6 Hz, $J_{CF2,CF3}$ = 19.8 Hz, CF_2) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{15}H_{13}F_5N_3O^+$ $[M+H]^+$ 346.0973; found 346.0973. . HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 16.28 min, λ = 214 nm. m.p.: 105 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.23.

1-(4-Bromophenyl)-4,4,4-trifluoro-3-(pyrazin-2-ylamino)butan-1-one (3a)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with 4-bromoacetophenone (203 mg, 1.02 mmol). After stirring at 40 °C (2 h), aqueous workup, flash chromatography (^{c}hex/EtOAc 3/1 → 2/1) and recrystallization (^{c}hex/EtOAc 9/1) the β-amino ketone **3a** (132 mg, 0.35 mmol, 62 %) was obtained as a colorless crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.04 (dd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.4 Hz, 1H, H6), 7.96 (d, $J_{H3,H6}$ = 1.4 Hz, 1H, H3), 7.94 – 7.89 (m, 2H, H2$_{ph}$, H6$_{ph}$), 7.82 (d, $J_{H5,H6}$ = 2.7 Hz, 1H, H5), 7.78 – 7.73 (m, 2H, H3$_{ph}$, H5$_{ph}$), 7.46 (d, $J_{NH,CH}$ = 8.2 Hz, 1H, NH), 5.48 – 5.35 (m, 1H, CH), 3.62 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 9.8 Hz, 1H, CH_2), 3.52 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 3.3 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.57 (C=O), 154.01 (C2), 141.46 (C6), 135.19 (C1), 133.13 (C3), 133.09 (C5), 131.98 (C3$_{ph}$, C5$_{ph}$), 130.26 (C2$_{ph}$, C6$_{ph}$), 127.87 (C-Br), 126.29 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3), 47.26 (q, $^2J_{C,F}$ = 30.3 Hz, CH), 37.28 (CH_2) ppm. ^{19}F NMR (471 MHz, DMSO-d_6): δ = – 74.37 (d, $J_{CF3,CH}$ = 7.6 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{14}H_{12}BrF_3N_3O^+$ $[M+H]^+$ 374.0110; found 374.0112. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.74 min, λ = 220 nm. m.p.: 112 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.24.

4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-(pyrazin-2-ylamino)butan-1-one (3b)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with 4-methoxyacetophenone (153 mg, 1.02 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (^{c}hex/EtOAc 3/1 → 2/1) and recrystallization (^{c}hex/EtOAc 9/1) the β-amino ketone **3b** (199 mg, 0.61 mmol, 90 %) was obtained as a colorless crystalline solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.03 (dd, $J_{H6,H5}$ = 2.6 Hz, $J_{H6,H3}$ = 1.4 Hz, 1H, H6), 7.99 – 7.93 (m, 3H, H3, H2$_{ph}$, H6$_{ph}$), 7.81 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.47 (d, $J_{NH,CH}$ = 8.3 Hz, 1H, NH), 7.05 (m, 2H, H3$_{ph}$, H5$_{ph}$), 5.52 – 5.34 (m, 1H, CH), 3.85 (s, 3H, OMe), 3.57 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 9.9 Hz, 1H, CH_2), 3.42 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 3.2 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 193.51 (C=O), 163.59 (C-OMe), 154.04 (C2), 141.47 (C6), 133.10 (C3), 133.01 (C5), 130.64 (C2$_{ph}$, C6$_{ph}$), 129.17 (C1$_{ph}$), 126.40 (q, $^1J_{C,F}$ = 283.0 Hz, CF_3), 114.11 (C3$_{ph}$, C5$_{ph}$), 55.73 (OMe), 47.36 (q, $^2J_{C,F}$ = 30.3 Hz, CH), 36.84 (CH_2) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.34 (d, $J_{CF3,CH}$ = 7.8 Hz, CF_3) ppm. HR-EI-MS (m/z) calc. for $C_{15}H_{14}F_3N_3O_2^+$ $[M]^+$ 325.1038; found 325.1043. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.60 min, λ = 220 nm. m.p.: 135 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.11.

4,4,4-Trifluoro-1-(2-methoxyphenyl)-3-(pyrazin-2-ylamino)butan-1-one (3c)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with 2-methoxyacetophenone (0.14 mL, 1.02 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (^{c}hex/EtOAc 3/1 → 2/1) and recrystallization (^{c}hex/EtOAc 9/1) the β-amino ketone **3c** (194 mg, 0.59 mmol, 88 %) was obtained as a colorless crystalline solid ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.97 (dd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.95 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.79 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.60 – 7.49 (m, 3H, $H2_{ph}$, $H4_{ph}$, $H5_{ph}$), 7.20 (d, $J_{NH,CH}$ = 8.2 Hz, 1H, NH), 7.03 – 6.97 (m, 1H, $H3_{ph}$), 5.47 – 5.37 (m, 1H, CH), 3.91 (s, 3H, OMe), 3.46 (dd, $J_{CH2,CH2}$ = 17.4 Hz, $J_{CH2,CH}$ = 4.2 Hz, 1H, CH_2), 3.40 (dd, $J_{CH2,CH2}$ = 17.4 Hz, $J_{CH2,CH}$ = 9.2 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.16 (C=O), 158.68 (C-OMe), 153.95 (C2), 141.39 (C6), 134.64 ($C4_{ph}$), 133.16 (C3), 132.95 (C5), 129.99 ($C2_{ph}$), 126.51 ($C1_{ph}$), 126.30 (q, $^1J_{C,F}$ = 282.9 Hz, CF_3) 120.71 ($C3_{ph}$), 112.68 ($C5_{ph}$), 55.97 (OMe), 47.31 (q, $^2J_{C,F}$ = 30.1 Hz, CH), 42.49 (CH_2) ppm. ^{19}F NMR (471 MHz, DMSO-d_6): δ = – 74.52 (d, $J_{CF3,CH}$ = 7.7 Hz, CF_3) ppm. HR-EI-MS (m/z) calc. for $C_{15}H_{14}F_3N_3O_2^+$ $[M]^+$ 325.1038; found 325.1044. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.62 min, λ = 220 nm. m.p.: 134 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.14.

Methyl 4-(4,4,4-trifluoro-3-(pyrazin-2-ylamino)butanoyl)benzoate (3d)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with methyl-4-acetylbenzoate (120 mg, 0.68 mmol). After stirring at rt (2.5 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) and recrystallization (^{c}hex) the desired β-amino ketone **3d** (130 mg, 0.37 mmol, 82 %) was obtained as a colorless crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10 (d, $J_{H2ph,H3ph}$ = $J_{H5ph,H6ph}$ = 2.1 Hz, 4H, $H2_{ph}$, $H3_{ph}$, $H5_{ph}$, $H6_{ph}$), 8.04 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.96 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.82 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.46 (d, $J_{NH,CH}$ = 8.2 Hz, 1H, NH), 5.49 – 5.36 (m, 1H, CH), 3.69 (dd, $J_{CH2,CH2}$ = 17.9 Hz, $J_{CH2,CH}$ = 9.7 Hz, 1H, CH_2), 3.59 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 3.1 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.84 (C=O), 165.46 (COOMe), 153.85 (C2), 141.22 (C6), 139.39 ($C1_{ph}$), 133.47 (C5), 133.00 ($C4_{ph}$), 132.96 (C3), 129.42 ($C3_{ph}$, $C5_{ph}$), 128.38 ($C2_{ph}$, $C6_{ph}$), 52.47 (CH_3), 47.12 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 37.50 (CH_2) ppm.* ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.38 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{16}H_{15}F_3N_3O_3^+$ $[M+H]^+$ 354.1060; found 354.1061. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.62 min, λ = 220 nm. m.p.: 121 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.17.

* Due to low intensity the signal of CF_3 could not be observed.

4,4,4-Trifluoro-1-(4-nitrophenyl)-3-(pyrazin-2-ylamino)butan-1-one (3e)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 4'-nitroacetophenone (111 mg, 0.68 mmol). After stirring at rt (1 h) followed by stirring at 40 °C (2 h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at −78 °C for 10 min, 4'-nitroacetophenone (75 mg, 0.45 mmol) was added and the reaction mixture was stirred at 40 °C (20 h). Subsequent aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) and recrystallization (^{c}hex/EtOAc 9/1) furnished the β-amino ketone **3e** (115 mg, 0.34 mmol, 75 %) as a yellow crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.41 – 8.30 (m, 2H, $H3_{ph}$, $H5_{ph}$), 8.26 – 8.18 (m, 2H, $H2_{ph}$, $H6_{ph}$), 8.04 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.96 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.83 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.47 (d, $J_{NH,CH}$ = 8.1 Hz, 1H, NH), 5.52 – 5.33 (m, 1H, CH), 3.77 – 3.60 (m, 2H, 2 × CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.63 (C=O), 154.01 (C2), 150.24 (C-NO_2), 141.46 (C6), 140.72 (C3), 133.17 (C5), 129.70 ($C2_{ph}$, $C6_{ph}$), 126.23 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3) 123.98 ($C3_{ph}$, $C5_{ph}$), 47.25 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 37.90 (CH_2) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.47 (d, $J_{CF3,CH}$ = 7.8 Hz, CF_3) HR-ESI-MS (positive, m/z) calc. for $C_{14}H_{12}F_3N_4O_3^+$ $[M+H]^+$ 341.0856; found 341.0859. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.62 min, λ = 220 nm. m.p.: 163 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.14.

4-(4,4,4-Trifluoro-3-(pyrazin-2-ylamino)butanoyl)benzonitrile (3f)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 4'-cyanoacetophenone (99 mg, 0.68 mmol). After stirring at rt (1 h) followed by stirring at 40 °C (1h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at −78 °C (10 min), 4'-cyanoacetophenone (65 mg, 0.45 mmol) was added and the reaction mixture was stirred at 40 °C (1 h). Subsequent aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) and recrystallization (^{c}hex) furnished the β-amino ketone **3f** (131 mg, 0.41 mmol, 91 %) as a colorless crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18 – 8.09 (m, 2H, $H3_{ph}$, $H5_{ph}$), 8.05 – 8.02 (m, 2H, $H2_{ph}$, $H6_{ph}$), 8.01 (m, 1H, H6), 7.96 (d, $J_{H3,H6}$ = 1.4 Hz, 1H, H3), 7.82 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.46 (d, $J_{NH,CH}$ = 8.1 Hz, 1H, NH), 5.53 – 5.28 (m, 1H, CH), 3.68 (dd, $J_{CH2,CH2}$ = 18.1 Hz, $J_{CH2,CH}$ = 9.3 Hz, 1H, CH_2), 3.61 (dd, $J_{CH2,CH2}$ = 18.0 Hz, $J_{CH2,CH}$ = 3.9 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.84 (C=O), 154.01 (C2), 141.45 (C6), 139.30 ($C1_{ph}$), 133.16 (C3), 133.15 (C5), 132.94 ($C2_{ph}$, $C6_{ph}$), 128.88 ($C3_{ph}$, $C5_{ph}$), 126.24 (q, $^1J_{C,F}$ = 282.7 Hz, CF_3), 118.22 (C≡N), 115.61 (C-CN), 47.24 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 37.69 (CH_2) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.37 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{15}H_{12}F_3N_4O^+$ $[M+H]^+$ 321.0958; found 321.0959. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.56 min, λ = 220 nm. m.p.: 185 °C. R_f (^{c}Hex/EtOAc = 1:1) = 0.37.

4,4,4-Trifluoro-1-(perfluorophenyl)-3-(pyrazin-2-ylamino)butan-1-one (3g)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 2',3',4',5',6'-pentafluoroacetophenone (0.10 mL, 0.68 mmol). After stirring at rt (1 h) followed by stirring at 40 °C (2 h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at −78 °C (10 min), 2',3',4',5',6'-pentafluoroacetophenone (0.07 mL, 0.45 mmol) was added and the

reaction mixture was stirred at 40 °C (20 h). Subsequent aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc 4/1) and recrystallization (^{c}hex/EtOAc 9/1) furnished the β-amino ketone **3g** (61 mg, 0.16 mmol, 35 %) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 – 7.97 (m, 2H, H6, H3), 7.84 (d, $J_{H5,H6}$ = 2.3 Hz, 1H, H5), 7.70 (d, $J_{NH,CH}$ = 8.8 Hz, 1H, NH), 5.51 – 5.37 (m, 1H, CH), 3.55 (dd, $J_{CH2,CH2}$ = 17.7 Hz, $J_{CH2,CH}$ = 4.0 Hz, 1H, CH_2), 3.40 (dd, $J_{CH2,CH2}$ = 17.7 Hz, $J_{CH2,CH}$ = 9.7 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 189.83 (C=O), 153.88 (C2), 146.07 – 145.78 (m, C-F), 144.42 – 144.10 (m, C-F), 143.55 - 143.31 (m, C-F), 141.56 (C6), 139.00 - 138.65 (m, C-F), 136.52 - 136.16 (m, C-F), 133.64 (C5), 133.49 (C3), 126.01 (q, $^1J_{C,F}$ = 283.0 Hz, CF_3), 113.99 - 113.63 (m, C-F), 47.15 (q, $^2J_{C,F}$ = 30.8 Hz, CH), 43.49 (CH_2) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.68 (d, $J_{CF3,CH}$ = 7.8 Hz, CF_3), – 140.87 – –141.17 (m, F2, F6), – 149.30 (tt, $J_{F4,F3}$ = $J_{F4,F5}$ = 22.2 Hz, $J_{F4,F2}$ = $J_{F4,F6}$ = 4.4 Hz, F4), – 160.93 – –161.21 (m, F3, F5) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{14}H_8F_8N_3O^+$ $[M+H]^+$ 386.0534; found 386.0534. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.74 min, *λ* = 220 nm. m.p.: 115 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.30.

4,4,4-Trifluoro-1-(furan-2-yl)-3-(pyrazin-2-ylamino)butan-1-one (3h)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMSD (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 2-acetylfuran (75 mg, 0.68 mmol). After stirring at rt (2 h), aqueous workup and column chromatography (^{c}hex/EtOAc 1.5/1 → 1/1) the β-amino ketone **3h** (75 mg, 0.26 mmol, 58 %) was obtained as a light yellow oil. ^{1}H NMR (800 MHz, DMSO-d_6): δ = 8.02 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 8.00 (dd, $J_{H5furan,H4furan}$ = 1.7 Hz, $J_{H5furan,H3furan}$ = 0.7 Hz, 1H, $H5_{furan}$), 7.95 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.80 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.57 (d, $J_{NH,CH}$ = 8.5 Hz, 1H, NH), 7.52 (dd, $J_{H3furan,H4furan}$ = 3.6 Hz, $J_{H3furan,H5furan}$ = 0.7 Hz 1H, $H3_{furan}$), 6.73 (dd, $J_{H4furan,H3furan}$ = 3.6 Hz, $J_{H4furan,H5furan}$ = 1.7 Hz, 1H, $H4_{furan}$), 5.47 – 5.29 (m, 1H, CH), 3.43 – 3.37 (m, 1H, CH_2), 3.31 (dd, $J_{CH2,CH2}$ = 17.1 Hz, $J_{CH2,CH}$ = 3.8 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 183.44 (C=O), 153.91 (C2), 151.57 ($C2_{furan}$), 148.36 ($C5_{furan}$), 141.45 (C6), 133.15 (C3, C5), 129.19 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3), 119.42 ($C3_{furan}$), 112.92 ($C4_{furan}$), 47.02 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 36.95 (CH_2) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.52 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{12}H_{11}F_3N_3O_2^+$ $[M+H]^+$ 286.0798; found 286.0797 HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 12.68 min, *λ* = 214 nm. R_f (^{c}Hex/EtOAc = 1:1) = 0.32.

4,4,4-Trifluoro-1-(1-methyl-1H-indol-3-yl)-3-(pyrazin-2-ylamino)butan-1-one (3i)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 1-(1-methyl-1H-indol-3-yl)ethan-1-one (117 mg, 0.68 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (CH_2Cl_2 → CH_2Cl_2/(CH_2Cl_2/MeOH 10:1) 7/3) and recrystallization (^{c}hex) the β-amino ketone (105 mg, 0.30 mmol, 67 %) was obtained as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.46 (s, 1H, $H2_{in}$), 8.12 (d, $J_{H7in,H6in}$ = 7.6 Hz, 1H, $H7_{in}$), 8.03 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.98 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.79 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.54 (m, 2H, NH, $H4_{in}$), 7.32 – 7.25 (m, 1H, $H5_{in}$), 7.21 (td, $J_{H6in,H7in/H5in}$ = 7.6 Hz, $^4J_{H6in,H4in}$ = 1.0 Hz, 1H, $H6_{in}$), 5.59 – 5.41 (m, 1H, CH), 3.89 (s, 3H, NCH_3), 3.45 (dd, $J_{CH2,CH2}$ = 16.5 Hz, $J_{CH2,CH}$ = 9.8 Hz, 1H, CH_2), 3.26 (dd, $J_{CH2,CH2}$ = 16.5 Hz, $J_{CH2,CH}$ = 3.5 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.98 (C=O), 154.06 (C2), 141.51 (C6), 138.37 ($C2_{in}$), 137.39 (C_{quart}-N), 133.11 (C3), 132.92 (C5), 126.53 (q, $^1J_{C,F}$ = 283.0 Hz, CF_3) 125.75 ($C3_{in}$), 123.21 ($C5_{in}$), 122.46 ($C6_{in}$), 121.47 ($C7_{in}$), 115.00 (C_{quart}), 110.81 ($C4_{in}$), 47.42 (q, $^2J_{C,F}$ = 30.1 Hz, CH), 37.64 (CH_2), 33.35 (CH_3) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.34 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{17}H_{16}F_3N_4O^+$ $[M+H]^+$ 349.1271; found 349.1273. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.60 min, *λ* = 220 nm. m.p.: 198 °C. R_f (^{c}Hex/EtOAc = 1:1) = 0.17.

(*E*)-6,6,6-trifluoro-1-phenyl-5-(pyrazin-2-ylamino)hex-1-en-3-one (3j)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with (*E*)-4-phenylbut-3-en-2-one (99 mg, 0.68 mmol). After stirring at rt (2 h), aqueous workup and column chromatography (^{c}hex/EtOAc 3/1 → 1/1) the β-amino ketone (92 mg, 0.29 mmol, 64 %) was obtained as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.99 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.80 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.74 – 7.70 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.67 (d, $J_{Ha,Hb}$ = 16.3 Hz, 1H, H_a), 7.53 (d, $J_{NH,CH}$ = 8.5 Hz, 1H, NH), 7.47 – 7.42 (m, 3H, $H3_{ph}$, $H4_{ph}$, $H5_{ph}$,), 6.96 (d, $J_{Hb,Ha}$ = 16.3 Hz, 1H, H_b), 5.48 – 5.31 (m, 1H, CH), 3.32 – 3.24 (m, 1H, CH_2), 3.19 (dd, $J_{CH2,CH2}$ = 17.3 Hz, $J_{CH2,CH}$ = 3.6 Hz, 1H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 195.11 (C=O), 154.02 (C2), 143.33 (C_a), 141.45 (C6), 134.32 ($C1_{ph}$), 133.18 (C3), 133.05 (C5), 130.88 ($C4_{ph}$), 129.16 ($C3_{ph}$, $C5_{ph}$), 128.68 ($C2_{ph}$, $C6_{ph}$), 126.31 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3) 126.10 (C_b), , 47.20 (q, $^2J_{C,F}$ = 30.3 Hz, CH) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.50 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{16}H_{15}F_3N_3O^+$ $[M+H]^+$ 322.1162; found 322.1160. R_f (^{c}Hex/EtOAc = 1:1) = 0.55.

4,4,4-Trifluoro-2-methyl-1-phenyl-3-(pyrazin-2-ylamino)butan-1-one (3k)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with propiophenone (0.09 mL, 0.68 mmol). After stirring at rt (2 h), aqueous workup and column chromatography (^{c}hex/EtOAc 3/1 → 2/1) the β-amino ketone **3k** (95 mg, 0.31 mmol, 68 %) was obtained as a colorless solid (mixture of diastereomeres). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 – 7.98 (m, 4H, H6, H3, $H2_{ph}$, $H6_{ph}$), 7.80 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.71 – 7.65 (m, 1H, $H4_{ph}$), 7.60 – 7.53 (m, 3H, $H3_{ph}$, $H5_{ph}$, NH), 5.36 – 5.23 (m, 1H, CH), 4.17 (dq, $J_{CHCH3,CH}$ = 14.2 Hz, $J_{CHCH3,CH3}$ = 7.0 Hz 1H, C*H*CH_3), 1.25 (dd, $J_{CH3,CHCH3}$ = 7.0 Hz, $J_{CH3,CF3}$ = 1.1 Hz 3H, CH_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 199.81 (C=O), 153.69 (C2), 141.17 (C6), 135.21 ($C1_{ph}$), 133.65 (C5), 133.12 ($C4_{ph}$), 132.96 (C3), 128.90 ($C3_{ph}$, $C5_{ph}$), 128.43 ($C2_{ph}$, $C6_{ph}$), 126.13 (q, $^1J_{C,F}$ = 284.3 Hz, CF_3), 52.21 (q, $^2J_{C,F}$ = 28.8 Hz, CH), 26.32 (*C*HCH_3), 14.60 (d, $^4J_{C,F}$ = 1.9 Hz, CH_3) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 69.65 (dd, $J_{CF3,CH}$ = 8.4 Hz, $J_{CF3,CH3}$ = 1.1 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{15}H_{15}F_3N_3O^+$ $[M+H]^+$ 310.1162; found 310.1160. HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 15.79 min, 15.97 min, *λ* = 214 nm. m.p.: 95 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.37.

4,4,4-Trifluoro-2,2-dimethyl-1-phenyl-3-(pyrazin-2-ylamino)butan-1-one (3l)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 2-methyl-1-phenylpropan-1-one (0.1 mL, 0.68 mmol). After stirring at rt (3 h), aqueous workup and column chromatography (^{c}hex/EtOAc 3/1 → 2/1) the β-amino ketone **3l** (32 mg, 0.10 mmol, 22 %) was obtained as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.20 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 8.00 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.82 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.75 – 7.68 (m, 1H, $H4_{ph}$), 7.67 – 7.61 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.58 – 7.51 (m, 1H, NH), 7.47 (m, 2H, $H3_{ph}$, $H5_{ph}$), 6.01 (m, 1H, CH), 1.40 (s, 3H, CH_3), 1.27 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 206.17 (C=O), 154.05 (C2), 141.02 (C6), 137.80 ($C1_{ph}$), 133.52 (C5), 133.14 ($C4_{ph}$), 131.20 (C3), 128.36 ($C3_{ph}$, $C5_{ph}$), 127.29 ($C2_{ph}$, $C6_{ph}$), 125.73 (q, $^1J_{C,F}$ = 284.7 Hz, CF_3), 54.13 (q, $^2J_{C,F}$ = 27.6 Hz, CH), 49.48 ($C(CH_3)_2$), 24.02 (CH_3), 20.37 (d, $^4J_{C,F}$ = 1.1 Hz, CH_3) ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 67.66 (d, $J_{CF3,CH}$ = 8.9 Hz, CF_3) ppm. HR-ESI-MS (positive, m/z) calc. for $C_{16}H_{17}F_3N_3O^+$ $[M+H]^+$ 324.1318; found 324.1318. HPLC (0.1 % TFA; 0 min, 4 % B → 15 min, 100 % B, flow: 1 mL/min): *tR* = 15.83 min, λ = 214 nm. m.p.: 130 °C. R_f (^{c}Hex/EtOAc = 2:1) = 0.29.

2-(2,6-Dichlorophenyl)-4,4,4-trifluoro-3-(pyrazin-2-ylamino)butanenitrile (3m)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with 2,6-dichlorphenylacetonitrile (202 mg, 1.09 mmol). After stirring at rt (2.5 h), aqueous workup, column chromatography (^{c}hex/EtOAc 5/1 → 3/1) and washing with toluene the β-amino ketone **3m** (148 mg, 0.41 mmol, 44 %) was obtained as a colorless solid (mixture of diastereomeres). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (d, $J_{H3ar,H4ar}$ = 9.6 Hz, 1H, $H3_{ar}$), 8.18 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 8.09 (dd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.94 (d, $J_{H5,H6}$ = 2.7 Hz, 1H, H5), 7.65 (s, 2H, NH, $H5_{ar}$), 7.53 (t, $J_{H4ar,H3ar/H5ar}$ = 8.1 Hz, 1H, $H4_{ar}$), 6.22 – 6.07 (m, 1H, CH), 5.51 (d, $J_{CHCN,CH}$ = 10.5 Hz, 1H, CHCN) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.60 (C2), 140.63 (C6), 135.21 ($C1_{ph}$), 133.83 (C5), 132.89 (C3), 131.79 ($C2_{ph}$, $C6_{ph}$), 129.30 ($C4_{ph}$), 128,21 (q, $^1J_{C,F}$ = 283.9 Hz, CF_3), 126.23 ($C3_{ph}$, $C5_{ph}$), 114.98 (C≡N), 50.71 (q, $^2J_{C,F}$ = 30.2 Hz, *C*-CF_3), 32.00 (*C*-CN). ^{19}F NMR (471 MHz, DMSO-d_6): δ = – 71.63 (br s, CF_3) ppm. HR-EI-MS (m/z) calc. for $C_{14}H_9Cl_2F_3N_4^+$ $[M]^+$ 360.0156; found 360.0177. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.68 min, 1.73, λ = 220 nm.

Diethyl 2-(2,2,2-trifluoro-1-(pyrazin-2-ylamino)ethyl)malonate (3n)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.42 mL, 1.42 mmol) and reacted with diethyl malonate (0.16 mL, 1.02 mmol). After stirring at rt (2 h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.68 mL, 0.68 mmol) was added. Stirring was continued at −78 °C (10 min), diethyl malonate (0.1 mL, 0.68 mmol) was added and the reaction mixture was stirred at 40 °C (2 h). Subsequent aqueous workup and column chromatography (^{c}hex/EtOAc 3/1) furnished the desired β-amino ketone **3n** (134 mg, 0.40 mmol, 40 %) as a light yellow oil. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.09 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 8.07 (dd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.87 (d, $J_{H5,H6}$ = 2.7 Hz, 1H, H5), 7.71 (d, $J_{NH,CH}$ = 9.5 Hz, 1H, NH), 5.73 – 5.59 (m, 1H, CH), 4.23 – 3.94 (m, 4H, 2 × CH_2), 1.16 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3H, CH_3), 1.01 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.19 (C=O), 164.99 (C=O), 153.23 (C2), 141.06 (C6), 133.57 (C5), 133.31 (C3), 124.90 (q, $^1J_{C,F}$ = 283.5 Hz, CF_3), 61.97 (CH_2), 61.70 (CH_2), 51.66 ($CH(CO_2Et)_2$), 49.70 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 13.63 (CH_3), 13.51 (CH_3) ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ = – 72.79 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. HR-EI-MS (m/z) calc. for $C_{13}H_{16}F_3N_3O_4^+$ $[M]^+$ 335.1093; found 335.1104. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.62 min, λ = 220 nm. R_f (^{c}Hex/EtOAc = 2:1) = 0.31.

Ethyl 4,4,4-trifluoro-3-(pyrazin-2-ylamino)butanoate (3o)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (90 mg, 0.41 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.94 mL, 0.94 mmol) and reacted with ethylacetate (0.06 mL, 0.62 mmol). After stirring at rt (1 h), aqueous workup and flash chromatography (^{c}hex → ^{c}hex/EtOAc 3/1) the β-amino ester **3o** (27 mg, 0.10 mmol, 25 %) was obtained as a light yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.12 – 7.91 (m, 2H, H6, H3), 7.82 (d, $J_{H5,H6}$ = 2.3 Hz, 1H, H5), 7.65 (d, $J_{NH,CH}$ = 8.9 Hz, 1H, NH), 5.40 – 5.18 (m, 1H, CH), 4.03 (m, 2H, OCH_2), 2.92 (dd, $J_{CH2,CH2}$ = 16.2 Hz, $J_{CH2,CH}$ = 4.2 Hz, 1H, CH_2), 2.72 (dd, $J_{CH2,CH2}$ = 16.2 Hz, $J_{CH2,CH}$ = 10.0 Hz, 1H, CH_2), 1.06 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 168.76 (C=O), 153.64 (C2), 141.15 (C6), 133.11 (C5), 133.06 (C3), 125.57 (q, $^1J_{C,F}$ = 283.2 Hz, CF_3), 60.47 (OCH_2), 47.83 (q, $^2J_{C,F}$ = 30.7 Hz, CH), 33.58 (CH_2), 13.76 (CH_3). ^{19}F NMR (376 MHz, DMSO-d_6): δ = – 74.89 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. HR-EI-MS (m/z) calc. for $C_{10}H_{12}F_3N_3O_2^+$ $[M]^+$ 263.0882; found 263.0898. HPLC-MS (0.05 % formic acid; 0 min, 0 % B → 2.0 min, 100 % B, flow: 3.3 mL/min): *tR* = 1.43 min, λ = 220 nm. R_f (^{c}Hex/EtOAc = 2:1) = 0.15.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561324.

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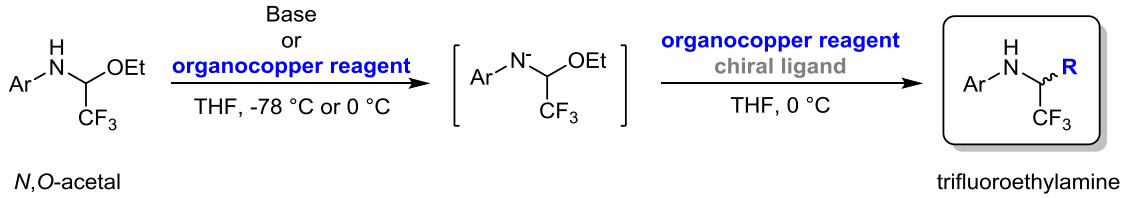
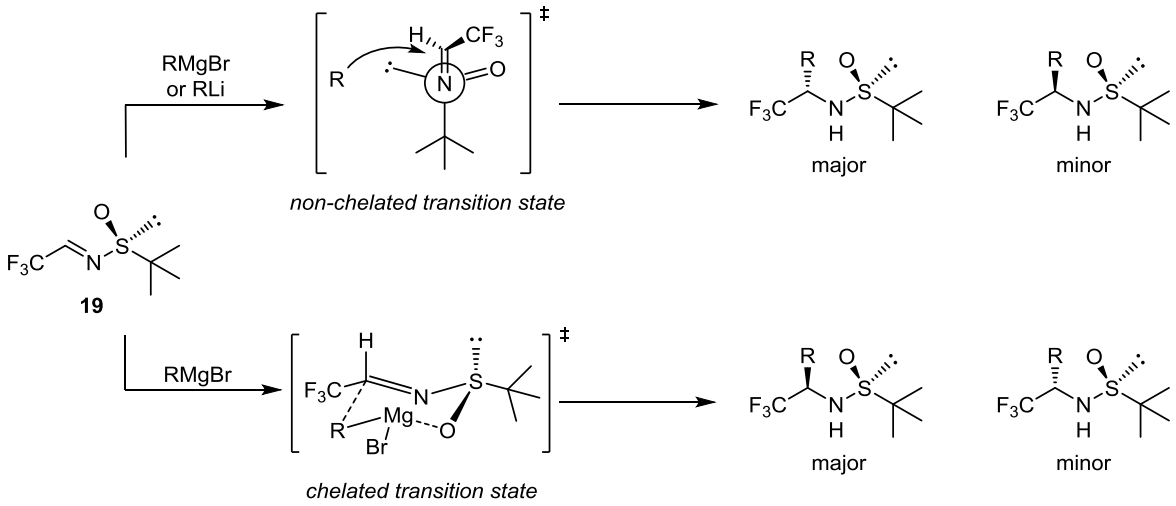
4. Strategy toward a Stereoselective Synthesis of Trifluoroethylamines



Background

As soon as a compound exhibits a good profile in preclinical testing and is considered as a potential clinical candidate, stereoselective synthesis of the target molecule is typically required in drug discovery. Even though being particularly interesting as amide surrogates, the enantioselective preparation of chiral trifluoroethylamines has only been scarcely pursued in drug design. Also, the protocols developed in this thesis only provided racemic products, thus making attempts toward stereoselective procedures highly desirable.

To date, two main approaches to control stereochemistry during trifluoroethylamine formation are reported in literature: (i) auxiliary-based methods and (ii) the application of chiral ligands.[143, 150-152] Both strategies require the presence of (transient) imine species which are subsequently attacked by an appropriate nucleophile. Procedures using auxiliary substituents exploit the directing influence of the chiral auxiliary moiety during formation of the diastereomeric products. The *Ellman´*s auxiliary is commonly used in the enantioselective synthesis of amines from ketones and aldehydes.[185-186] The resulting *N-tert*-butanesulfinyl aldimine and ketamine are reactive intermediates which can be reacted with a wide range of nucleophiles, including organomagnesium and -lithium reagents.[185-187] Regarding the synthesis of enantioenriched trifluoroethylamines, *N-tert*-butanesulfinamide is widely used to introduce a chiral center by formation of a trifluoromethylated imine **19**, which is subsequently reacted with organolithium or *Grignard* reagents (see Scheme 18). The influence of the auxiliary is predicted to proceed either *via* a non-chelated or a chelated transition state model.[143]



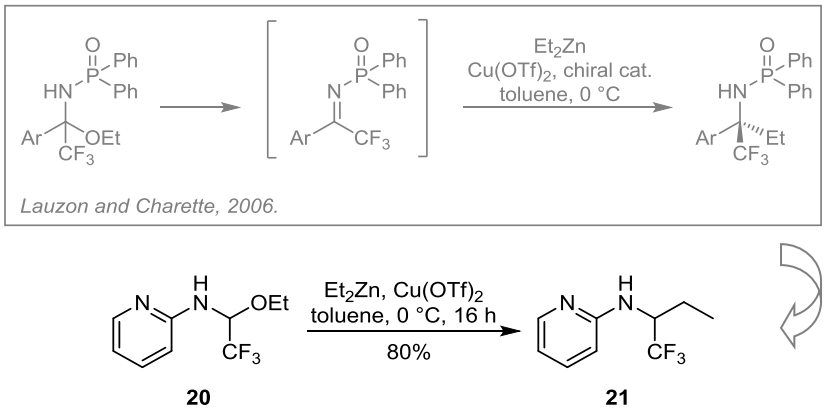
Scheme 18. Predicted transition state models for diastereoselectivity.[143]

Interestingly, organolithium reagents favor addition from the less hindered face indicating a non-chelated transition state, whereas most *Grignard* reagents seem to react *via* a six-membered chelated transition state, in which the oxygen atom of the auxiliary coordinates to magnesium directing the addition of the carbon nucleophile preferably to the *re*-side.[143]

Even though asymmetric addition reactions using organomagnesium reagents are reported, the majority of these synthetic strategies so far are controlled by chiral substrates.[143, 150, 158, 188] However, auxiliary-based protocols exclude initial *N*-functionalization and require additional cleaving steps. While stereocontrolled synthesis *via* application of chiral ligands require only catalytic amounts of the precious ligand to be employed, diastereoselective auxiliary-based approaches using stoichiometric amounts are rather expensive. Thus, and regarding precedence in the literature, we aimed at developing a stereocontrolled approach toward generation of trifluoroethylamines using chiral ligands. In a reported procedure, *Lauzon* and *Charette* accessed *N*-phosphinoyl-substituted trifluoroethylamines in a copper-catalyzed addition of dimethyl and diethyl zinc using a chiral ligand.[151] We initially focused on modifying our developed protocol toward addition of organozinc reagents in a copper-catalyzed reaction to elucidate a possible ligand-based enantioselective synthesis of trifluoroethylamines from trifluoromethylated *N*,*O*-acetals.

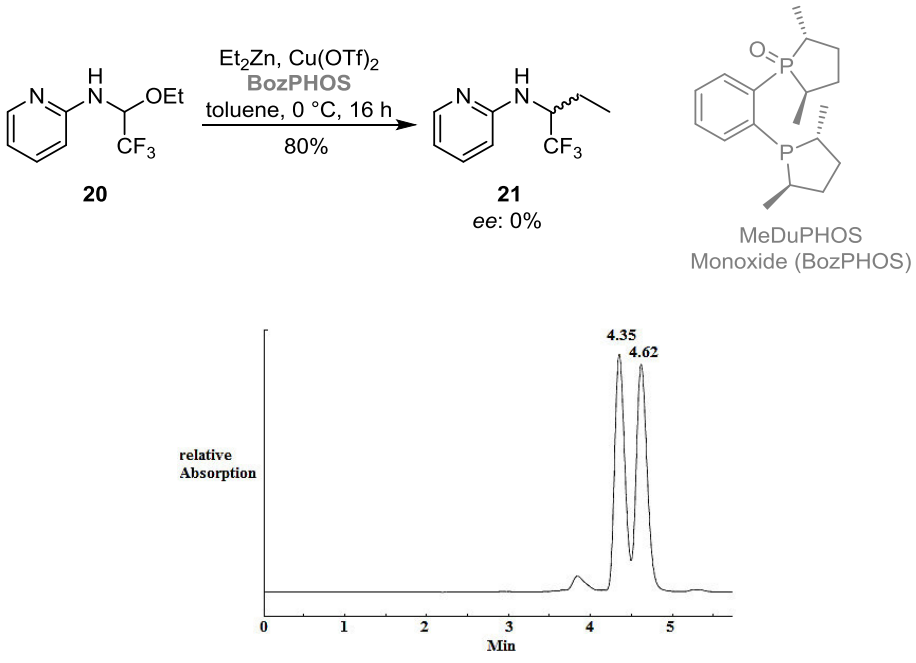
Results and Discussion

Initially, we transferred the procedure by *Lauzon* and *Charette* to the conversion of *N*-aryl hemiaminal ethers to gain insight into copper-catalyzed reactions. To our delight, reaction of 2-pyridyl *N*,*O*-acetal **20** with commercially available Et_2Zn and catalytic amounts of $Cu(OTf)_2$ proceeded smoothly and furnished the corresponding amine **21** in 80% yield without formation of any byproducts (Scheme 19).



Scheme 19. Synthesis of *N*-(1,1,1-trifluorobutan-2-yl)pyridin-2-amine **21**.

To alter stereoselectivity of the carbon-carbon bond formation, MeDuPHOS monoxide (BozPHOS) was employed as a chiral ligand and the resulting amine **21** was analyzed *via* chiral HPLC. In contrast to the reported conversion of *N*-phosphinoyl hemiaminal ethers, the addition of the chiral ligand had no effect on the ratio of the two enantiomers as illustrated in the HPLC spectrum of the isolated product in Scheme 20. However, screening of further chiral ligands should be pursued in terms of a collaboration to investigate the stereoselectivity of this procedure.

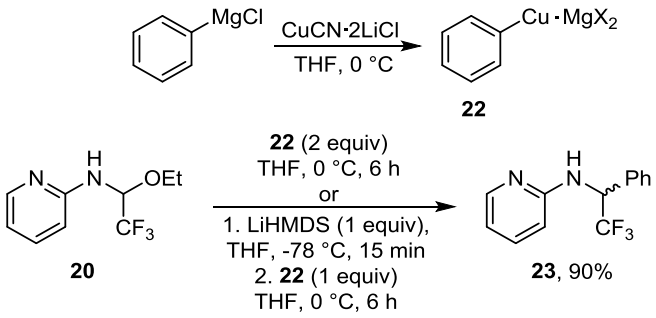


Scheme 20. Synthesis of amine **21** adding MeDuPHOS monoxide and HPLC spectrum of the isolated product.

As the procedure reported by *Lauzon* and *Charette* is limited to the use of diethyl- and dimethylzinc species, we then turned our attention to the transmetallation of previously used organomagnesium reagents into the corresponding organocopper species. Thus, we aimed at enhancing the accessibility of a broad scope of functionalization patterns of the potentially chiral trifluoroethylamines. Due to their throttled reactivity, organocopper reagents are applicable to a large substrate and ligand scope and have been successfully employed in stereoselective addition reactions to imines in the presence of chiral ligands.[151, 188-189] Therefore,

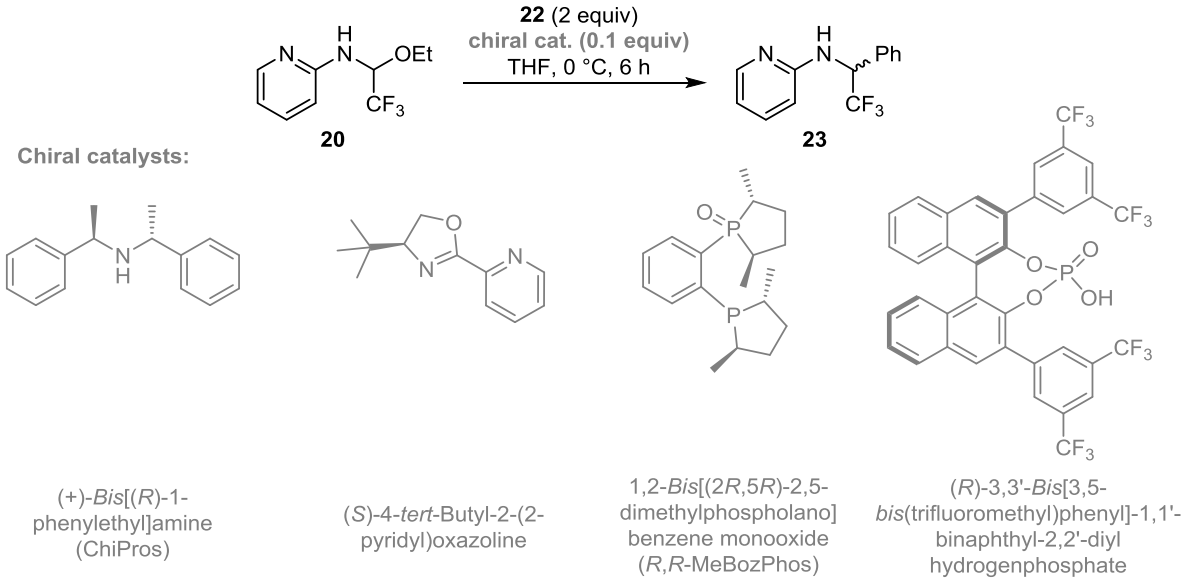
transmetallation of previously used organomagnesium reagents to less reactive organocopper(I) species was pursued.

In situ conversion of phenylmagnesium chloride (2 equiv) to phenylcopper(I) **22** using CuCN·2LiCl and subsequent reaction with one equivalent of *N*,*O*-acetal **20** furnished the corresponding trifluoroethylamine **23** in excellent yield (Scheme 21). Interestingly, the basicity of the copper reagent was sufficient to deprotonate the hemiaminal ether as no external base was needed for a complete conversion of the starting material. In a subsequent experiment the *N*,*O*-acetal **20** was deprotonated with one equivalent of lithium *bis*(trimethylsilyl)amide (LiHMDS) before addition of the phenylcopper species (1 equiv). Fortunately, employing an external base did not compromise product yield.



Scheme 21. Synthesis of trifluoroethylamine **23**.

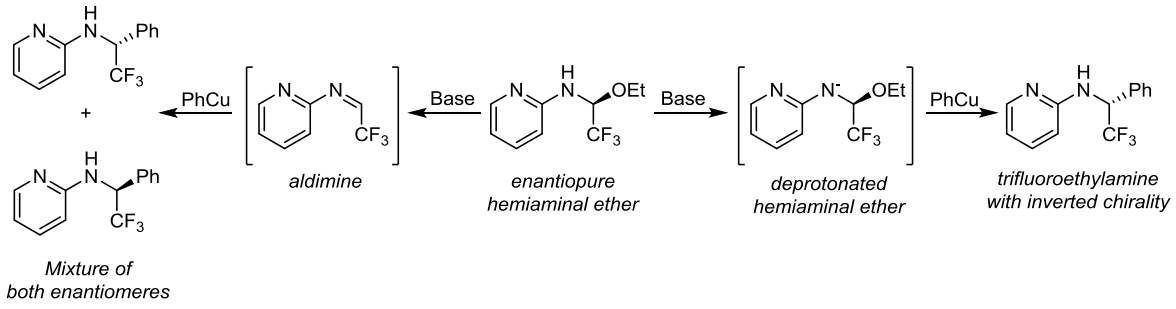
With a successful modified synthetic protocol in hand, we investigated the effect of chiral ligands in preliminary experiments. Using a variety of ligand classes, we aimed at gaining insight into the structural requirements of the ligands directing stereoselectivity. Thus, we screened a first set of chiral ligands (chiral amine, oxazoline, phosphate and phospholane ligands depicted in Scheme 22) by adding 0.1 equivalents of a chiral ligand to the organocopper reagent. Unfortunately, no stereocontrol was observed in these reactions.



Scheme 22. Synthesis of **23**, screening different classes of chiral ligands.

Although somehow surprisingly at first sight, the lack of stereocontrol might be attributed to mechanistic considerations. As described previously, we expected the addition reaction to proceed *via* a prochiral aldimine intermediate. Formation of an enantioselective transition state by coordination of the aldimine to a copper-ligand complex might then result in a preferred conformation of the trifluoroethylamine. However, it is also possible that the nucleophilic attack proceeds *via* a S_N2-type mechanism resulting in a formal inversion of configuration.

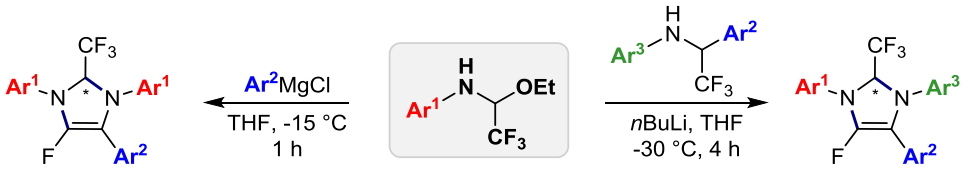
To draw conclusions from the preliminary experiments, the mechanism of the reaction needs to be elucidated in the future. Thus, a racemic mixture of the hemiaminal ether should be separated (i.e. *via* preparative chiral HPLC). Subsequently, the enantiopure substrate can be reacted under the stated reaction conditions. Stereochemical analysis of the resulting product may then give insight into the transition state of the mechanism (Scheme 23). With the profound knowledge of the reaction intermediates regarding the postulated aldimine formation, a successful asymmetric synthesis of *N*-aryl trifluoroethylamines may be developed. Due to time constraints and limited resources of chiral ligands this project will be pursued in terms of a collaboration in the near future.



Scheme 23. Mechanistic considerations for stereoselective synthesis of trifluoroethylamines. Conversion of enantiopure hemiaminal ether could either result in enantiopure formation of the corresponding trifluoroethylamine *via* deprotonation of the substrate or in a mixture of both enantiomers suggesting an *in situ* formation of an aldimine.

5. One-Pot Synthesis of Substituted Trifluoromethylated 2,3-Dihydro-1*H*-imidazoles

A. Deutsch, C. Jessen, C. Deutsch, K. Karaghiosoff and A. Hoffmann-Röder, *Org. Lett.* **2016**, 18 (14), 3474–3477.

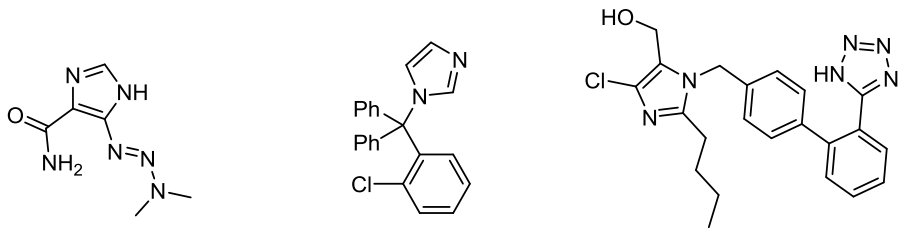


Declaration of Contribution

I developed a method to access novel trifluoromethylated 2,3-dihydro-1*H*-imidazoles in a one-pot reaction starting from trifluoromethylated *N*,*O*-acetals and aryl *Grignard* reagents. In the course of his bachelor thesis, *Christoph Jessen* synthesized a set of functionalized imidazole derivatives by variation of the *N*,*O*-acetals and the arylmagnesium reagents under my supervision.[190] To elucidate the mechanism of this reaction, *Prof. Dr. K. Karaghiosoff* and I performed low temperature NMR experiments. With the knowledge gained from these experiments, I extended the methodology to the synthesis of further functionalized fluoroalkylated imidazoles by conversion of trifluoroethylamines and *N*,*O*-acetals under basic conditions.

Background

The imidazole motif is present in many major building blocks of living organisms, e.g. the amino acid histidine, the purine-based DNA nucleobases, vitamin B12 and histamine. Ever since its discovery in the 19th century, the development and potential application of imidazoles has become a flourishing, rapidly growing field of interest.[191] The unique structure of the imidazole core, which is highly polar and amphoteric, has multiple beneficial binding modes allowing imidazole derivatives to bind with a large number of enzymes and biological systems.[192] Due to their high potency imidazole-based research has a prominent role in medicinal chemistry.[193-195] For instance, imidazole related compounds can be found in clinical drugs with anticancer, antiparasitic, antifungal, antibacterial, antihypertensive and anti-HIV activity.[196-200] A few selected examples are depicted in Scheme 24.

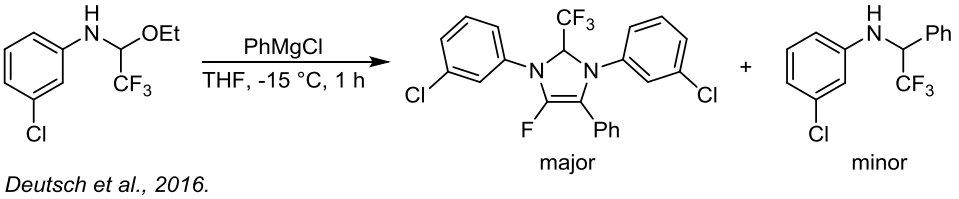


Scheme 24. Selected examples of imidazole-based drugs.

Even though numerous examples of biologically active imidazole-based drugs are available, medicinal scaffolds containing a fluorinated imidazole core are quite limited.[201-202] Therefore, simple synthetic strategies toward novel fluorinated imidazole derivatives, supplementing the positive effects of fluorination (see I.2) and the biological potential of imidazole structures, may be highly rewarding.

In the course of our project on the synthesis of trifluoromethylated amines from *N*,*O*-acetals and functionalized *Grignard* reagents, we found by serendipity that the 3-chlorophenyl-substituted *N*,*O*-acetal reacts with an excess of phenylmagnesium chloride forming a *N*-aryl trifluoromethylated imidazole derivative bearing an additional fluorine in position C-4. Suprisingly, the previously obtained trifluoroethylamine was only isolated in a low yield (Scheme 25). These structurally novel and highly functionalized imidazole derivatives aroused our interest to further investigate the scope and mechanism of this complex one-pot reaction. After optimization of the reaction conditions, we therefore studied the scope of imidazole formation by variation of the *N*,*O*-acetals and functionalized *Grignard* reagents employed. In addition, low temperature NMR experiments were conducted to elucidate a possible reaction mechanism, which enabled us to extend the method to higher substituted fluorinated imidazole derivatives by reacting trifluoromethylated *N*,*O*-acetals and trifluoroethylamines under basic reaction conditions.[203]

Synthesis of highly functionalized, fluorinated imidazoles:



Deutsch et al., 2016.

Scheme 25. Synthesis of novel trifluoromethylated imidazoles.[203]

Organic LETTERS

Letter

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One-Pot Synthesis of Substituted Trifluoromethylated 2,3-Dihydro-1*H*-imidazoles

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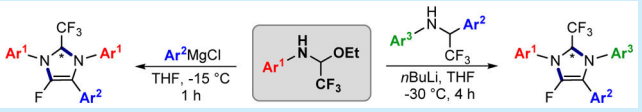
Supporting Information

ABSTRACT: An operationally simple one-pot reaction for the preparation of a novel class of racemic trifluoromethylated 2,3-dihydro-1*H*-imidazoles derived from electron-poor *N*,*O*-acetals and aryl Grignard reagents is described. In addition, access to highly functionalized 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles was accomplished by reaction of *N*-aryl hemiaminal ethers and *N*-aryl trifluoroethylamines in the presence of an excess of *n*-butyllithium.



Owing to their ability to modify important biological and physicochemical properties, fluorinated substructures are widely employed in the synthesis of agrochemicals and pharmaceuticals.[1] The rationale for the incorporation of fluorine substituents mostly relies on their positive effects on metabolic stability, bioavailability, lipophilicity, and binding selectivity/affinity of the parent compound.[1a] Driven by these potential rewards, research on innovative methods for the preparation of specifically fluorinated molecules is of considerable interest. In particular, improved strategies for efficient and controlled incorporation of CF_3 groups are highly desired.[2] Beyond the growing number of approaches toward late stage fluorinations,[3] the use of fluorinated building blocks for quick and flexible scaffold assembly is still a vital strategy pursued in medicinal chemistry.[4]

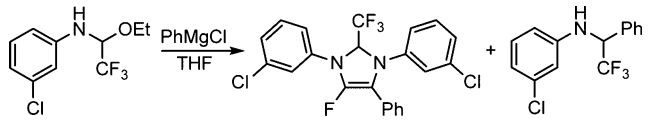
Despite a large and diverse set of known biologically active compounds possessing imidazole ring structures,[5] the number of pharmaceuticals and agrochemicals comprising fluorinated imidazole and benzimidazole analogs is yet surprisingly limited.[6] This is most presumably due to difficulties in quickly accessing a large number of diverse fluorinated imidazole derivatives during drug discovery. Similarly, pharmacophores containing fluorinated or trifluoromethylated imidazolone derivatives have remained scarce, although 2-imidazolones are present in numerous biologically active compounds with intriguing pharmacological activities.[7]

Recently, we reported the usage of shelf-stable trifluoroacetaldehyde-derived hemiaminal ether building blocks to efficiently access functionalized di- and trifluoromethylated *N*-aryl amine derivatives.[8] In the course of these studies, we also observed formation of unprecedented pentasubstituted 2,3-dihydro-1*H*-imidazoles, bearing a CF_3 group at C-2 and an additional fluorine substituent at C-4 (Figure 1). We now present a straightforward one-pot protocol to access various racemic and highly substituted 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles, which may be regarded as novel versatile CF_3-isosteres of 2-imidazolones for potential pharmaceutical applications.

Figure 1. 2-Imidazolone and trifluoromethylated 2,3-dihydro-1*H*-imidazole.

In our initial study, we found that treating 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** with an excess of phenylmagnesium chloride (PhMgCl, 3 equiv) in tetrahydrofuran (THF) provided trifluoromethylated imidazole derivate **2a** as the main product instead of targeted trifluoroethylamine **3a**, which was only formed in minor amounts (Scheme 1).

Scheme 1. Conversion of Hemiaminal Ether 1a with PhMgCl



1a **2a**, 70% **3a**, 16%

Moreover, by applying the same reaction conditions to hemiaminal ether **1b**, 2-trifluoromethyl-2,3-dihydro-1*H*-imidazole **2b** was obtained as the sole reaction product and no traces of the corresponding trifluoromethylated amine were observed. Interestingly, this transformation required 2.5 equiv of PhMgCl to proceed with full conversion, whereas reduced amounts of

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the Grignard reagent afforded mixtures of hemiaminal ether **1b** and 1*H*-imidazole **2b**. Increasing the reaction temperature of up to 0 °C failed to improve the yield by promoting formation of significant amounts of byproducts, again.

However, the rapid and clean formation of product **2b** at −15 °C in THF encouraged us to explore the scope and generality of this transformation (Figure 2). To our delight,

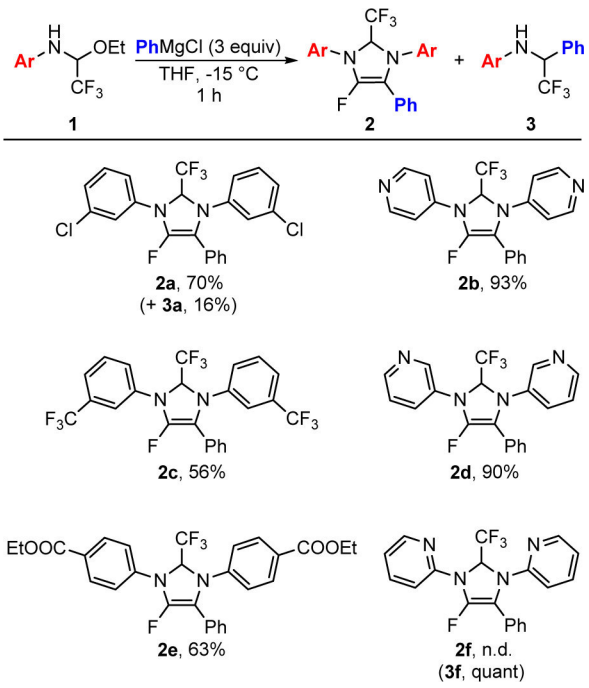


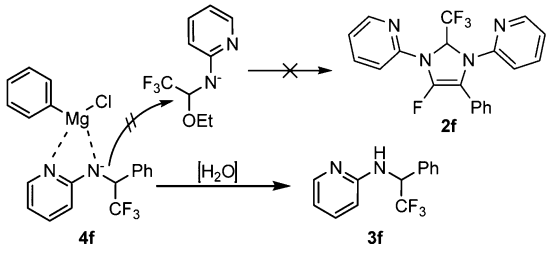
Figure 2. Scope of the reaction of hemiaminal ether **1** with PhMgCl.

diverse *N*-aryl hemiaminal ethers were readily converted into 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles in moderate to high yields. Thereby, even labile functionalities, such as halides and ethyl esters, proved compatible with the reaction conditions.

N,*O*-Acetals derived from electron-poor aminopyridines are a notable exception, where the substitution pattern strongly influences the reaction outcome. Thus, complete conversion to the desired CF_3-imidazole derivatives was only observed for 4-aminopyridyl hemiaminal ether **1b** and 3-aminopyridyl hemiaminal ether **1d**. Contrarily, 2-aminopyridyl derivative **1f** provided the corresponding trifluoroethylamine **3f** exclusively, most presumably due to a stabilizing metal chelate of the deprotonated aminopyridine unit **4f**,[9] which prevents further attack to a second *N*,*O*-acetal molecule, as shown in Scheme 2.

After investigating the scope of *N*,*O*-acetals, we turned our attention to the applicability of functionalized aromatic Grignard reagents for this transformation (Figure 3). Thus, 1-

Scheme 2. Presumed Chelation of Metalated Intermediate 4f



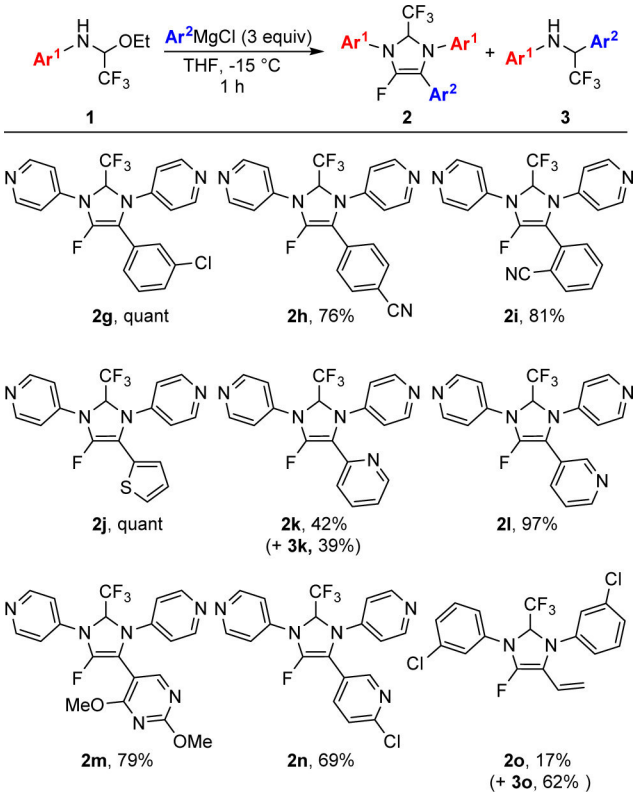


Figure 3. Scope of the reaction of hemiaminal ether **1** with aryl Grignard reagents.

bromo-2-chlorobenzene was converted into the corresponding Grignard reagent by treatment with *i*PrMgCl·LiCl in THF. The latter was then added to a THF solution of the hemiaminal ether **1b** at −15 °C to provide the desired 2-trifluoromethyl-2,3-dihydro-1*H*-imidazole **2g** in quantitative yield. Similarly, Grignard reagents prepared from 4- and 2-bromobenzonitrile afforded the functionalized imidazole derivatives **2h** and **2i** in high yields. As summarized in Figure 3, the reaction is general for Grignard reagents having electron-deficient aryl and heteroaryl groups. It should be noted, however, that reaction of pyrid-2-ylmagnesium chloride with *N*,*O*-acetal **1b** again provided significant amounts of trifluoroethylamine **3k** as a byproduct, most presumably again due to complexation phenomena. Finally, also vinylmagnesium chloride was less effective as a substrate by furnishing increased amounts of trifluoroethylamine **3o**, whereas simple alkyl Grignard reagents failed in this reaction.

A plausible reaction mechanism for the 2-trifluoromethyl-2,3-dihydro-1*H*-imidazole formation is proposed in Scheme 3. Thereby the reaction is initiated by deprotonation of the *N*,*O*-acetal **1b**. The resulting anionic species **5b** then undergoes a nucleophilic substitution reaction with PhMgCl to form the deprotonated trifluoroethylamine **4b**. Subsequent nucleophilic attack at a second *N*,*O*-acetal **5b** affords intermediate **6b**, which after transformation into difluoroenamine **7b** cyclizes under fluoride elimination to the desired reaction product **2b**.

To verify the proposed reaction mechanism, we initially performed low temperature NMR studies, which unfortunately did not disclose any intermediates owing to the high reaction rate. We therefore decided to examine the reaction in a stepwise manner and subjected hemiaminal ether **1b** to deprotonation with 1 equiv of *n*BuLi. Recorded NMR spectra

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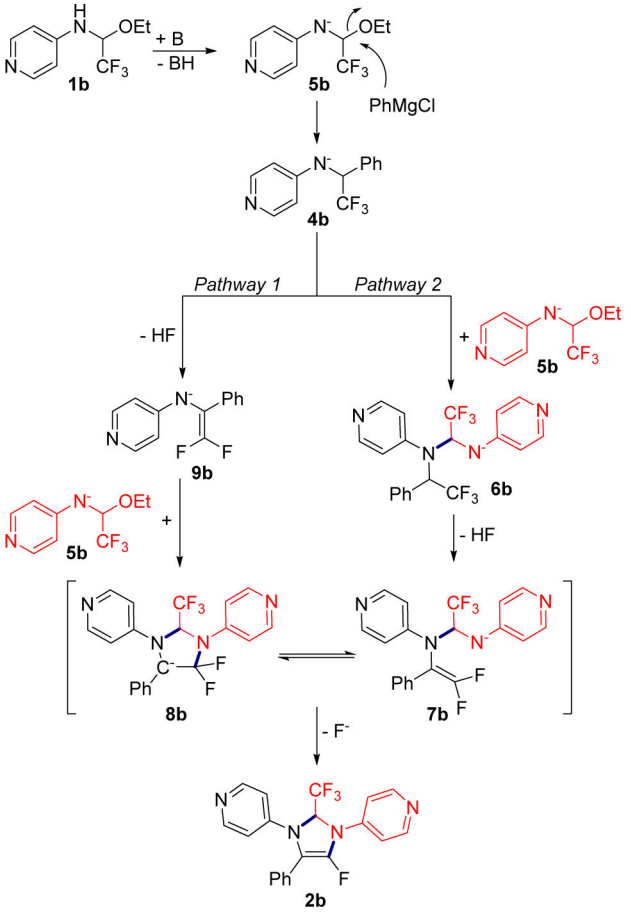
Scheme 3. Proposed Mechanisms for the Formation of Trifluoromethylated 2,3-Dihydro-1*H*-imidazole 2b



of the reaction mixture proved formation of two deprotonated species, which after treatment with iodomethane yielded the corresponding *N*-methylated products. Alternatively, formation of a transient imine species could be postulated, which however was not observed under these conditions.[10] In principle, the reaction could then proceed further, either via substitution product **6b** (*pathway 2*) or involvement of an enamine species **9b** (*pathway 1*), resulting from **4b** by HF elimination. To distinguish between these two possible routes, we aimed at preparation of *gem*-difluoroenamine **9b**, which however was not feasible by treatment of *N*-(2,2,2-trifluoro-1-phenylethyl)-pyridine-4-amine **3b** with PhMgCl. In contrast, using more basic *n*BuLi and **3b** furnished **9b**, which was proven by characteristic resonance signals at −100/−107 ppm in the corresponding ^{19}F NMR spectra (see Supporting Information (SI)).[11] Interestingly, upon increasing the temperature above −30 °C, compound **9b** undergoes exchange of one of the vinylic fluorine atoms by a butyl group (see SI). Since this transformation was not observed under the reaction conditions leading to formation of 1*H*-imidazoles (i.e., in the presence of Grignard reagents), the direct nucleophilic attack of **4b** at *N*,*O*-acetal **5b** to generate **6b** was considered more likely, although formation of intermediate **9b** cannot be fully excluded. Next, generation of intermediate **6b** was attempted by combining a solution of hemiaminal ether **1b** and 1 equiv of *n*BuLi with a solution of trifluoroethylamine **3b** and 1 equiv of PhMgCl at −60 °C. Aqueous workup then provided both substrates and the desired trifluoromethylated 1*H*-imidazole **2b** in a 1:1:1.7 ratio as determined by ^{19}F NMR spectroscopy (see SI).

The possibility of conducting the initial deprotonation step separately led us to investigate the synthesis of 2-trifluoromethyl-2,3-dihydro-1*H*-imidazole derivatives bearing two different *N*-aryl substitution patterns (Figure 4). Therefore,

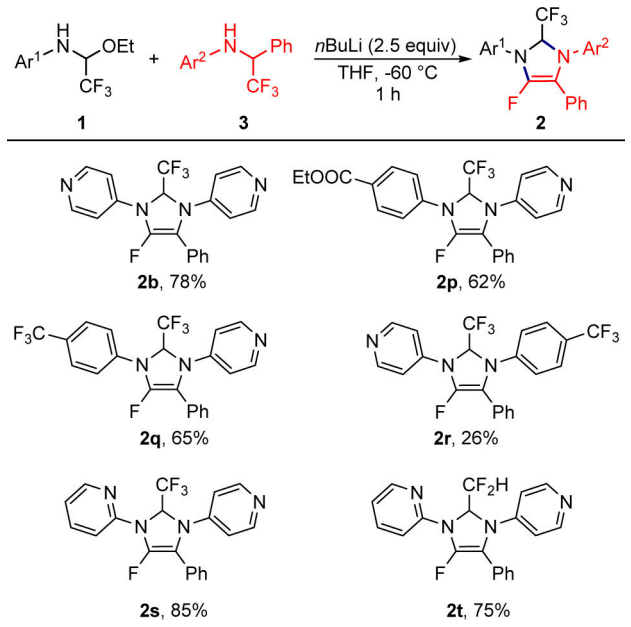


Figure 4. Synthesis of further functionalized 2-CF_3-2,3-dihydro-1*H*-imidazole derivatives.

equimolar amounts of ethyl 4-((1-ethoxy-2,2,2-trifluoroethyl)-amino)benzoate **1e** and trifluoroethylamine **3b** were deprotonated separately with *n*BuLi/PhMgCl and merged, to furnish the desired imidazole derivative **2p** in 62% isolated yield. To our delight, a comparable yield of **2p** was also obtained by a one-pot protocol, in which a solution of both substrates in THF was treated with 2.5 equiv of *n*BuLi. For instance, subjecting trifluoroethylamine **3b** and *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline **1q** to these conditions provided the corresponding trifluoromethylated imidazole **2q** in 65% isolated yield. Interestingly, reversal of the substitution pattern reaction, i.e., by reaction of *N*,*O*-acetal **1b** and *N*-(2,2,2-trifluoro-1-phenylethyl)-4-(trifluoromethyl)aniline **3r**, resulted in a diminished isolated yield of 26% of the desired product **2r** and large amounts of unreacted substrate. Moreover, the protocol allows preparation of 1*H*-imidazole derivatives bearing *N*-2-pyridyl substituents, which were previously difficult to access. However, this transformation is limited to reactions of 2-pyridyl-substituted hemiaminal ethers such as **1f**, whereas trifluoroethylamines bearing the 2-pyridyl substituent are not compatible. Finally, the product portfolio was also extended toward hitherto unknown 2-difluoromethyl-2,3-dihydro-1*H*-imidazole derivatives, e.g. **2t**, which was efficiently prepared from *N*-(1-ethoxy-2,2-difluoroethyl)pyridin-2-amine **1t** and **3b**.

In summary, we have devised a rapid and practical method for the synthesis of racemic 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles. The latter belong to a novel class of fluorinated imidazole derivatives of high pharmaceutical potential, which are accessible by condensation of *N*-aryl hemiaminal ethers with aryl Grignard reagents or *N*-aryl trifluoroethylamines. Crossover and control experiments have provided the first

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insights into the reaction mechanism. The operational simplicity of the protocol and the ready availability of the starting materials make this a very convenient approach for the synthesis of novel structurally diverse imidazole building blocks. With regard to their complex substitution patterns, the synthesis of reported 2-trifluoromethyl-2,3-dihydro-1*H*-imidazoles might be of particular interest for future pharmacological applications. Hence, their use for targeted synthesis is currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01672.

Experimental procedures and data for all new compounds, and NMR studies (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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DOI: 10.1021/acs.orglett.6b01672
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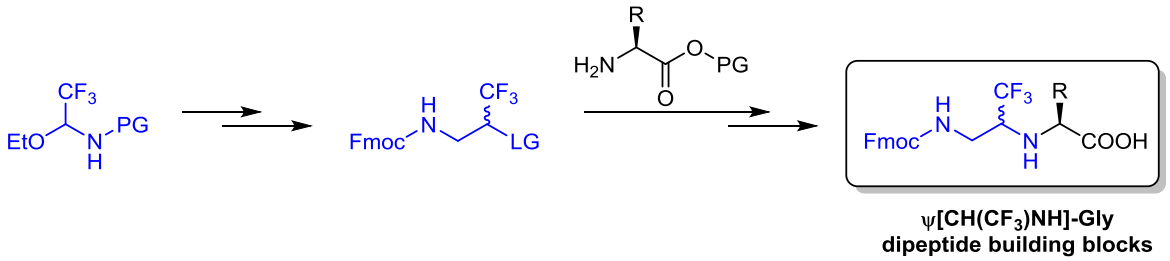
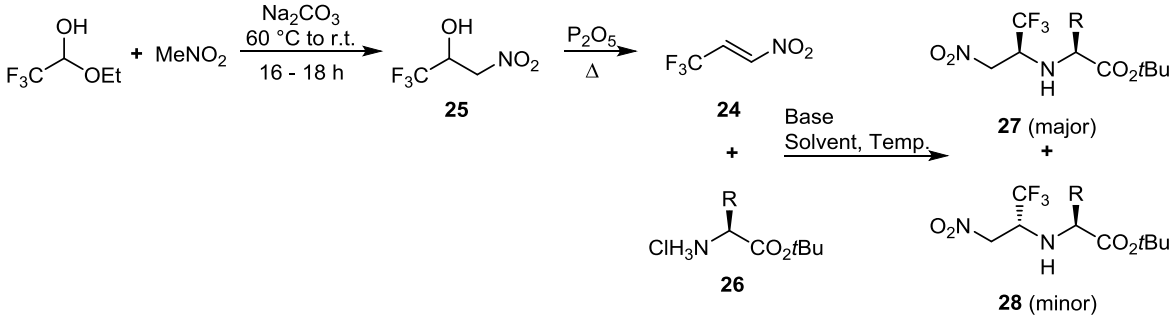
6. Strategy toward ψ[CH(CF$_3$)NH]-Gly Dipeptide Building Blocks for Peptide Synthesis



Background

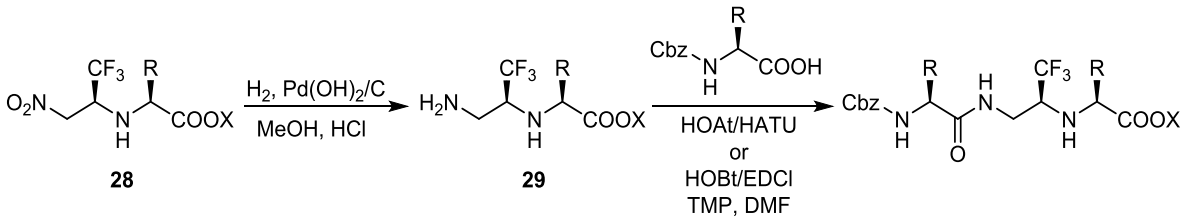
The remarkable therapeutic potential of peptides is mainly limited by their inadequate oral bioavailability, membrane permeability, metabolic stability and their physicochemical properties. The development of appropriate peptidomimetics to avoid these restrictions and to take advantage of the high biological activity of this structural motif is therefore highly rewarding. Substitution of one or multiple peptide bonds by enzymatically stable mimics is a promising approach, but has not gained much attention for trifluoroethylamines in medicinal research up to now.[123-125, 204-207]

One of the first synthetic strategies to access short peptides containing trifluoroethylamine building blocks was reported by *Zanda* and co-workers (Scheme 22).[205] Their protocol toward ψ[CH(CF$_3$)NH]-Gly peptides relies on the use of trifluoro-1-nitropropene **24** to incorporate the trifluoromethyl group. Substrate **24** can be prepared by a *Henry* reaction of TFAE and nitromethane, followed by subsequent dehydration of the intermediate nitroaldol product **25** using P_2O_5. The key step of this route comprises an *aza-Michael* reaction between the trifluoromethylated nitroalkene **24** and the corresponding hydrochloric salts of *α*-amino acid esters **26** to provide the desired trifluoromethylated *β*-nitro-*α*-amino esters **27** and **28**. The stereochemistry of this *aza-Michael* reaction is strongly influenced by the solvent, the base and the substitution pattern of the starting amino acid ester **26**. The best diastereoselectivity is observed using 1.1 equivalents of *N*,*N*-diisopropylethylamine (DIPEA) as a base in toluene, whereas use of $NaHCO_3$ or 2,2,6,6-tetramethylpiperidine (TMP) resulted in reduced yields of compounds **27** and **28**.[205]



Scheme 26. Synthesis of the trifluoromethylated nitroalkene **24** and subsequent *aza-Michael* reaction.[205]

Subsequent hydrogenation of the nitro group using *Pearlmans* catalyst provides trifluoromethylated dipeptide building block **29**, which can be further condensed to α-amino acids using standard coupling conditions to furnish the corresponding pseudo-tripeptides (Scheme 27).[205]



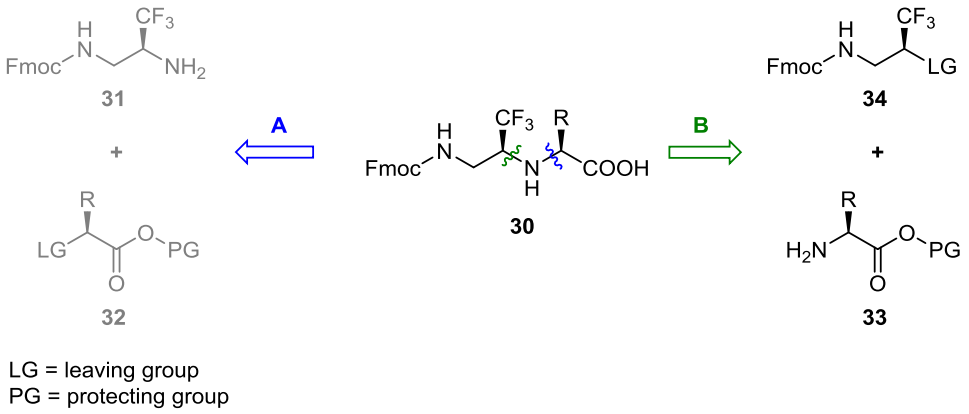
Scheme 27. Synthesis of ψ[CH(CF_3)NH]-Gly tripeptide.[205]

Regarding our previous work on the synthesis of *N*-aryl trifluoroethylamines, we sought to apply this method to access ψ[CH(CF_3)NH]-Gly dipeptide building blocks. Whereas the approach by *Zanda* and co-workers requires coupling of a second amino acid in an early stage of the synthetic route and has found little application in peptide synthesis, we aimed at a more convenient strategy toward ψ[CH(CF_3)NH]-Gly building blocks for the synthesis of larger peptides by late-stage coupling of a second amino acid substrate to provide a large number of diverse trifluoromethylated dipeptides.

Results and Discussion

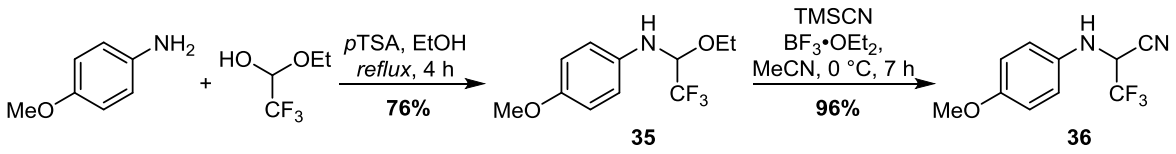
Retrosynthetic analysis to access ψ[CH(CF_3)NH]-Gly dipeptide building blocks **30** disclosed two principle strategies (Scheme 28). On the one hand, the amino acid building block could be inserted by reaction of trifluoroethylamine **31** with an amino acid precursor **32** featuring a leaving group (LG) (Strategy **A**). Alternatively, protected amino acid **33** could function as the nucleophile to attack the trifluoromethylated building block **34** (Strategy **B**). In the course of her master thesis, *Elen Baumann* investigated the synthesis of the pseudo-peptide building blocks following strategy **A**.[208] The major challenge of strategy **A** was the hitherto unreported coupling of a trifluoroethylamine building block **31** with a suitable amino acid precursor **32** due to the electron-withdrawing effect of the trifluoromethyl moiety adjacent to the amine. Additionally to the steric hindrance, this resulted in a diminished nucleophilicity of the amino group and prohibited the reaction with an electrophile. Furthermore, this procedure requires synthesis of amino acid precursors by introducing an appropriate leaving group to allow nucleophilic attack of the trifluoroethylamine **31**. In contrast, strategy **B** relies on coupling of readily available *C*-terminal protected building blocks. Furthermore, the electron-

withdrawing effect of the trifluoromethyl moiety should facilitate the attack of a nucleophile. Thus, strategy **B** was pursued in the following, even though a more elegant approach featuring a trifluoromethylated acetal is conceivable.



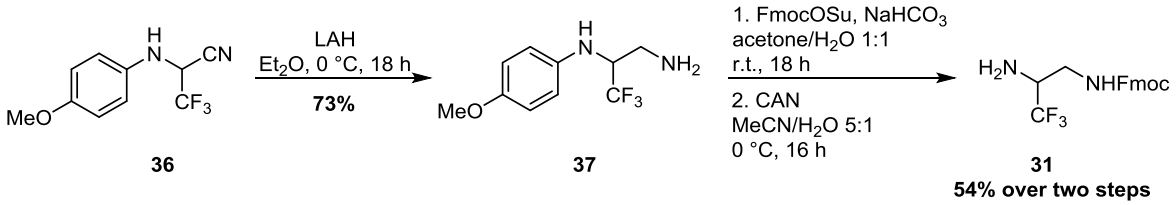
Scheme 28. Retrosynthetic strategies **A** and **B** toward ψ[CH(CF_3)NH]-Gly dipeptide building block **30**.

Initially, the preparation of trifluoromethylated *N*,*O*-acetal **35** was accomplished with *para*-anisidine, TFAE and catalytic amounts of *para*-toluenesulfonic acid (*p*TSA) in good yield following a procedure reported by *Gong et al.* (Scheme 29).[153] Implementing *para*-methoxyphenyl (PMP) as a protecting group for the amino group allows its selective deprotection in the presence of a further Fmoc protecting group, which is commonly used in SPPS protocols. A subsequent *Strecker*-type reaction of **35** with TMSCN in the presence of catalytic amounts of $BF_3{\cdot}Et_2O$ provided the nitrile **36** as a racemic mixture in excellent yield.[209]



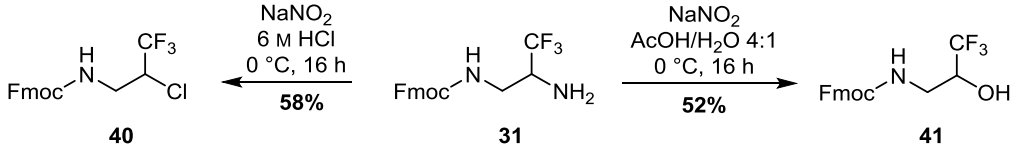
Scheme 29. Synthesis of trifluoromethylated nitrile **36**.

Nitrile **36** was subsequently reduced using lithiumaluminium hydride (LAH), providing **37** with a free amino group in 73% yield. With compound **37** in hand, diamine **31** was accessible within two synthetic steps (Scheme **30**). In the first step, the unprotected amino group of **37** was treated with Fmoc *N*-hydroxysuccinimide ester using standard conditions furnishing compound **38** after recrystallization from dichloromethane in 67% yield. Next, deprotection of the PMP group was addressed, which however turned out to be rather challenging. Thus, different oxidation strategies had to be tested to identify a suitable protocol. Following a mild protocol by *Verkade et al.* using trichloroisocyanuric acid (TCCA) as an oxidizing agent did not result in the deprotection of PMP moiety. Similarly, procedures using 2-iodoxybenzoic acid (IBX) or bis(acetoxy)iodobenzene (BAIB) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) did not provide the desired product **31** in satisfying yield. Finally, compound **31** was obtained in good yield of 81% by treatment of **38** with an excess of ceric ammonium nitrate (CAN). Interestingly, rapid conversion of the starting material to the corresponding imine intermediate took place, whereas the subsequent hydrolysis proceeded sluggishly and required more than 16 hours for complete conversion.



Scheme 30. Synthesis of trifluoromethylated diamine **31**.

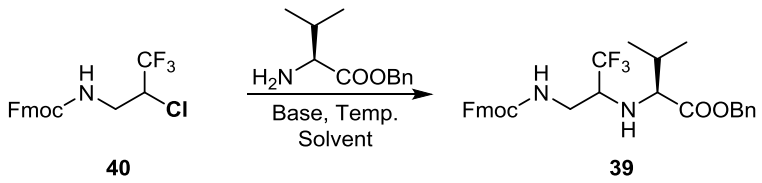
Next, the unprotected amine moiety (**31**) needed to be converted into an appropriate leaving group to allow the nucleophilic attack by the amino acid building block. Thus, different approaches to obtain the ψ[CH(CF_3)NH]-Gly-Val dipeptide **39** were investigated, including the conversion of the amino group into a chloride (compound **40**) and hydroxyl moiety (compound **41**) for subsequent condensation. Compound **40** was obtained by diazotization of **31** using $NaNO_2$ and 6 M hydrochloric acid in moderate yield (Scheme 31). Analogously, amine **31** was converted into the corresponding hydroxyl compound **41** upon treatment with $NaNO_2$ and acetic acid.



Scheme 31. Synthesis of compounds **40** and **41.**

With compounds **40**, **41** and a benzyl-protected L-valine derivative in hand, formation of ψ[CH(CF_3)NH]-Gly-Val dipeptide **39** was studied by screening different reaction conditions. Initially, the chloride **40** and the valine derivative were refluxed in CH_2Cl_2 using triethylamine or DIPEA as base (Table 3). As no reaction between the substrates occurred under these conditions, the solvent was replaced with dimethylformamid (DMF) to enable heating of the reaction to 100 °C. This however resulted in a partial deprotection of the Fmoc-protecting group without displaying any formation of the dipeptide building block **39**.

Table 3. *Reaction condition for coupling of chloride **40** with benzyl-protected L-valine*

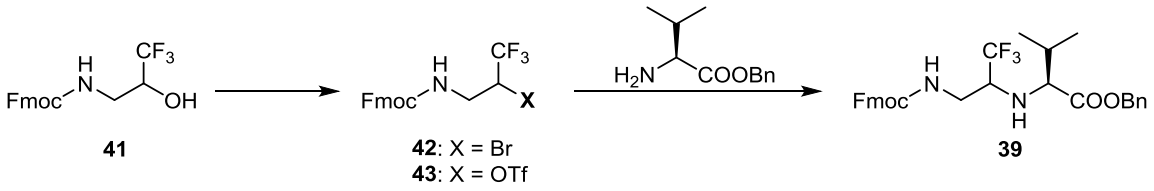


Substrate	Temperature	Base	Solvent	Observation
40	40 °C	NEt_3	CH_2Cl_2	no reaction
40	40 °C	DIPEA	CH_2Cl_2	no reaction
40	100 °C	NEt_3	DMF	decomposition
40	100 °C	DIPEA	DMF	decomposition

Alternatively, reacting compound **41** under *Appel* conditions (*via* compound **42**) and subsequent addition of the benzyl-protected amino acid did not result in formation the desired dipeptide **39** (Table 4). However,

protection of **41** using triflate anhydride (*via* compound **43**) and subsequent reaction with the amino acid resulted in formation of traces of the desired ψ[CH(CF_3)NH]-Gly-Val dipeptide **39**. Due to the poor conversion rate, compound **39** could not be isolated after work-up. Interestingly, significant amounts of substrate **41** were re-isolated, indicating a presumable lack of reactivity as a result of the sterically demanding trifluoromethyl moiety. In addition, deactivation of the hydroxyl group by to the strong electron-withdrawing character of the trifluoromethyl moiety might hamper its nucleophilicity toward triflate anhydride and triphenylphosphine.

Table 4. *Reaction condition for coupling of substrates **41** with benzyl-protected L-valine*



Substrate	Reagents	Temperature	Solvent	Observation
41	CBr_4, PPh_3	r.t. → 40 °C	CH_2Cl_2	no reaction
41	TfO_2, 2,6-lutidine	-78 °C → 0 °C	CH_2Cl_2	traces of **39**

To further optimize and develop of a more elegant synthetic strategy, e.g. by using a trifluoromethylated acetal precursor for subsequent incorporation into peptide model systems, further synthetic studies are currently pursued in the group. Moreover, using acetals may also enable access toward novel ψ[CH(CF_3)O]-pepsipeptide building blocks (Figure 24). The successfully prepared amine building block **31** could also be implemented in the preparation of retro-invers ψ[CH(CF_3)NH]-Gly peptides.

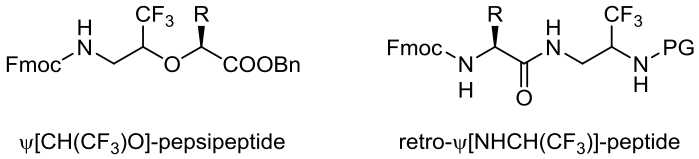
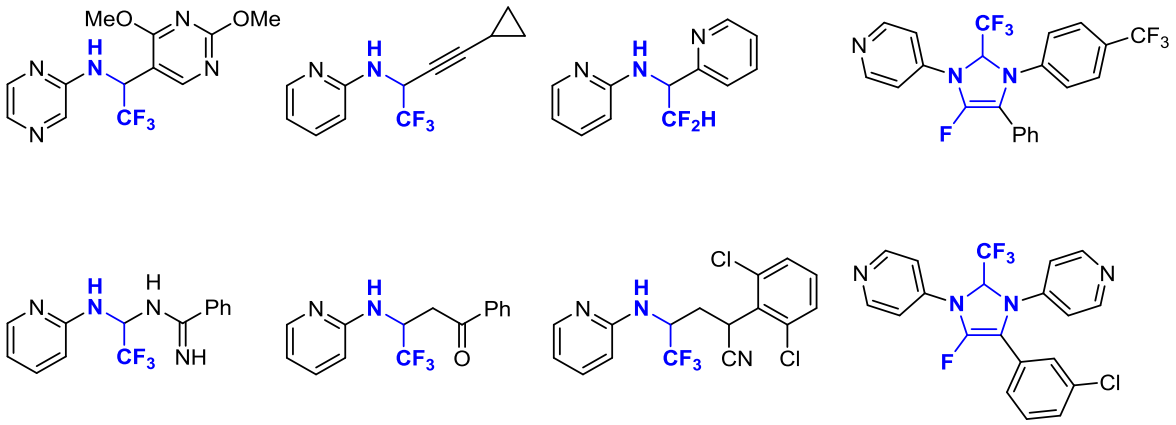


Figure 24. Structures of ψ[CH(CF_3)O]-pepsipeptides and retro-invers ψ[CH(CF_3)NH]-Gly peptide building blocks.

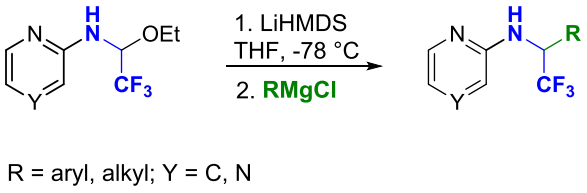
IV. Conclusion and Outlook

In summary, several strategies toward novel trifluoromethylated amine scaffolds for application in lead structure research have been developed and executed. A selection of these fluoroalkylated compounds is depicted in Scheme 32.



Scheme 32. Selected examples of synthesized fluoroalkylated compounds.

Focusing on the synthesis of trifluoroethylamines as bioisosteric replacements for amide moieties, a range of highly functionalized derivatives were successfully synthesized. These novel trifluoromethylated scaffolds might be of particular interest for pharmaceutical applications. Initially, *N*-aryl substituted hemiaminal ethers were reacted with simple alkyl-, alkenyl, and phenylmagnesium reagents to furnish trifluoroethylamines in good to excellent yields. Moreover, to access hemiaminal ethers with *N*-heteroaryl and electron-poor *N*-aryl substituents, an improved method using microwave assisted reaction conditions was established. Subsequently, the strategy toward trifluoroethylamines was successfully extended to the use of functionalized *Grignard* reagents, enabling the synthesis of rather complex target molecules (Scheme 33).



Scheme 33. Synthesis of functionalized *N*-aryl trifluoromethylated amines.

The sublime applicability of our methodology in more complex building blocks was proven by preparation of bioisosteric analogs of the androgen receptor antagonist DIMN and 1,2-dihydroquinazolin-4-(1*H*)-thione in good yield (Figure 25a and b).

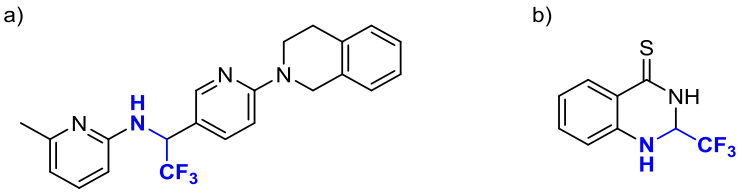
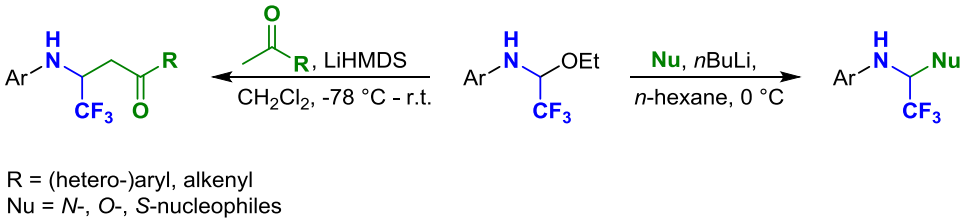


Figure 25 Synthesized trifluoroethylamine bioisosteres of a) nicotinamide DIMN and b) 1,2-dihydroquinazolin-4(1*H*)-thione.

In addition, the newly developed method effectively furnished novel functionalized difluoroethylamines. This structural motif exhibits promising properties as the difluoromethyl moiety can alter the pK_a value of adjacent amines but is still a weak hydrogen-bond donor in contrast to the trifluoromethyl group.

Besides the synthesis of fluoromethylated amines using organometallic reagents, novel synthetic approaches were investigated to access further complex trifluoromethylated scaffolds by conversion of *N*-aryl hemiaminal ethers with heteroatom nucleophiles as well as *C*-nucleophiles (Scheme 34). Thus, amines, benzamidines, *O*- and *S*-nucleophiles were successfully reacted with an appropriate hemiaminal ether under basic conditions furnishing the desired trifluoromethylated compounds in good to excellent yields. Additionally, an efficient one-pot procedure for the synthesis of fluorinated *β*-amino carbonyl compounds was accomplished under *Mannich*-type reaction conditions. These were applied to a large variety of hemiaminal ethers as well as *C*-nucleophiles.

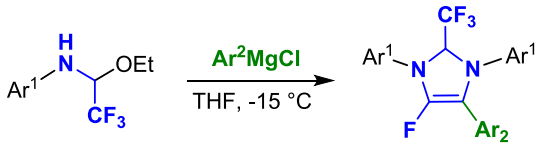


Scheme 34. Conversion of *N*-aryl hemiaminal ethers with *C*-, *N*-, *O*- and *S*-nucleophiles.

In terms of future work, synthesis of additional trifluoromethylated structures and biological evaluation of these bioisosteres in comparison to their parent structures could be beneficial to elucidate the influence of this bioisosteric replacement on binding affinity, ADME and pharmacokinetic parameters. In this context, the synthesized novel *N*-aryl tri- and difluoroethylamines should be evaluated regarding their biological activity and pharmacological properties. Furthermore, trifluoromethylated *β*-amino carbonyl compounds could be deployed as precursors of *β*-trifluoromethyl *β*-amino acids and subsequently be incorporated into peptide mimetics.

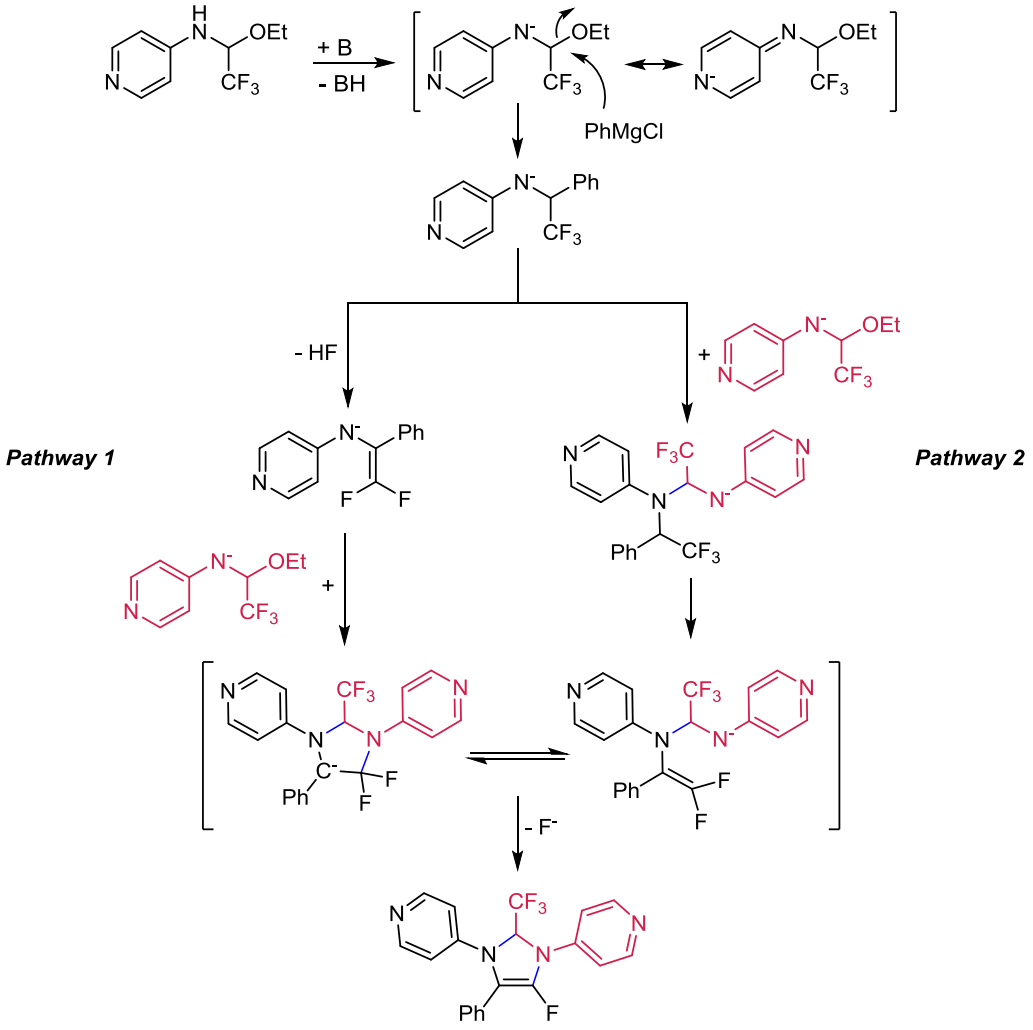
Regarding the stereoselectivity of the conversions, first attempts toward an enantioselective conversion of the hemiaminal ethers with nucleophiles have been made. Initially, the synthesis was successfully transferred to the use of organocopper reagents. Preliminary experiments aiming at an asymmetric formation of trifluoroethylamines *via* chiral ligands were performed. Although these efforts remained unsuccessful, the extension of the procedure to organocopper reagents facilitates access to a broad scope of substrates and ligands. In the future, the mechanism of the reaction should be elucidated and additional chiral ligands should be screening within scientific collaborations.

During investigations on the scope trifluoroethylamines accessible *via* our procedure, formation of a hitherto unknown class of fluorinated imidazole derivatives was observed. Thus, trifluoromethylated 2,3-dihydro-1*H*-imidazoles were obtained from trifluoromethylated *N*,*O*-hemiaminal ethers featuring electron-withdrawing substituents and aryl *Grignard* reagents in an one-pot reaction (Scheme 35).



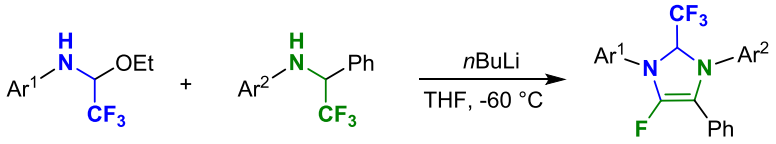
Scheme 35. One-pot synthesis of trifluoromethylated 2,3-dihydro-1*H*-imidazoles.

The mechanism of this formation was studied *via* low-temperature NMR experiments by disassembling two proposed pathways in separate experiments (Scheme 36). Deprotonating the hemiaminal ether with *n*BuLi at -60 °C revealed formation of two deprotonated species, whereas aldimine formation could not be detected under the stated reaction conditions. Moreover, formation of a difluoroenamine species was observed treating an appropriate trifluoroethylamine with *n*BuLi, which however was not feasible using PhMgCl.



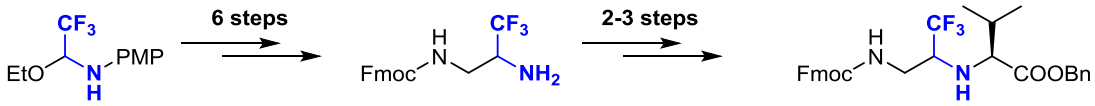
Scheme 36. Proposed mechanistic pathways of 2-CF_3-2,3-dihydro-1*H*-imidazole formation.

These experiments suggested a mechanism according to *pathway 2*, which was confirmed in further experiments and finally led to the development of a modified protocol providing access to various highly functionalized fluoromethylated imidazoles from trifluoroethylamines and hemiaminal ethers (Scheme 37).



Scheme 37. Synthesis of further functionalized 2-CF_3-2,3-dihydro-1*H*-imidazole derivatives.

Due to the significance of peptide mimetics in drug discovery and our experience in synthetic approaches toward trifluoroethylamines, a strategy toward ψ[CH(CF_3)NH]-Gly dipeptide building blocks was developed. The key diamino intermediate was obtained in six synthetic steps starting from the PMP-protected *N*,*O*-acetal (Scheme 38). Furthermore, first studies toward finding an appropriate leaving group for the subsequent coupling with a second amino acid were undertaken. Prospective optimization of this approach and the following incorporation in a model peptide sequence may give an insight into the influence of the bioisosteric replacement in terms of stability and structure.



Scheme 38. Strategy toward ψ[CH(CF_3)NH]-Gly dipeptide building blocks.

As summarized above, synthetic approaches toward functionalized fluoroalkylated scaffolds for medicinal chemistry research have been established. The conversion of fluorinated *N*,*O*-acetals with various nucleophiles, including carbon and heteroatom nucleophiles, allow efficient synthesis of a broad range of fluoroalkylated compounds. These functionalized fluoroalkylated compounds are particularly interesting as potential building blocks for drug development and biomedical applications.

EXPERIMENTAL PROCEDURES

V. EXPERIMENTAL PROCEDURES

1. Material and Methods

All reactions were carried out under argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. Dry THF was freshly distilled from sodium and benzophenone under argon. Commercially available reagents and solvents were used without further purification. *Grignard* reagents were purchased from *Aldrich* or synthesized with the described procedure. All microwave irradiation experiments were carried out in a CEM Explorer^{TM} microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 200 W utilizing the standard absorbance level of 300 W maximum power. The reactions were carried out in 10 mL Pyrex vessels sealed with CEM plastic crimp tops equipped with magnetic stirrers. The temperature was measured with an infrared sensor on the outer surface of the process vial. After the irradiation period, the reaction vessel was cooled rapidly (1−2 min) to ambient temperature using a nitrogen jet.

Reactions were monitored by TLC with pre-coated silica gel 60 F_{254} aluminium plates (*Merck KGaA*, Darmstadt) using UV light as the visualizing agent. The crude products were purified by standard flash chromatography or MPLC with a *CombiFlash Rf Teledyne ISCO* or by standard flash chromatography using silica gel (35–70 µm) from *Acros Organics*. Analytical RP-HPLC was measured on a *JASCO* system with a *Phenomenex Luna* C18 column (5 µm, 250 × 4.6 mm). ESI- and HR-ESI-mass spectra were recorded on a Thermo Finnigan LTQ FT or on a Bruker maxis equipped with a *Waters Acquity UPLC* using a *Kinetex* C18 column (2.6 µ, 100 A) at 40 °C. HPLC-MS was performed on *Agilent 1100* and *Agilent 1200* systems using *Chromolith Speed ROD* RP-18e columns. In all cases, mixtures of water (eluent A) and acetonitrile (eluent B) were used as solvents. if required, 0.05% formic acid or 0.1% TFA were added. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Varian 300 MHz and 600 MHz spectrometer or on a Bruker Avance II 400 MHz spectrometer in DMSO-d_6 or $CDCl_3$. The chemical shifts are reported in ppm relative to the signal of the deuterated solvent. Multiplicities are given as: s (singlet), br s (broad singlet), d (doublet), t (triplet), and m (multiplet). Melting points were measured on a Melting Point B-540 Büchi. IR spectra were measured on a Perkin-Elmer *FT-IR Spektrum BXII* spectrometer with a Smiths *Dura SampIIR II* ATR.

2. Experimental Procedures and Analytical Data: *Synthesisof functionalized α-trifluoroethyl amine scaffolds via Grignard addition to N-aryl hemiaminal ethers*

The complete supporting information including the experimental procedures and NMR spectra of all compounds is available on the *RSC Advances* website (DOI: 10.1039/c3ra47708h) and on the CD in the book cover of this thesis. The compounds are numbered according to the publication.

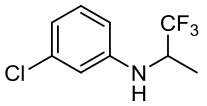
2.1 General procedure for the synthesis of trifluoroethylamines

A dry *Schlenk* flask was flushed with argon, equipped with a magnetic stirrer and a septum and charged with *N*-aryl hemiaminal ether in dry THF (ca. 0.05 M). The solution was cooled to −15 °C, the *Grignard* reagent (2 equiv) was added drop wise, and the solution was stirred at −15 °C until complete consumption of the starting material (ca. 1 h, TLC and LC-MS control). Then, the solution was quenched with 1:1 THF/H_2O (12 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. Purification by flash chromatography furnished the desired amines **2a**-**j**, **3a**-**h**, **5** and **6**.

2.2 Experimental data

3-Chloro-*N*-(2,2,2-trifluoro-1-methylethyl)aniline 2a

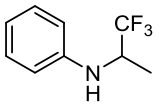
According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (152 mg, 0.60 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.86 mL, 1.20 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 80:20) to give the desired amine **2a** (116 mg, 87%) as a light yellow oil.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.09 (t, J = 8.1 Hz, 1 H, H5), 6.78 (t, J = 2.1 Hz, 1 H, H2), 6.68 (dd, J = 8.2 Hz, 2.0 Hz, 1 H, H6), 6.60 (ddd, J = 7.8 Hz, 1.9 Hz, 0.7 Hz, 1 H, H4), 6.26 (d, J = 9.0 Hz, 1 H, NH), 4.45 – 4.30 (m, 1 H, CH), 1.28 (d, J = 6.8 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = −75.76 (d, $J_{CF3,CH}$ = 7.0 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 148.64 (C1), 133.59 (C3), 130.33 (C5), 126.77 (q, $J_{C,F}$ = 284.0 Hz, CF_3), 116.29 (C4), 111.94 (C2), 111.32 (C6), 49.07 (q, $J_{C,F}$ = 29.5 Hz, $C$$CF_3$), 14.28 ($CH_3$) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3420 (br, vw), 1598 (s), 1510 (m), 1482 (m), 1252 (m), 1133 (vs), 1022 (s), 990 (m), 841 (w), 764 (m), 680 (m) cm^{-1}. **HPLC-MS** (0.1% TFA. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.52 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_9H_{10}ClF_3N^+$ $[M+H]^+$ 224.0448, found 224.0448.

N-(2,2,2-Trifluoro-1-methylethyl)aniline 2b[[139]]

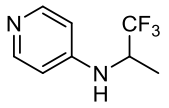
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1b**[139] (200 mg, 0.91 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.30 mL, 1.82 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 80:20) to give the desired amine **2b** (109 mg, 63%) as a light yellow liquid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.15 – 7.01 (m, 2 H, H3. H5), 6.71 (d, J = 7.8 Hz, 2 H, H2, H6), 6.59 (tt, J = 7.4 Hz, 1.0, 1 H, H4), 5.88 (d, J = 8.9 Hz, 1 H, NH), 4.38 – 4.20 (m, 1 H, CH), 1.29 (d, J = 6.8 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = −75.70 (d, $J_{CF3,CH}$ = 7.2 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 147.00 (C_q), 128.84 (CH_{ar}), 126.90 (q, $J_{C,F}$ = 284.2 Hz, CF_3), 116.85 (CH_{ar}), 112.58 (CH_{ar}), 49.31 (q, $J_{C,F}$ = 29.4 Hz, $C$$CF_3$), 14.35 ($CH_3$) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3406 (br, vw), 3026 (vw), 1603 (m), 1511 (m), 1497 (m), 1387 (w), 1250 (s), 1166 (m) 1127 (vs), 1018 (s), 946 (w), 747 (s), 691 (s) cm^{-1}. **HPLC-MS** (0.1% TFA. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.19 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_9H_{11}ClF_3N^+$ $[M+H]^+$ 190.0838, found 190.0838.

N-(2,2,2-Trifluoro-1-methylethyl)aminopyridine 2c

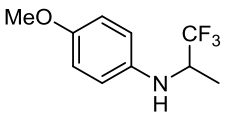
Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1c** (196 mg, 0.89 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.27 mL, 1.78 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 80:20) to give the desired amine **2c** (137 mg, 81%) as a white solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 (dd, J = 4.8 Hz, 1.5 Hz, 2 H, H3. H5), 6.81 (d, J = 9.0 Hz, 1 H, NH), 6.66 (dd, J = 4.9 Hz, 1.5 Hz, 2 H, H2. H4), 4.56 – 4.41 (m, 1 H, CH), 1.30 (d, J = 6.8 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = −75.82 (d, $J_{CF3,CH}$ = 7.2 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 152.50 (C1), 149.54 (CH_{ar}), 126.56 (q, $J_{C,F}$ = 284.0 Hz, CF_3), 107.71 (CH_{ar}), 48.13 (q, $J_{C,F}$ = 29.9 Hz, $C$$CF_3$), 14.06 ($CH_3$) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3234 (w), 2994 (br, w), 1602 (s), 1533 (m), 1325 (w), 1267 (m), 1220 (s), 1162 (s), 1138 (vs), 1020 (s), 992 (s), 812 (s), 673 (m) cm^{-1}. **HPLC-MS** (0.1% TFA. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 1.07 min, λ = 220 nm. **mp** 148 °C. **HRMS** (ESI+): *m/z* calcd. for $C_8H_{10}F_3N_2^+$ $[M+H]^+$ 191.0791, found 191.0798.

4-Methoxy-*N*-(2,2,2-trifluoro-1-methylethyl)aniline 2d[[210]]

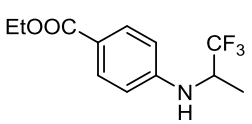
According to the general procedure, 4-methoxy-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1d**[[211]] (190 mg, 0.76 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.09 mL, 1.52 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 60:40) to give the desired amine **2d** (67 mg, 40%) as a light yellow liquid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.75 – 6.65 (m, 4H, 4 × H_{ar}), 5.46 (d, J = 9.0 Hz, 1 H, NH), 4.24 – 4.09 (m, 1 H, CH), 3.64 (s, 3 H, OCH_3), 1.26 (d, J = 6.8 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –75.65 (d, $J_{CF3,CH}$ = 7.3 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 151.34 (C_q), 141.07 (C_q), 127.01 (q, $J_{C,F}$ = 284.3 Hz, CF_3), 114.44 (CH_{ar}), 113.91 (CH_{ar}), 55.25 (OCH_3), 50.36 (q, $J_{C,F}$ = 29.0 Hz, CCF_3), 14.44 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3386 (br, vw), 2942 (br, vw), 1511 (vs), 1457 (w), 1273 (w), 1232 (s), 1130 (vs), 1018 (s), 946 (w), 819 (s), 666 (m) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min, 4% B → 2.8 min, 100% B, flow: 2.4 mL/min): t_R = 2.25 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{10}H_{13}F_3NO^+$ $[M+H]^+$ 220.0944, found 220.0941.

Ethyl-*N*-(2,2,2-trifluoro-1-methylethyl)4-aminobenzoate 2e

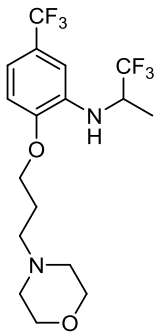
Following the general procedure, ethyl-*N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-aminobenzoate **1e** (220 mg, 0.76 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.08 mL, 1.51 mmol) in dry THF (12 mL). The desired amine **2e** (186 mg, 94%) was isolated after workup as a yellow solid without further purification.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.72 (d, J = 8.8 Hz, 2 H, 2 × H_{ar}), 6.79 (m, 3 H, NH . 2 × H_{ar}), 4.58 – 4.40 (m, 1 H, CH), 4.22 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 1.32 (d, J = 6.7 Hz, 3 H, $CHCH_3$), 1.27 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –75.76 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 165.63 (*C*OOEt), 151.29 (C1), 130.75 (C3. C5), 124.07 (q, $J_{C,F}$ = 284.8 Hz, CF_3), 117.68 (C4), 111.74 (C2. C6), 59.65 (CH_2), 48.78 (q, $J_{C,F}$ = 29.7 Hz, CCF_3), 14.25 (CH_3), 14.17 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 2251 (m), 2976 (br, vw), 1684 (s), 1601 (s), 1265 (w), 1286 (s), 1251 (vs), 1148 (vs), 1124 (s), 1097 (s), 1015 (s), 847 (m), 769 (vs), 700 (s) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.35 min, λ = 220 nm. **mp** 86 °C. **HRMS** (ESI+): *m/z* calcd. for $C_{12}H_{15}F_3NO_2^+$ $[M+H]^+$ 262.1049, found 262.1049.

2-(3-Morpholinopropoxy)-5-(trifluoromethyl)-*N*-(2,2,2-trifluoro-1-methylethyl)aniline 2f

According to the general procedure, 2-(3-morpholinopropoxy)-5-(trifluoromethyl)-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1f** (184 mg, 0.43 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 1.08 mL, 0.86 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, CH_2Cl_2 → CH_2Cl_2/MeOH 85:15) to give the desired amine **2f** (97 mg, 57%) as a yellow liquid.

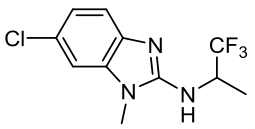


^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.08 (s, 1 H, H2), 7.04 – 6.95 (m, 2 H, H4. H5), 5.05 (d, J = 9.5 Hz, 1 H, NH), 4.66 – 4.53 (m, 1 H, CH), 4.15 – 4.10 (m, 2 H, CH_2), 3.58 – 3.55 (m, 4 H, 2 × CH_2), 2.42 (t, J = 7.1 Hz, 2 H, CH_2), 2.39 – 2.32 (m, 4H, 2 × CH_2), 1.97 – 1.87 (m, 2 H, CH_2), 1.36 (d, J = 6.7 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = –59.89 (CF_3), –75.75 (d, $J_{CF3,CH}$ = 7.3 Hz, $CHCF_3$) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 148.25 (C_q), 136.56 (C_q), 126.73 (CF_3), 124.68 (CF_3), 121.48 (CH_{ar}), 114.44 (CCF_3), 111.03 (CH_{ar}),

107.02 (CH_{ar}), 66.77 (CH_2), 66.13 (CH_2), 54.71 (CH_2), 53.31 (CH_2), 49.24 (*C*HCF$_3$), 25.47 ($CH_2CH_2CH_2$), 14.44 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3420 (br, vw), 2956 (br, vw), 1606 (w), 1532 (w), 1447 (m), 1328 (w), 1256 (m), 1109 (vs), 960 (w), 861 (m), 874 (w) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 1.73 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{17}H_{23}F_6N_2O_2^+$ $[M+H]^+$ 401.1658, found 401.1657.

(6-Chloro-1-methyl-1*H*-benzoimidazol-2-yl)-(2,2,2-trifluoro-1-methylethyl)amine 2g

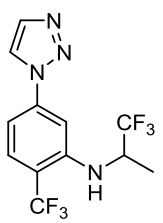
According to the general procedure, (6-chloro-1-methyl-1*H*-benzoimidazol-2-yl)-(1-ethoxy-2,2,2-trifluoroethyl)amine **1g** (32 mg, 0.07 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.10 mL, 0.15 mmol) in dry THF (5 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 70:30) to give the desired amine **2g** (14 mg, 69%) as a light yellow liquid.



^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 7.32 (d, *J* = 2.0 Hz, 1 H, H_{ar}), 7.20 (dd, *J* = 8.4 Hz, 2.6 Hz, 2 H, NH. H_{ar}), 6.99 (dd, *J* = 8.3 Hz, 2.1 Hz, 1 H, H_{ar}), 4.86 (dp, *J* = 15.1 Hz, 7.5 Hz, 1 H, CH), 3.55 (s, 3 H, NCH_3), 1.41 (d, *J* = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d$_6$): δ = –75.96 (d, $J_{CF3,CH}$ = 7.9 Hz, 1 H, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d$_6$): δ = 154.61 (C_q), 140.54 (C_q), 136.22 (C_q), 126.16 (q, $J_{C,F}$ = 282.4 Hz, CF_3), 124.75 (C_q), 120.44 (CH_{ar}), 116.19 (CH_{ar}), 107.99 (CH_{ar}), 49.66 (q, $J_{C,F}$ = 30.8, *C*CF$_3$), 28.63 (NCH_3), 13.88 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3064 (br, w), 1707 (w), 1597 (m), 1563 (m), 1453 (m), 1265 (s), 1135 (vs), 1058 (m), 916 (w), 807 (m), 670 (w) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 1.47 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{11}H_{12}ClF_3N_3$ $[M+H]^+$ 278.0666, found 278.0668.

2-(1,2,3-Triazol-1-yl)-5-(trifluoromethyl)-*N*-(2,2,2-trifluoro-1-methylethyl)aniline 2h

According to the general procedure, 2-(1,2,3-triazol-1-yl)-5-(trifluoromethyl)-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1h** (175 mg, 0.49 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.71 mL, 0.99 mmol) in dry THF (12 mL). The desired amine **2h** (154 mg, 96%) was isolated after workup as a yellow solid without further purification.

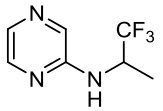


^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 8.61 (d, *J* = 1.1 Hz, 1 H, $H_{triazole}$), 8.05 (d, *J* = 1.1 Hz, 1 H, $H_{triazole}$), 7.62 – 7.56 (m, 1 H, H3), 7.52 (s, 1 H, H6), 7.18 (dd, *J* = 8.3 Hz, 1.3 Hz, 1 H, H2), 6.24 (d, *J* = 9.3 Hz, 1 H, NH), 4.85 – 4.74 (m, 1 H, CH), 1.32 (d, *J* = 6.7 Hz, 3 H, CH_3). **^{19}F NMR** (376 MHz, DMSO-d$_6$): δ = -61.41 (CF_3), -75.85(d, $J_{CF3,CH}$ = 7.0 Hz, $CHCF_3$) ppm. **^{13}C NMR** (101 MHz, DMSO-d$_6$): δ = 140.77 (C_q), 133.97 (CH_{ar}), 130.59 (q, $J_{C,F}$ = 32.0 Hz, *C*CF$_3$), 126.45 (CH_{ar}), 126.41 (q, $J_{C,F}$ = 283.6 Hz, HC*C*F$_3$), 126.27 (CH_{ar}), 125.41 (C_q), 123.78 (q, $J_{C,F}$ = 272.6 Hz, CF_3), 113.96 (CH_{ar}), 110.63 (CH_{ar}), 49.21 (q, $J_{C,F}$ = 29.7 Hz, H*C*CF$_3$), 14.15 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3282 (br, vw), 3155 (vw), 1620 (w), 1597 (w), 1448 (m), 1345 (m), 1285 (m), 1166 (m), 1125 (vs), 1092 (vs), 979 (s), 858 (m), 815 (s), 781 (m), 668 (m) cm^{-1}. **HPLC-MS** (0.05% formic

acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.40 min, λ = 220 nm. **mp** 83 °C. **HRMS** (ESI+): *m/z* calcd. for $C_{12}H_{11}F_6N_4^+$ $[M+H]^+$ 325.0882, found 325.0886.

N-(2,2,2-Trifluoro-1-methylethyl)aminopyrazine 2i

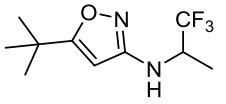
Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyrazine **1i** (50 mg, 0.23 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.32 mL, 0.45 mmol) in dry THF (5 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 4:1) to give the desired amine **2i** (35 mg, 80%) as a white solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (dd, J = 2.7 Hz, 1.5 Hz, 1 H, H5), 7.96 (d, J = 1.4 Hz, 1 H, H2), 7.90 (d, J = 2.7 Hz, 1 H, H4), 4.88 (m, 1 H, CH), 4.57 (d, J = 8.9 Hz, 1 H, NH), 1.42 (dd, J = 6.9 Hz, 0.6 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −77.67 (d, $J_{CF3,CH}$ = 7.3 Hz, $CHCF_3$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.86 (C1), 141.60 (C5), 134.27 (C4), 132.72 (C2), 125.80 (q, $J_{C,F}$ = 281.9 Hz, CF_3), 47.46 (q, $J_{C,F}$ = 31.2 Hz, CCF_3), 14.76 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3256 (w), 3057 (w), 1601 (m), 1521 (s), 1457 (m), 1398 (m), 1268 (s), 1163 (s), 1135 (vs), 1096 (s), 1023 (s), 1000 (m), 825 (s) cm^{-1}. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.95 min, λ = 214 nm. **mp** 81 °C. **HRMS** (ESI+): *m/z* calcd. for $C_7H_9F_3N_3^+$ $[M+H]^+$ 192.0743, found 192.0742.

5-(*tert*-Butyl)-*N*-(2,2,2-trifluoro-1-methylethyl)isoxazol-3-amine 2j

According to the general procedure, 5-(*tert*-butyl)-*N*-(1-ethoxy-2,2,2-trifluoroethyl)isoxazol-3-amine **1j** (100 mg, 0.38 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.54 mL, 0.76 mmol) in dry THF (6 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 4:1) to give the desired amine **2j** (66 mg, 74%) as a white solid.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.48 (s, 1 H, H_{ar}), 4.19 (m, 1 H, C*H*CH_3), 3.90 (s, 1 H, NH), 1.40 (d, J = 6.9 Hz, 3 H, CHC*H*$_3$), 1.30 (s, 9 H, 3 × CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −78.10 (d, $J_{CF3,CH}$ = 6.9 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 181.24 (-HC*C*O-), 162.87 (-HC*C*N-), 125.67 (d, $J_{C,F}$ = 280.7 Hz, CF_3), 89.75 (-C*C*HC-), 51.34 (q, $J_{C,F}$ = 31.1 Hz, CCF_3), 32.77 ($(CH_3)_3C$), 28.60 (3 × CH_3), 14.92 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3297 (br, w), 2970 (w), 1612 (m), 1551 (m), 1459 (m), 1265 (m), 1183 (m), 1135 (vs), 1016 (m), 981 (m), 781 (m) cm^{-1}. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 14.63 min, λ = 214 nm. **mp** 98 °C. **HRMS** (ESI+): *m/z* calcd. for $C_{10}H_{16}F_3N_2O^+$ $[M+H]^+$ 237.1209, found 237.1208.

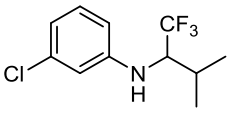
3-Chloro-*N*-(2,2,2-trifluoro-1-isopropylethyl)aniline 3a

Reaction with *i*PrMgCl:

Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with *i*PrMgCl (1.0 M in THF, 1.58 mL, 1.58 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 20:1) to give the desired amine **3a** (139 mg, 70%) as a light yellow liquid together with the side product 3-chloro-*N*-2,2,2-trifluoroethyl)aniline **4** (26 mg, 16%, light yellow liquid).

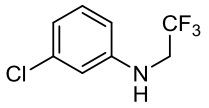
Reaction with *i*PrMgCl·LiCl:

According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (165 mg, 0.65 mmol) was reacted with *i*PrMgCl·LiCl (1.1 M in THF, 1.18 mL, 1.30 mmol) in dry THF (8 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/ethyl acetate 40:1) to give the desired amine **3a** (112 mg, 68%) as a light yellow liquid together with the side product 3-chloro-*N*-2,2,2-trifluoroethyl)aniline **4** (40 mg, 30%, light yellow liquid).



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.07 (t, J = 8.1 Hz, 1 H, H5), 6.88 (t, J = 2.1 Hz, 1 H, H2), 6.76 (dd, J = 8.1 Hz, 2.0 Hz, 1 H, H6), 6.58 (ddd, J = 7.8 Hz, 1.9 Hz, 0.7 Hz, 1 H, H4), 6.08 (d, J = 10.1 Hz, 1 H, NH), 4.29 – 4.09 (m, 1 H, NHC*H*), 2.16 – 2.00 (m, 1 H, CH), 0.98 (t, J = 6.1 Hz, 6 H, 2 × CH_3) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = −70.57 (d, $J_{CF3,CH}$ = 8.4 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 149.82 (C1), 133.60 (C3), 130.29 (C5), 126.59 (q, $J_{C,F}$ = 285.6 Hz, CF_3), 116.05 (C4), 111.92 (C2), 111.12 (C6), 57.63 (q, $J_{C,F}$ = 26.9 Hz, *C*CF_3), 28.15 (CH), 19.40 (CH_3), 17.48 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3429 (br, vw), 2969 (w), 1597 (s), 1509 (m), 1483 (m), 1261 (m), 1135 (vs), 1079 (s), 990 (m), 842 (br,m), 763 (m), 679 (s) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.70 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{11}H_{14}ClF_3N^+$ $[M+H]^+$ 252.0761, found 252.0761.

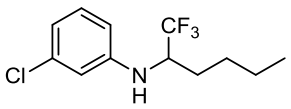
3-Chloro-*N*-(2,2,2-trifluoroethyl)aniline 4



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.10 (t, J = 8.1 Hz, 1 H, H5), 6.78 (t, J = 2.1 Hz, 1 H, H2), 6.68 (dd, J = 8.1 Hz, 2.0 Hz, 1 H, H6), 6.62 (ddd, J = 7.8 Hz, 2.0 Hz, 0.8 Hz, 1 H, H4), 6.49 (t, J = 6.9 Hz, 1 H, NH), 3.95 (qd, J = 9.7 Hz, 7.0 Hz, 2 H, CH_2) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = −70.61 (t, $J_{CF3,CH}$ = 9.5 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 149.06 (C1), 133.62 (C3), 130.37 (C5), 125.71 (q, $J_{C,F}$ = 281.1 Hz, CF_3), 116.46 (C4), 111.69 (C2), 111.13 (C6), 43.65 (q, $J_{C,F}$ = 32.3 , *C*CF_3) ppm. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.24 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_8H_8ClF_3N^+$ $[M+H]^+$ 210.0292, found 210.0291.

3-Chloro-*N*-(2,2,2-trifluoro-1-butylethyl)aniline 3b

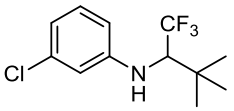
According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with *n*BuMgBr (2.0 M in Et_2O, 0.79 mL, 1.58 mmol) in dry THF (12 mL). The desired amine **3b** (197 mg, 94%) was isolated after workup without further purification as a light yellow liquid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.08 (t, J = 8.1 Hz, 1 H, H5), 6.80 (t, J = 2.1 Hz, 1 H, H2), 6.70 (dd, J = 8.3 Hz, 1.8 Hz, 1 H, H6), 6.59 (ddd, J = 7.8 Hz, 1.9 Hz, 0.7 Hz, 1 H, H4), 6.20 (d, J = 9.1 Hz, 1 H, NH), 4.26 – 4.12 (m, 1 H, CH), 1.76 – 1.64 (m, 1 H, CH_2), 1.62 – 1.49 (m, 1 H, CH_2), 1.47 – 1.21 (m, 4 H, 2 × CH_2), 0.85 (t, J = 7.1 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = −74.78 (d, $J_{CF3,CH}$ = 7.4 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 149.48 (C1), 133.61 (C3), 130.35 (C5), 126.63 (q, $J_{C,F}$ = 284.4 Hz, CF_3), 116.08 (C4), 111.67 (C2), 111.04 (C6), 53.40 (q, $J_{C,F}$ = 28.4 Hz, *C*CF_3), 27.80 (CH_2), 26.99 (CH_2), 21.70 (CH_2), 13.70 (CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3420 (br, vw), 2959 (w), 2932 (w), 1598 (s), 1509 (m), 1483 (m), 1250 (m), 1167 (m), 1130 (vs), 1088 (s), 990 (m), 764 (m), 679 (s) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.87 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{12}H_{16}ClF_3N^+$ $[M+H]^+$ 266.0918, found 266.0918.

3-Chloro-*N*-(2,2,2-trifluoro-1-*tert*-butylethyl)aniline 3c

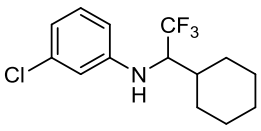
Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with *tert*-BuMgBr (2.0 M in Et_2O, 0.79 mL, 1.58 mmol) in dry THF (12 mL). The reaction time was 3 h. The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 20:1) to give the desired amine **3c** (120 mg, 57%) as a light yellow liquid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.07 (t, J = 8.1 Hz, 1 H, H5), 6.94 (t, J = 2.1 Hz, 1 H, H2), 6.82 (dd, J = 8.3 Hz, 1.8 Hz, 1 H, H6), 6.57 (ddd, J = 7.8 Hz, 1.9 Hz, 0.7 Hz, 1 H, H4), 6.07 (d, J = 10.7 Hz, 1 H, NH), 4.22 – 4.04 (m, 1 H, CH), 1.05 (s, 9H, 3 × CH_3) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = −66.68 (d, $J_{CF3,CH}$ = 8.6 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 150.02 (C1), 133.60 (C3), 130.28 (C5), 126.94 (q, $J_{C,F}$ = 286.8 Hz, CF_3) 115.98 (C4), 111.94 (C2), 111.18 (C6), 60.37 (q, $J_{C,F}$ = 25.7 Hz, *C*CF_3), 34.41 (C_q), 26.74 (3 × CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3433 (br, vw), 2967 (w), 1698 (br, w), 1599 (s), 1510 (m), 1481 (m), 1251 (m), 1156 (s), 1106 (vs), 990 (m), 762 (m), 679 (s) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.63 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{12}H_{16}ClF_3N^+$ $[M+H]^+$ 266.0918, found 266.0912.

3-Chloro-*N*-(2,2,2-trifluoro-1-cyclohexylethyl)aniline 3d

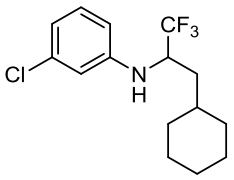
Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (177 mg, 0.70 mmol) was reacted with cyclohexylmagnesium bromide (1.0 M in THF, 1.40 mL, 1.40 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 20:1) to give the desired amine **3d** (159 mg, 78%) as a light yellow oil.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.06 (t, J = 8.1 Hz, 1 H, H5), 6.84 (t, J = 2.1 Hz, 1 H, H2), 6.73 (dd, J = 8.3 Hz, 1.8 Hz, 1 H, H6), 6.57 (ddd, J = 7.9 Hz, 1.9 Hz, 0.7 Hz, 1 H, H4), 6.08 (d, J = 10.1 Hz, 1 H, NH), 4.19 – 4.05 (m, 1 H, CH), 1.81 – 1.55 (m, 6 H, 3 × CH_2), 1.25 – 1.04 (m, 5 H, CH. 2 × CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = –70.05 (d, $J_{CF3,CH}$ = 8.4 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 149.79 (C1), 133.60 (C3), 130.33 (C5), 126.54 (q, $J_{C,F}$ = 285.6 Hz, CF_3), 116.03 (C4), 111.84 (C2), 111.03 (C6), 57.45 (q, $J_{C,F}$ = 27.0 Hz, *C*CF_3), 37.89 (CH), 28.96 (CH_2), 27.19 (CH_2), 25.50 (CH_2), 25.45 (CH_2), 25.36 (CH_2) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3425 (br, w), 2923 (m), 2855 (w), 1597 (vs), 1510 (m), 1264 (m), 1238 (s), 1146 (vs), 1119 (vs), 1093 (m), 990 (m), 835 (m), 761 (s), 679 (vs) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.96 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{14}H_{18}ClF_3N^+$ $[M+H]^+$ 292.1074, found 292.1071.

3-Chloro-*N*-(2,2,2-trifluoro-1-methylcyclohexylethyl)aniline 3e

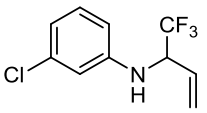
Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (200 mg, 0.79 mmol) was reacted with cyclohexylmethylmagnesium bromide (0.5 M in Et_2O, 3.16 mL, 1.58 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 3:2) to give the desired amine **3e** (62 mg, 26%) as a colorless oil together with the side product 3-chloro-*N*-2,2,2-trifluoroethyl)aniline **4** (32 mg, 19%, light yellow liquid).



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.08 (t, J = 8.1 Hz, 1 H, H5), 6.81 (t, J = 2.1 Hz, 1 H, H2), 6.71 (dd, J = 8.2 Hz, 1.8 Hz, 1 H, H6), 6.58 (ddd, J = 7.8 Hz, 1.9 Hz, 0.7 Hz, 1 H, H4), 6.21 (d, J = 9.0 Hz, 1 H, NH), 4.33 – 4.19 (m, 1 H, NHC*H*), 1.74 – 1.34 (m, 8 H, 4 × CH_2), 1.26 – 0.93 (m, 4 H, 2 × CH_2), 0.92 – 0.78 (m, 1 H, CH) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = –74.91 (d, $J_{CF3,CH}$ = 9.0 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 149.26 (C1), 133.62 (C3), 130.40 (C5), 126.84 (q, $J_{C,F}$ = 284.6 Hz, CF_3), 116.08 (C4), 111.61 (C2), 110.90 (C6), 51.12 (q, $J_{C,F}$ = 28.4 Hz, *C*CF_3), 35.29 (CH_2), 33.32 (CH_2), 32.95 (CH), 31.35 (CH_2), 25.87 (CH_2), 25.70 (CH_2), 25.39 (CH_2) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3421 (br, vw), 2922 (m), 2852 (w), 1598 (vs), 1509 (m), 1449 (m), 1254 (s), 1150 (s), 1122 (vs), 1091 (s), 990 (m), 844 (br,m), 763 (m), 679 (s) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.83 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{15}H_{20}ClF_3N^+$ $[M+H]^+$ 306.1231, found 306.1228.

3-Chloro-*N*-(2,2,2-trifluoro-1-vinylethyl)aniline 3f

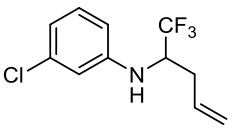
Following the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (229 mg, 0.90 mmol) was reacted with vinylmagnesium bromide (1.0 M in THF, 1.81 mL, 1.81 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 4:1) to give the desired amine **3f** (131 mg, 62%) as a colorless oil.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.11 (t, J = 8.1 Hz, 1 H, H5), 6.87 (t, J = 2.1 Hz, 1 H, H2), 6.77 (dd, J = 8.0 Hz, 2.0 Hz, 1 H, H6), 6.64 (ddd, J = 7.8 Hz, 2.0 Hz, 0.8 Hz, 1 H, H4), 6.48 (d, J = 9.7 Hz, 1 H, NH), 5.86 (ddd, J = 16.8 Hz, 10.4 Hz, 6.2 Hz, 1 H, CH_2=C*H*), 5.56 (d, J = 17.1 Hz, 1 H, HCH_{trans}=CH), 5.43 (d, J = 10.4 Hz, 1 H, HCH_{cis}=CH), 5.10 – 4.97 (m, 1 H, CH) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = −73.77 (d, $J_{CF3,CH}$ = 7.7 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 148.36 (C1), 133.62(C3), 130.36 (C5), 129.80 (CH_2=*C*H), 125.52 (q, $J_{C,F}$ = 283.4 Hz, CF_3), 120.83 (*C*H_2=CH), 116.70 (C4), 112.31 (C2), 111.71 (C6), 55.83 (q, $J_{C,F}$ = 29.4 Hz, *C*CF_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3417 (br, vw), 3029 (br, vw), 1597 (s), 1482 (m), 1250 (m), 1156 (s), 1114 (vs), 991 (m), 941 (m), 847 (m), 764 (s), 679 (s) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.53 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{10}H_{10}ClF_3N^+$ $[M+H]^+$ 236.0448, found 236.0452.

3-Chloro-*N*-(2,2,2-trifluoro-1-allylethyl)aniline 3g

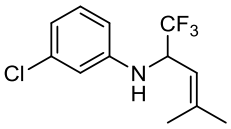
According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (230 mg, 0.91 mmol) was reacted with allylmagnesium bromide (1.0 M in MeTHF, 1.81 mL, 1.81 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 4:1) to give the desired amine **3g** (191 mg, 84%) as a colorless oil.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.07 (t, J = 8.1 Hz, 1 H, H5), 6.79 (t, J = 2.1 Hz, 1 H, H2), 6.69 (dd, J = 8.2 Hz, 1.8 Hz, 1 H, H6), 6.61 – 6.57 (d, J = 8.0 Hz, 1, H4), 6.26 (d, J = 9.3 Hz, 1 H, NH), 5.77 (ddt, J = 17.0 Hz, 10.2 Hz, 6.8 Hz, 1 H, H_2C=C*H*CH_2), 5.17 (dd, J = 17.2 Hz, 1.7 Hz, 1 H, HCH_{trans}=CH), 5.09 – 5.04 (dd, J = 10.2 Hz, 1.7 Hz, 1 H, HCH_{cis}=CH), 4.35 (tqd, J = 11.0 Hz, 7.4 Hz, 3.9 Hz, 1 H, CH), 2.55 – 2.45 (m, 1 H, CH_2) 2.40 – 2.28 (m, 1 H, CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = −74.47 (d, $J_{CF3,CH}$ = 7.3 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 149.14 (C1), 133.60 (H_2C=*C*H), 132.95 (C3), 130.35 (C5), 126.33 (q, $J_{C,F}$ = 284.7 Hz, CF_3), 118.24 (H_2*C*=CH), 116.26 (C4), 111.81 (C2), 111.19 (C6), 53.17 (q, $J_{C,F}$ = 28.4 Hz, *C*CF_3), 32.53 (CH_2) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3417 (br, vw), 1597 (vs), 1509 (m), 1482 (m), 1322 (w), 1275 (m), 1246 (s), 1122 (vs), 1093 (s), 991 (m), 844 (m), 764 (s), 679 (s) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.65 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{12}H_{14}ClF_3N^+$ $[M+H]^+$ 250.0605, found 250.0604.

3-Chloro-*N*-(2,2,2-trifluoro-1-dimethylvinylethyl)aniline 3h

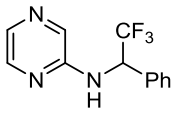
According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (180 mg, 0.71 mmol) was reacted with 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 2.84 mL, 1.42 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/CH_2Cl_2 4:1) to give the desired amine **3h** (159 mg, 85%) as a light yellow liquid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.09 (t, J = 8.05 Hz, 1 H, H5), 6.87 (t, J = 2.1 Hz, 1 H, C2), 6.75 (dd, J = 8.2 Hz, 1.9 Hz, 1 H, H6), 6.61 (ddd, J = 5.6 Hz, 2.8 Hz, 2.2 Hz, 1 H, H4), 6.31 (d, J = 8.6 Hz, 1 H, NH), 5.16 (d, J = 8.6 Hz, 1 H, *H*C=C(CH$_3$)$_3$), 4.98 – 4.87 (m, 1 H, CH), 1.75 (d, J = 0.8 Hz, 3 H, CH$_3$), 1.73 (d, J = 0.7 Hz, 3 H, CH$_3$). **^{19}F NMR** (376 MHz, DMSO-d_6): δ = −74.16 (d, $J_{CF3,CH}$ = 7.2 Hz, CF$_3$) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 148.46 (C1), 139.75 ((CH$_3$)$_2$*C*=CH), 133.59 (C3), 130.30 (C5), 126.22 (q, $J_{C,F}$ = 284.8 Hz, CF$_3$), 116.91 (C4 / (CH$_3$)$_2$C=*C*H), 116.42 (C4 / (CH$_3$)$_2$C=*C*H), 112.13 (C2), 111.43 (C6), 52.37 (q, $J_{C,F}$ = 29.8 Hz, *C*CF$_3$), 25.39 (CH$_3$), 18.57 (CH$_3$) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3417 (br, vw), 3029 (br, w), 1598 (m), 1482 (m), 1379 (w), 1164 (s), 1114 (vs), 990 (m), 866 (w), 764 (w), 680 (s) cm^{-1}. **HPLC-MS** (0.05% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.74 min, λ = 220 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{12}H_{14}ClF_3N^+$ $[M+H]^+$ 264.0761, found 264.0763.

***N*-(2,2,2-Trifluoro-1-phenylethyl)aminopyrazine 5**

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyrazine **1i** (200 mg, 0.90 mmol) was reacted with PhMgBr (1.5 M in THF, 1.18 mL, 1.81 mmol) in dry THF (12 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 10:1) to give the desired amine **5** (174 mg, 76%) as yellow oil.

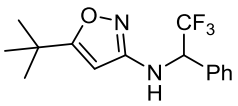


^{1}H NMR (599 MHz, $CDCl_3$): δ = 8.04 – 8.02 (m, 1 H, H5), 8.01 (s, 1 H, H2), 7.91 (d, J = 2.6 Hz, 1 H, H4), 7.49 – 7.45 (m, 2 H, 2 × H$_{phenyl}$), 7.43 – 7.38 (m, 3 H, 3 × H$_{phenyl}$), 5.89 (p, J = 7.9 Hz, 1 H, CH), 5.26 (d, J = 9.0 Hz, 1 H, NH) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = −73.81 (d, $J_{CF3,CH}$ = 7.8 Hz, CF$_3$) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 152.48 (C1), 141.61 (C5), 134.65 (C4), 133.53 (C1$_{phenyl}$), 132.95 (C2), 129.20 (CH$_{phenyl}$), 128.94 (CH$_{phenyl}$), 127.86 (CH$_{phenyl}$), 127.85 (CH$_{phenyl}$), 124.91 (q, $J_{C,F}$ = 282.0 Hz, CF$_3$), 55.64 (q, $J_{C,F}$ = 30.9 Hz, *C*CF$_3$) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3258 (br, w), 3036 (w), 1594 (m), 1515 (s), 1396 (m), 1250 (s), 1168 (s), 1147 (s), 1114 (vs), 1003 (s), 825 (m), 696 (s) cm^{-1}. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 13.48 min, λ = 214 nm. **HRMS** (ESI+): *m/z* calcd. for $C_{12}H_{11}F_3N_3^+$ $[M+H]^+$ 254.0900, found 254.0899.

5-(*tert*-Butyl)-*N*-(2,2,2-trifluoro-1-phenylethyl)isoxazol-3-amine 6

Following the general procedure, 5-(*tert*-butyl)-*N*-(1-ethoxy-2,2,2-trifluoroethyl)isoxazol-3-amine **1j** (200 mg, 0.88 mmol) was reacted with PhMgBr (1.5 M in THF, 1.15 mL, 1.77 mmol) in dry THF (12 mL). The crude

product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 10/1) to give the desired amine **6** (189 mg, 72%) as a white solid.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 – 7.33 (m, 5 H, 5 × H_{phenyl}), 5.49 (s, 1 H, $H_{isoxazole}$), 5.25 – 5.09 (m, 1 H, CH), 4.52 (d, J = 6.3 Hz, 1 H, NH), 1.27 (d, J = 0.4 Hz, 9 H, 3 × CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −74.37 (d, $J_{CF3,CH}$ = 7.6 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 181.34 (-HC*C*O-), 162.55 (-HC*C*N-), 133.62 ($C1_{phenyl}$), 129.19 (CH_{phenyl}), 128.87 (CH_{phenyl}), 127.78 (CH_{phenyl}), 127.77 (CH_{phenyl}), 124.71 (d, $J_{C,F}$ = 281.8 Hz, CF_3), 89.95 (-C*C*HC-), 59.44 (q, $J_{C,F}$ = 31.0 Hz, *C*CF_3), 32.77 ($(CH_3)_3C$), 28.63 (CH_3), 28.58 (2 × CH_3) ppm. **FT-IR** (ATR): $\tilde{\upsilon}$ = 3261 (br, w), 2971 (w), 1611 (m), 1549 (m), 1402 (w), 1254 (m), 1170 (s), 1119 (vs), 977 (w), 910 (w), 695 (s) cm^{-1}. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 15.83 min, λ = 214 nm. **mp** 78°C. **HRMS** (ESI+): *m/z* calcd. for $C_{15}H_{18}F_3N_2O^+$ $[M+H]^+$ 299.1366, found 299.1365.

3. Experimental Procedures and Analytical Data: *Convenient Access to Di- and Trifluoroethylamines for Lead Structure Research*

The complete supporting information including the NMR spectra of all compounds is available on the *European Journal of Organic Chemistry* website (DOI: 10.1002/ejoc.201501576) and on the CD in the book cover of this thesis. The compounds are numbered according to the publication.

3.1 Typical Procedures

Typical Procedure for the microwave synthesis of the hemiaminal ethers (TP1)

A dry microwave tube equipped with a magnetic stirrer was charged with an arylamine (1 equiv) and *p*TSA·H_2O (0.05 equiv). The starting material was solved in toluene and TFAE/ difluoroacetaldehyde ethyl hemiacetal (1.2 equiv) was added. The microwave tube was sealed and the mixture was reacted at 180 °C for 30 minutes (max. 200 W).

The solvent was evaporated and the crude product was purified by flash chromatography (SiO_2).

Typical Procedure for the synthesis of the hemiaminal ether (TP2)

A roundbottom flask equipped with a magnetic stirrer was charged with an arylamine (1 equiv) and *p*TSA·H_2O (0.05 equiv). The starting material was solved in ethanol and TFAE/ difluoroacetaldehyde ethyl hemiacetal (1.2 equiv) was added. The mixture was refluxed at 90 °C until the reaction showed no further conversion.

The solvent was evaporated and the product was purified by flash chromatography (SiO_2).

Typical Procedure for the magnesium insertion (TP3)[212]

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with *i*PrMgCl·LiCl (1.25 M in THF, 1.1 equiv). The neat aryl bromide (1 equiv) was added at the appropriate temperature. The reaction mixture was stirred at the stated temperature, while the completion of the Br/Mg exchange was monitored by GC-analysis.

Typical Procedure for the addition of the functionalized Grignard reagent to the hemiaminal ether (TP4)

The hemiaminal ether (0.045 mmol, 1 equiv) was solved in freshly distilled THF (5 mL) in a dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum and cooled to -78 °C. NaHMDS or LiHMDS (1 M in THF, 0.045 mmol, 1 equiv) was added and the reaction was stirred for 15 min until the deprotonation was complete. The *Grignard* reagent was added dropwise with a syringe and the solution was allowed to warm up to the appropriate temperature. The reaction was stirred until GC-analysis showed the complete conversion. After the reaction was completed sat. NH_4Cl solution was added and the mixture was

extracted three times with Et_2O. The solvent was evaporated and the product was purified by flash chromatography (SiO_2).

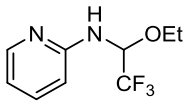
Typical procedure for the synthesis of CF_2H-amines with RMgX (TP5)

In a dry, argon-flushed Schlenk-flask a hemiaminal ether (1 equiv) was dissolved in dry THF. The solution was cooled to 0 °C, RMgX (2 eq) was added dropwise, and the solution was stirred at 0 °C until complete consumption of the starting material (ca. 2 h, TLC control). Then the solution was quenched with saturated NH_4Cl-solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated in *vacuo*. Purification by flash chromatography (SiO_2) furnished the desired amines.

3.2 Experimental data

_N_-(1-Ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (1a)

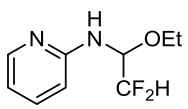
The hemiaminal ether **1a** was prepared according to **TP1**. 2-Aminopyridine (100 mg, 1.06 mmol), *p*TSA·H_2O (10 mg, 0.05 mmol) and TFAE (0.15 mL, 1.28 mmol) were reacted in a CEM microwave reactor in toluene (2 mL). Flash column chromatography (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **1a** as a white solid (196 mg, 82%).



R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.45. **mp** 84 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.13 (ddd, $J_{H6,H5}$ = 5.0 Hz, $J_{H6,H4}$ = 1.9 Hz, J = 0.9 Hz, 1 H, H6), 7.48 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.73 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 1.0 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 5.1 Hz, 1 H, H3), 6.01 (dq, $J_{CH,NH}$ = 10.2 Hz, $J_{CH,CF3}$ = 5.1 Hz, 1 H, CH), 4.89 (d, $J_{NH,CH}$ = 10.4 Hz, 1 H, NH), 3.86 – 3.66 (m, 2 H, CH_2), 1.22 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -80.66 (d, $J_{CF3,CH}$ = 5.0 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 156.19 (C2), 148.06 (C6), 138.13 (C4), 123.27 (q, $J_{C,F}$ = 282.2 Hz, CF_3), 115.66 (C5), 109.24 (C3), 78.50 (q, $J_{C,F}$ = 33.9 Hz, $CHCF_3$), 65.35 (CH_2), 15.30 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_9H_{12}ON_2F_3^+$ $[M+H]^+$ 221.0902, found 221.0898. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.21 min, λ = 214 nm.

_N_-(1-Ethoxy-2,2-difluoroethyl)pyridine-2-amine (1b)

Following **TP1**, 2-aminopyridine (100 mg, 1.06 mmol), *p*TSA·H_2O (10 mg, 0.05 mmol) and difluoroacetaldehyde ethyl hemiacetal (0.15 mL, 1.28 mmol) were reacted in a CEM microwave reactor in toluene (2.5 mL). Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 100:1:1 → 10:2:0.1) furnished **1b** (84 mg, 39%) as a white solid.

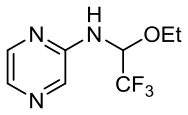


R_f (cyclohexane/ethyl acetate 1:1) = 0.74. **mp** <40 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.11 (ddd, $J_{H6,H5}$ = 5.0 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.45 (ddd, $J_{H4,H3}$ = 8.4 Hz, $J_{H4,H5}$ = 7.3 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.70 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz,

$J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.3 Hz, $J_{H3,H6}$ = $J_{H3,H5}$ = 0.9 Hz, 1 H, H3), 5.86 (ddd, $J_{H,F}$ = 55.1 Hz, $J_{H,F}$ = 53.3 Hz, $J_{CHF2,CH}$ = 2.3 Hz, 1 H, CHF_2), 5.74 – 5.70 (m, 1 H, CH), 4.94 (d, $J_{NH,CH}$ = 10.0 Hz, 1 H, NH), 3.71 (ddq, $J_{CH2,CH}$ = 44.3 Hz, $J_{CH2,CH2}$ = 9.6 Hz, $J_{CH2,CH3}$ = 7.0 Hz, 1 H, CH_2), 1.21 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -129.66 (ddd, $J_{F,F}$ = 286.6 Hz, $J_{F,H}$ = 54.7 Hz, $J_{F,CH}$ = 8.2 Hz, CHF_2), -133.95 (ddt, $J_{F,F}$ = 286.7 Hz, $J_{F,H}$ = 55.8 Hz, $J_{F,CH}$ = 12.4 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.84 (C2), 148.00 (C6), 137.89 (C4), 115.09 (C5), 113.74 (dd, $J_{C,F}$ = 246.4 Hz, $J_{C,F}$ = 244.7 Hz, CHF_2), 108.90 (C3), 79.35 (dd, $J_{C,F}$ = 26.8 Hz, $J_{C,F}$ = 22.7 Hz, CH), 64.36 (CH_2), 15.31 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_9H_{13}F_2N_2O^+$ $[M+H]^+$ 203.0990, found 203.0991. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 7.41 min, λ = 214 nm.

N-(1-Ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (1c)

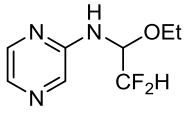
The hemiaminal ether 1c was prepared according to TP1. Aminopyrazine (100 mg, 1.05 mmol), *p*TSA·H_2O (10 mg, 0.05 mmol) and TFAE (0.17 mL, 1.26 mmol) were reacted in a CEM microwave reactor in toluene (2 mL). Flash column chromatography (cyclohexane/ethyl acetate/NEt_3 3:1:0.1) furnished 1c as a white solid (181 mg, 78%).



R_f (cyclohexane/ethyl acetate/NEt_3 2:1:0.05) = 0.55. **mp** 110 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.05 (ddd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.5 Hz, $J_{H6,NH}$ = 0.4 Hz, 1 H, H6), 8.03 (dd, $J_{H3,H6}$ = 1.5 Hz, $J_{H3,H5}$ = 0.4 Hz, 1 H, H3), 7.99 (dd, $J_{H5,H6}$ = 2.8 Hz, $J_{H5,H3}$ = 0.4 Hz, 1 H, H5), 5.94 (dq, $J_{CH,NH}$ = 10.0 Hz, $J_{CH,CF3}$ = 5.0 Hz, 1 H, CH), 5.26 (d, $J_{NH,CH}$ = 10.1 Hz, 1 H, NH), 3.93 – 3.64 (m, 2 H, CH_2), 1.23 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -80.71 (d, $J_{CF3,CH}$ = 5.1 Hz, $CHCF_3$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 152.56 (C2), 141.73 (C6), 135.68 (C5), 133.17 (C3), 122.87 (q, $J_{C,F}$ = 282.2 Hz, CF_3), 78.01 (q, $J_{C,F}$ = 34.3 Hz, *C*HCF_3), 65.69 (CH_2), 15.11 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_9H_{12}F_3N_3O^+$ $[M+H]^+$ 222.0849, found 222.0848. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 13.99 min, λ = 214 nm.

N-(1-Ethoxy-2,2-difluoroethyl)pyrazin-2-amine (1d)

Following **TP1**, aminopyrazine (100 mg, 1.05 mmol), *p*TSA·H_2O (10 mg, 0.05 mmol) and difluoroacetaldehyde ethyl hemiacetal (0.15 mL, 1.28 mmol) were reacted in a CEM microwave reactor in toluene (2.5 mL). Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 100:2:1 → 10:2:0.1) furnished **1d** (95 mg, 44%) as a white solid.

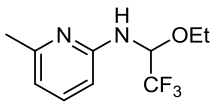


R_f (cyclohexane/ethyl acetate 1:1) = 0.55. **mp** 64-65 °C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.03 – 8.01 (m, 2 H, H3, H6), 7.95 (dd, $J_{H5,H6}$ = 2.7 Hz, $J_{H5,H3}$ = 1.0 Hz, 1 H, H5), 5.87 (dddd, $J_{H,F}$ = 55.7 Hz, $J_{H,F}$ = 54.8 Hz, $J_{CHF2,CH}$ = 2.2 Hz, $J_{CHF2,NH}$ = 1.3 Hz, 1 H, CHF_2), 5.75 – 5.68 (m, 1 H, CH), 5.26 (d, $J_{NH,CH}$ = 9.9 Hz, 1 H, NH), 3.78 – 3.62 (m, 1 H, CH_2), 1.21 (td, $J_{CH3,CH2}$ = 7.0 Hz, $J_{CH3,CH}$ = 1.2 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -129.03 (ddd, $J_{F,F}$ = 288.0 Hz, $J_{F,H}$ = 55.0 Hz, $J_{CHF2,CH}$ = 7.9 Hz, CHF_2), -134.70 (ddt, $J_{F,F}$ = 287.9 Hz, $J_{F,H}$ = 55.7 Hz, $J_{CHF2,CH}$ = 12.1 Hz, CHF_2) ppm.

^{13}C NMR (101 MHz, $CDCl_3$): δ = 153.27 (C2), 141.73 (C6), 135.17 (C5), 133.10 (C3), 113.41 (t, $J_{C,F}$ = 245.7 Hz, CHF_2), 78.94 (dd, $J_{C,F}$ = 27.6 Hz, $J_{C,F}$ = 22.5 Hz, CH), 64.73 (CH_2), 15.20 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_8H_{12}F_2N_3O^+$ $[M+H]^+$ 204.0943, found 204.0943. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 11.43 min, λ = 214 nm.

N-(1-Ethoxy-2,2,2-trifluoroethyl)-6-methylpyridin-2-amine (1e)

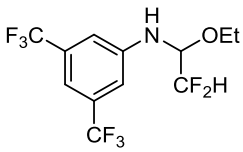
The hemiaminal ether **1e** was prepared according to **TP1**. 6-Methylpyridinamine (300 mg, 2.77 mmol), *p*TSA·H_2O (26 mg, 0.14 mmol) and TFAE (0.43 mL, 3.32 mmol) were reacted in a CEM microwave reactor in toluene (4 mL). Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 20:1:0.1 → 10:1:0.1) furnished **1e** as a colorless oil (350 mg, 54%).



R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.40. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 7.36 (dd, $J_{H4,H3}$ = 8.1 Hz, $J_{H4,H5}$ = 7.4 Hz, 1 H, H4), 6.59 (dq, $J_{H5,H4}$ = 7.3 Hz, $J_{H5,CH3}$ = 0.6 Hz, 1 H, H5), 6.31 (dt, $J_{H3,H4}$ = 8.2 Hz, J = 0.6 Hz, 1 H, H3), 5.99 (dq, $J_{CH,NH}$ = 10.3 Hz, $J_{CH,CF3}$ = 5.1 Hz, 1 H, CH), 4.84 (d, $J_{NH,CH}$ = 10.4 Hz, 1 H, NH), 3.90 – 3.62 (m, 2 H, CH_2), 2.39 (s, 3 H, CH_3), 1.22 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, $CH_2C\mathit{H}_3$) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -80.49 (d, $J_{CF3,CH}$ = 4.8 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 157.53 (C6), 155.96 (C2), 138.69 (C4), 123.72 (q, $J_{C,F}$ = 282.3 Hz, CF_3), 115.18 (C5), 106.04 (C3), 78.88 (q, $J_{C,F}$ = 33.7 Hz, $\mathit{C}HCF_3$), 65.57 ($\mathit{C}H_2CH_3$), 24.89 ($C\mathit{C}H_3$), 15.61 ($CH_2\mathit{C}H_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{10}H_{14}F_3N_2O^+$ $[M+H]^+$ 235.1053, found 235.1054. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.79 min, λ = 214 nm.

N-(1-Ethoxy-2,2-difluoroethyl)-3,5-*bis*(trifluoromethyl)aniline (1f)

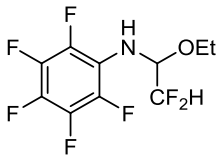
According to **TP2**, 3,5-*bis*(trifluoromethyl)aniline (0.50 g, 2.18 mmol), difluoroacetaldehyde ethyl hemiacetal (0.32 mL, 2.62 mmol) and *p*TSA·H_2O (21 mg, 0.11 mmol) were dissolved in EtOH (15 mL) and the reaction mixture was refluxed for 18 h. After removal of the solvent, flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 100:1:1 → 100:2:1) furnished **1f** (485 mg, 66%) as a white solid.



R_f (cyclohexane/ethyl acetate 4:1) = 0.66. **mp** 50-52 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.32 (s, 1 H, H4), 7.14 (s, 2 H, H2, H6), 5.87 (ddd, $J_{H,F}$ = 55.5 Hz, $J_{H,F}$ = 54.7 Hz, $J_{CHF2,CH}$ = 2.5 Hz, 1 H, CHF_2), 5.00 – 4.88 (m, 1 H, CH), 4.69 (d, $J_{NH,CH}$ = 9.3 Hz, 1 H, NH), 3.70 (ddq, $J_{CH2,CH2}$ = 41.2 Hz, $J_{CH2,CH}$ = 9.2 Hz, $J_{CH2,CH3}$ = 7.0 Hz, 2 H, CH_2), 1.24 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = 63.27 (2 × CF_3), -128.05 (dd, $J_{F,F}$ = 289.6 Hz, $J_{F,H}$ = 54.7 Hz, CHF_2), -133.54 (ddd, $J_{F,F}$ = 289.6 Hz, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 10.7 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 146.30 (C1), 132.96 (q, $J_{C,F}$ = 33.1 Hz, C3, C5), 123.40 (q, $J_{C,F}$ = 272.7 Hz, 2 × CF_3), 113.81 (C2, C6), 113.34 (t, $J_{C,F}$ = 246.9 Hz, CHF_2), 113.14 – 112.94 (m, C4), 82.68 (dd, $J_{C,F}$ = 27.8 Hz, $J_{C,F}$ = 23.3 Hz, CH), 64.21 (CH_2), 15.21 (CH_3) ppm. **HRMS** (ESI-): m/z calcd. for $C_{12}H_{11}F_8NO^-$ $[M-H]^-$ 336.0640, found 336.0646. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 20.02 min, λ = 214 nm.

***N*-(1-Ethoxy-2,2-difluoroethyl)-2,3,4,5,6-pentafluoroaniline (1g)**

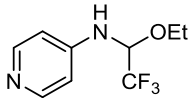
According to **TP2**, 2,3,4,5,6-pentafluoroaniline (1.00 g, 5.45 mmol), difluoroacetaldehyde ethyl hemiacetal (0.77 mL, 6.56 mmol) and *p*TSA·H_2O (52 mg, 0.27 mmol) were solved in EtOH (15 mL) and the reaction mixture was refluxed for 18 h. After removal of the solvent, flash column chromatography (SiO_2, gradient: cyclohexane/NEt_3 100:1 → cyclohexane/ethyl acetate/NEt_3 100:3:1) furnished **1g** (574 mg, 36%) as a colorless oil.



R_f (cyclohexane/ethyl acetate 7:1) = 0.73. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.81 (ddd, $J_{H,F}$ = 55.6 Hz, $J_{H,F}$ = 54.6 Hz, $J_{CHF2,CH}$ = 2.2 Hz, 1 H, CHF_2), 4.99 – 4.87 (m, 1 H, CH), 4.13 (d, $J_{NH,CH}$ = 11.1 Hz, 1 H, NH), 3.73 (ddq, $J_{CH2,CH}$ = 67.9 Hz, $J_{CH2,CH2}$ = 9.4 Hz, $J_{CH2,CH3}$ = 7.0 Hz, 1 H, CH_2), 1.22 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (377 MHz, $CDCl_3$): δ = -129.19 (ddd, $J_{F,F}$ = 289.8 Hz, $J_{F,H}$ = 54.8 Hz, $J_{F,H}$ = 7.1 Hz, CHF_2), -135.38 (ddt, $J_{F,F}$ = 289.2 Hz, $J_{F,H}$ = 55.3 Hz, $J_{CHF2,CH}$ = 9.9 Hz, CHF_2), -156.49 – -156.63 (m, 2 F, F2. F6), -163.13 (td, $J_{F5,F4}$ = $J_{F5,F6}$ = $J_{F3,F2}$ = $J_{F3,F4}$ = 22.1 Hz, $J_{F5,F3}$ = $J_{F3,F5}$ = 4.8 Hz, 2 F, F3, F5), -167.38 (tt, $J_{F4,F3}$ = $J_{F4,F5}$ = 21.9 Hz, $J_{F4,F2}$ = $J_{F4,F6}$ = 4.7 Hz, F4) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.33 – 137.45 (m), 139.84 – 137.00 (m), 136.89 –133.89 (m), 121.01 – 120.55 (m), 113.49 (t, $J_{C,F}$ = 246.4 Hz, CHF_2), 84.43 (ddt, $J_{C,F}$ = 27.1 Hz, $J_{C,F}$ = 23.1 Hz, $J_{C,F}$ = 3.9 Hz, CH), 65.07 (CH_2), 15.16 (CH_3) ppm. **HRMS** (ESI-): m/z calcd. for $C_{10}H_7F_7NO^-$ $[M-H]^-$ 290.0421, found 290.0422. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 18.81 min, λ = 214 nm.

***N*-(2,2,2-Trifluoro-1-ethoxyethyl)aminopyridine (1h)**

Following **TP1**, 4-aminopyridine (200 mg, 2.12 mmol), *p*TSA·H_2O (20 mg, 0.11 mmol) and TFAE (0.33 mL, 2.55 mmol) were reacted in a CEM microwave reactor in toluene (2.5 mL). Flash column chromatography (SiO_2, gradient: ethyl acetate → ethyl acetate/MeOH 10:1) furnished **1h** as a white solid (258 mg, 55%).

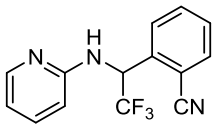


R_f = 0.11 (cyclohexane/ethyl acetate/NEt_3 1:1:0.01). **mp** 84 °C. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.24 – 8.05 (m, 2 H, H2, H6), 7.37 (d, $J_{NH,CH}$ = 10.0 Hz, 1 H, NH), 6.97 – 6.80 (m, 2 H, H3, H5), 5.70 (dq, $J_{CH,NH}$ = 10.3 Hz, $J_{CH,CF3}$ = 5.2 Hz, 1 H, CH), 3.82 – 3.47 (m, 2 H, CH_2), 1.13 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = -78.80 (d, $J_{CF3,CH}$ = 5.8 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 151.94 (C4), 149.84 (C2, C6), 123.06 (q, $J_{C,F}$ = 283.8 Hz, CF_3), 108.31 (C3, C5), 78.89 (q, $J_{C,F}$ = 33.3 Hz, *C*HCF_3), 63.52 (CH_2), 14.86 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_9H_{12}F_3N_2O^+$ $[M+H]^+$ 221.0896, found 221.0898. **HPLC-MS** (0.1% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 1.18 min, λ = 220 nm.

2-(2,2,2-Trifluoro-1-(pyridin-2-ylamino)ethyl)benzonitrile (2a)

(2-Cyanophenyl)magnesium chloride was prepared according to **TP3** from 2-bromobenzonitrile (91 mg, 0.50 mmol) in 1 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2a** as a light yellow oil (94 mg, 75%).

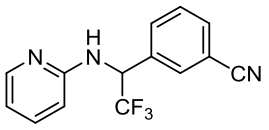


R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.45. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.44 (ddd, $J_{H6',H5'}$ = 4.9 Hz, $J_{H6',H4'}$ = 1.9 Hz, $J_{H6',H3'}$ = 0.9 Hz, 1 H, H6′), 8.04 (s, 2 H, NH, H3′), 7.85 – 7.75 (m, 2 H, H4, H4′), 7.71 – 7.52 (m, 3 H, H3, H5, H6), 7.11 (ddd, $J_{H5',H4'}$ = 7.3 Hz, $J_{H5',H6'}$ = 4.9 Hz, $J_{H5',H3'}$ = 1.0 Hz, 1 H, H5′), 6.59 – 6.46 (m, 1 H, CH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.06 (dd, $J_{CF3,CH}$ = 5.7 Hz, $J_{CF3,NH}$ = 1.2 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 152.50 (C2′), 148.23 (C6′), 138.11 (C4′), 134.87 (d, $J_{C,F}$ = 1.5 Hz, CF_3), 133.78 (C1), 132.16 (C6), 130.23 (C5), 130.21 – 118.74 (m, CF_3), 124.49 (d, $J_{C,F}$ = 1.9 Hz, C3), 122.84 (C4), 120.17 (C5′), 117.66 (CN), 61.67 (q, $J_{C,F}$ = 32.7 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{10}F_3N_3^+$ $[M+H]^+$ 278.0905, found 278.0899. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.83 min, λ = 214 nm.

3-(2,2,2-Trifluoro-1-(pyridin-2-ylamino)ethyl)benzonitrile (2b)

(3-Cyanophenyl)magnesium chloride was prepared according to **TP3** from 3-bromobenzonitrile (91 mg, 0.50 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished 2b as a light yellow oil (89 mg, 71%).

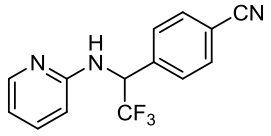


R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.45. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.09 (ddd, $J_{H6',H5'}$ = 5.1 Hz, $J_{H6',H4'}$ = 1.9 Hz, $J_{H6',H3'}$ = 0.9 Hz, 1 H, H6′), 7.80 (td, $J_{H6,H2}$ = $J_{H6,H4}$ = 1.4 Hz, $J_{H6,H3}$ = 0.6 Hz, 1 H, H6), 7.74 (dtt, $J_{H4,H3}$ = 7.9 Hz, $J_{H4,H2}$ = $J_{H4,H6}$ = 1.3 Hz, $J_{H4,CH}$ = $J_{H4,NH}$ = 0.7 Hz, 1 H, H4), 7.65 (dt, $J_{H2,H3}$ = 7.9 Hz, $J_{H2,H4}$ = $J_{H2,H6}$ = 1.4 Hz, 1 H, H2), 7.50 (t, $J_{H3,H2}$ = $J_{H3,H4}$ = 7.5 Hz, 1 H, H3), 7.45 (ddd, $J_{H4',H3'}$ = 8.3 Hz, $J_{H4',H5'}$ = 7.1 Hz, $J_{H4',H6'}$ = 1.8 Hz, 1 H, H4′), 6.69 (dddd, $J_{H5',H4'}$ = 7.2 Hz, $J_{H5',H6'}$ = 5.0 Hz, $J_{H6',H5'}$ = 0.9 Hz, $J_{H6',NH}$ = 0.3 Hz, 1 H, H5′), 6.53 (ddd, $J_{H3',H4'}$ = 8.4 Hz, $J_{H3',H5'}$ = $J_{H3',NH}$ = 0.7 Hz, 1 H, H3′), 6.01 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.0 Hz, 1 H, CH), 5.04 (d, $J_{NH,CH}$ = 8.7 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.60 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 155.77 (C2′), 148.11 (C6′), 138.02 (C4′), 136.57 (d, $J_{C,F}$ = 1.1 Hz, C5), 132.77 (C4), 132.68 (C2), 132.05 – 131.64 (m, C6), 129.83 (C3), 124.98 (q, $J_{C,F}$ = 281.7 Hz, CF_3), 118.56 (CN), 115.38 (C5′), 113.31 (C1), 109.22 (C3′), 55.92 (q, $J_{C,F}$ = 30.6 Hz, CH) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{11}N_3F_3^+$ $[M+H]^+$ 278.0905, found 278.0898. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.30 min, λ = 214 nm.

4-(2,2,2-Trifluoro-1-(pyridin-2-ylamino)ethyl)benzonitrile (2c)

(4-Cyanophenyl)magnesium chloride was prepared according to **TP3** from 4-bromobenzonitrile (91 mg, 0.50 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2c** as a light yellow oil (85 mg, 68%).

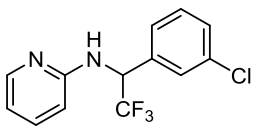


R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.45. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.08 (ddd, $J_{H6',H5'}$ = 5.0 Hz, $J_{H6',H4'}$ = 1.9 Hz, $J_{H6',H3'}$ = 0.9 Hz, 1 H, H6′), 7.72 – 7.65 (m, 2 H, H2, H6), 7.64 – 7.59 (m, 2 H, H3, H5), 7.44 (ddd, $J_{H4',H3'}$ = 8.3 Hz, $J_{H4',H5'}$ = 7.2 Hz, $J_{H4',H6'}$ = 1.9 Hz, 1 H, H4′), 6.68 (ddd, $J_{H5',H4'}$ = 7.2 Hz, $J_{H5',H6'}$ = 5.0 Hz, $J_{H6',H5'}$ = 0.9 Hz, 1 H, H5′), 6.51 (dt, $J_{H3',H4'}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3′), 6.01 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.0 Hz, 1 H, CH), 5.06 (d, $J_{NH,CH}$ = 8.9 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.38 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 155.81 (C2′), 148.09 (C6′), 140.02 (d, $J_{C,F}$ = 0.9 Hz, C4), 138.01 (C4′), 129.07 (q, $J_{C,F}$ = 1.2 Hz, C3, C5), 128.17 (C2, C6), 124.96 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 118.50 (CN), 115.36 (C5′), 113.13 (C1), 109.15 (C3′), 56.23 (q, $J_{C,F}$ = 30.6 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{11}N_3F_3^+$ $[M+H]^+$ 278.0905, found 278.0897. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 7.28 min, λ = 214 nm.

***N*-(1-(3-Chlorophenyl)-2,2,2-trifluoroethyl)pyridin-2-amine (2d)**

(3-Chlorophenyl)magnesium chloride was prepared according to **TP3** from 1-bromo-3-chlorobenzene (96 mg, 0.50 mmol) in 3 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 3 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2d** as a light yellow oil (97 mg, 75%).

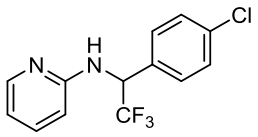


R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.40. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.11 (dddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, $J_{H6,NH}$ = 0.3 Hz, 1 H, H6), 7.48 (ddt, $J_{H2',H6'/H4'}$ = 1.9 Hz, $J_{H2',H6'/H4'}$ = 1.3 Hz, $J_{H2',H5'}$ = $J_{H2',CH}$ = 0.7 Hz, 1 H, H2′), 7.44 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 7.39 – 7.36 (m, 1 H, H6′), 7.36 – 7.29 (m, 2 H, H4′, H5′), 6.68 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz, $J_{H6,H5}$ = 0.9 Hz, 1 H, H5), 6.49 (dt, $J_{H3,H4}$ = 8.3 Hz, $J_{H3,H5}$ = $J_{H3,NH}$ = 0.9 Hz, 1 H, H3), 5.95 – 5.85 (m, 1 H, CH), 5.00 (d, $J_{NH,CH}$ = 9.4 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -80.36 (d, $J_{CF3,CH}$ = 4.6 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.19 (C2), 148.25 (C6), 138.05 (C4), 136.57 (d, $J_{C,F}$ = 1.0 Hz, C1′), 135.05 (C3′), 130.39 (C5′), 129.47 (C4′), 128.45 (q, $J_{C,F}$ = 1.2 Hz, C2′), 126.56 (q, $J_{C,F}$ = 1.2 Hz, C6′), 129.59 – 120.84 (CF_3), 115.24 (C5), 109.04 (C3), 56.13 (q, $J_{C,F}$ = 30.7 Hz, $CHCF_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{11}N_3F_3^+$ $[M+H]^+$ 287.0557, found 287.0557. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 11.35 min, λ = 214 nm.

***N*-(1-(4-Chlorophenyl)-2,2,2-trifluoroethyl)pyridin-2-amine (2e)**

(4-Chlorophenyl)magnesium chloride was prepared according to **TP3** from 1-bromo-4-chlorobenzene (96 mg, 0.50 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2e** as a light yellow oil (85 mg, 66%).

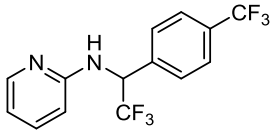


R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.40. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.10 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.47 – 7.38 (m, 3 H, H4, H2′, H6′), 7.38 – 7.33 (m, 2 H, H3′, H5′), 6.67 (dddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, $J_{H5,NH}$ = 0.3 Hz, 1 H, H5), 6.47 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3), 5.87 (dq, $J_{CH,NH}$ = 8.7 Hz, $J_{CH,CF3}$ = 7.9 Hz, 1 H, CH), 4.99 (d, $J_{NH,CH}$ = 9.0 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.88 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 156.20 (C2), 148.16 (C6), 137.93 (C4), 135.16 (C4′), 133.35 – 133.04 (m, C1′), 129.55 (q, $J_{C,F}$ = 1.2 Hz, C2′, C6′), 129.26 (C3′, C5′), 125.22 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 115.10 (C5), 108.88 (C3), 56.04 (q, $J_{C,F}$ = 30.6 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{13}H_{11}ClN_2F_3^+$ $[M+H]^+$ 287.0563, found 287.0557. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 11.43 min, λ = 214 nm.

***N*-(2,2,2-Trifluoro-1-(4-(trifluoromethyl)phenyl)ethyl)pyridin-2-amine (2f)**

(4-(Trifluoromethyl)phenyl)magnesium chloride was prepared according to **TP3** from 1-bromo-4-(trifluoromethyl)benzene (113 mg, 0.50 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2f** as a light yellow oil (105 mg, 73%).



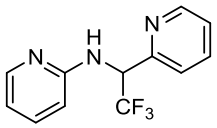
R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.50. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.10 (d, $J_{H6,H5}$ = 4.0 Hz, 1 H, H6), 7.66 (d, $J_{H3',H2'} = J_{H5',H6'}$ = 8.9 Hz, 2 H, H3′, H5′), 7.61 (d, $J_{H2',H3'} = J_{H6',H5'}$ = 8.8 Hz, 2 H, H2′, H6′), 7.44 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.68 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.50 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3), 6.00 (p, $J_{CH,CF3} = J_{CH,NH}$ = 8.0 Hz, 1 H, CH), 5.04 (d, $J_{NH,CH}$ = 8.9 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -62.84 (s, CCF_3), -73.60 (d, $J_{CF3,CH}$ = 7.9 Hz, $CHCF_3$) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 156.03 (C2), 148.14 (C6), 138.69 (C1′), 138.00 (C4), 131.38 (q, $J_{C,F}$ = 32.3 Hz, C4′), 128.68 (q, $J_{C,F}$ = 1.2 Hz, C2′, C6′), 126.00 (q, $J_{C,F}$ = 3.8 Hz, C3′, C5′), 125.13 (q, $J_{C,F}$ = 282.3 Hz, CH*C*F$_3$), 124.09 (q, $J_{C,F}$ = 272.2 Hz, C*C*F$_3$), 115.26 (C5), 109.02 (C3), 56.21 (q, $J_{C,F}$ = 30.6 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{11}N_2F_3^+$ $[M+H]^+$ 321.0826, found 321.0820. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 11.98 min, λ = 214 nm.

***N*-(2,2,2-Trifluoro-1-(pyridin-2-yl)ethyl)pyridin-2-amine (2g)**

Pyridin-2-ylmagnesium chloride was prepared according to **TP3** from 2-bromopyridine (50 µL, 0.55 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2g** as a light yellow oil (71 mg, 62%).

R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.35. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.64 (ddd, $J_{H6',H5'}$ = 4.9 Hz, $J_{H6',H4'}$ = 1.8 Hz, J = 1.0 Hz, 1 H, H6′), 8.12 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, J = 0.9 Hz, 1 H, H6), 7.78 – 7.67 (m, 1 H, H4′), 7.48 – 7.39 (m, 2 H, H3′, H4), 7.30 (ddd, $J_{H5',H4'}$ = 7.6 Hz, $J_{H5',H6'}$ = 4.9 Hz, $J_{H5',H3'}$ = 1.2 Hz, 1 H, H5′), 6.67 – 6.59 (m, 2 H, H3, H5), 6.17 (d, $J_{NH,CH}$ = 8.5 Hz, 1 H, NH), 6.08 (p, $J_{CH,NH}$ = $J_{CH,CF3}$ = 7.4 Hz, 1 H, CH) ppm.



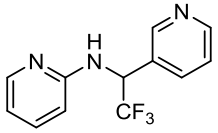
^{19}F NMR (282 MHz, $CDCl_3$): δ = -74.10 (d, $J_{CF3,CH}$ = 7.2 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 156.75 (C2), 152.26 (C2′), 149.49 (C6′), 147.76 (C6), 137.59 (C4), 136.89 (C4′), 125.08 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 124.39 (C3′), 124.00 (C5′), 114.56 (C5), 109.77 (C3), 55.83 (q, $J_{C,F}$ = 31.0 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{12}H_{11}F_3N_3^+$ $[M+H]^+$ 254.0900, found 254.0899. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.13 min, λ = 214 nm.

_N_-(2,2,2-Trifluoro-1-(pyridin-3-yl)ethyl) pyridin-2-amine (2h)

Pyridin-3-ylmagnesium chloride was prepared according to **TP3** from 3-bromopyridine (50 µL, 0.55 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2h** as a light yellow oil (79 mg, 69%).

R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.50. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.75 (d, $J_{H2',H4'}$ = 2.2 Hz, 1 H, H2′), 8.60 (dd, $J_{H6',H5'}$ = 4.8 Hz, $J_{H6',H4'}$ = 1.6 Hz, 1 H, H6′), 8.10 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.81 (dt, $J_{H4',H5'}$ = 8.2 Hz, $J_{H4',H2'}$ = $J_{H4',H6'}$ = 1.8 Hz, 1 H, H4′), 7.43 (ddd, $J_{H4,H3}$ = 8.8 Hz, $J_{H4,H5}$ = 7.3 Hz, $J_{H4,H6}$ = 1.8 Hz, 1 H, H4), 7.32 (ddd, $J_{H5',H4'}$ = 8.0 Hz, $J_{H5',H6'}$ = 4.8 Hz, $J_{H5',H2'}$ = 1.0 Hz, 1 H, H5′), 6.68 (ddd, $J_{H5,H4}$ = 7.1 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 1.0 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.4 Hz, J = 1.0 Hz, 1 H, H3), 6.02 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.2 Hz, 1 H, CH), 5.14 (d, $J_{NH,CH}$ = 9.0 Hz, 1 H, NH) ppm.

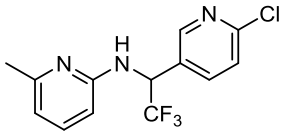


^{19}F NMR (282 MHz, $CDCl_3$): δ = -74.63 (q, J = 8.0 Hz, CF_3) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 155.74 (C2), 150.14 (C6′), 149.59 (C2′), 147.85 (C6), 137.76 (C4), 135.41 (C4′), 130.51 (C3′), 124.94 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 123.62 (C5′), 115.02 (C5), 108.91 (C3), 54.37 (q, $J_{C,F}$ = 31.0 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{12}H_{11}N_3F_3^+$ $[M+H]^+$ 254.0905, found 254.0899. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.33 min, λ = 214 nm.

***N*-(1-(6-Chloropyridin-3-yl)-2,2,2-trifluoroethyl)-6-methylpyridin-2-amine (2i)**

(6-Chloropyridin-3-yl)magnesium chloride was prepared according to **TP3** from 5-bromo-3-chloropyridine (218 mg, 1.13 mmol) in 1 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)-6-methylpyridin-2-amine (100 mg, 0.43 mmol) at 0 °C in 5 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3, 20:1:0.1) furnished **2i** as a white solid (84 mg, 65%).

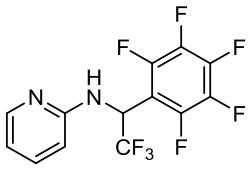


R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.40. mp 74 °C. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.53 (s, 1 H, H2′), 7.77 (dd, $J_{H4',H5'}$ = 8.4 Hz, $J_{H4',CH}$ = 2.4 Hz, 1 H, H4′), 7.35 (d, $J_{H5',H4'}$ = 8.0 Hz, 1 H, H5′), 7.32 (d, $J_{H5,H4}$ = 8.2 Hz, 1 H, H4), 6.60 – 6.47 (d, $J_{H5,H4}$ = 7.0 Hz, 1 H, H5), 6.29 (d, $J_{H5,H4}$ = 8.2 Hz, 1 H, H3), 5.95 (p, $J_{CH,CF} = J_{CH,NH}$ = 8.1 Hz, 1 H, CH), 4.92 (d, $J_{NH,CH}$ = 8.7 Hz, 1 H, NH), 2.35 (s, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.59 (d, $J_{CF3,CH}$ = 8.1 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 157.18 (C6), 154.96 (C2), 152.05 (C6′), 149.85 (C2′), 138.23 (C4, C4′), 129.92 (C3′), 124.88 (q, $J_{C,F}$ = 281.3 Hz, CF_3), 124.52 (C5′), 114.56 (C5), 105.54 (C3), 54.22 (q, $J_{C,F}$ = 31.2 Hz, *C*HCF$_3$), 24.40 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{13}H_{12}ClF_3N_3^+$ $[M+H]^+$ 302.0666, found 302.0664. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.50 min, λ = 214 nm.

***N*-(2,2,2-Trifluoro-1-(perfluorophenyl)ethyl)pyridin-2-amine (2j)**

(Perfluorophenyl)magnesium chloride was prepared from 1-bromo-2,3,4,5,6-pentafluorobenzene (60 µL, 0.50 mmol) solved in THF (0.50 mL). *i*PrMgCl (1.25 M, 0.44 mL, 0.55 mL) was added dropwise at -78 °C and the reaction was stirred for 45 min.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -78 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2j** as a light yellow oil (131 mg, 85%).

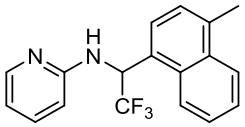


R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.45. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.13 (ddd, $J_{H6,H5}$ = 5.2 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.47 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H3,H6}$ = 1.9 Hz, 1 H, H4), 6.72 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.2 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.72 – 6.63 (m, 1 H, CH), 6.55 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3), 5.21 (d, $J_{NH,CH}$ = 10.6 Hz, 1 H, NH) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -74.63 (q, J = 7.9 Hz, CF_3), -141.29 (s, F2′, F6′), -152.01 (tt, $J_{F4',F3'} = J_{F4',F5'}$ = 20.9 Hz, $J_{F4',F2'} = J_{F4',F6'}$ = 2.7 Hz, F4′), -160.80 (td, $J_{F5',F4'} = J_{F5',F6'} = J_{F3',F2'} = J_{F3',F4'}$ = 22.0 Hz, $J_{F5',F3'} = J_{F3',F5'}$ = 7.8 Hz, F5′, F3′) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 155.30 (C2), 148.07 (C6), 147.54 – 144.58 (m, C2′, C6′), 143.52 – 140.32 (m, C3′, C5′), 138.12 (C4), 139.48 – 136.17 (m, C4′), 124.44 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 115.66 (C5), 109.47 (C3), 109.21 – 108.71 (m, C1′), 48.11 (q, $J_{C,F}$ = 34.3 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{13}H_7N_2F_8^+$ $[M+H]^+$ 343.0481, found 343.0474. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 14.56 min, λ = 214 nm.

***N*-(2,2,2-Trifluoro-1-(4-methylnaphthalen-1-yl)ethyl)pyridin-2-amine (2k)**

(4-Methylnaphthalen-1-yl)magnesium chloride was prepared according to **TP3** from 1-bromo-4-methylnaphthalen (158 mg, 0.50 mmol) in 18 h at 25 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at 25 °C in 18 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2k** as a light yellow oil (83 mg, 58%).

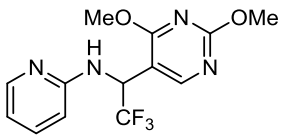


R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.45. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.29 – 8.22 (m, 1 H, H8′), 8.17 (dddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, $J_{H6,NH}$ = 0.3 Hz, 1 H, H6), 8.09 – 8.03 (m, 1 H, H5′), 7.64 (dd, $J_{H2',H3'}$ = 7.3 Hz, $J_{H2',CH}$ = 1.2 Hz, 1 H, H2′), 7.62 – 7.54 (m, 2 H, H6′, H7′), 7.39 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 7.35 (dd, $J_{H3',H2'}$ = 7.4 Hz, $J_{H3',CH3}$ = 0.9 Hz, 1 H, H3′), 6.81 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 7.7 Hz, 1 H, CH), 6.66 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.41 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3), 5.04 (d, $J_{NH,CH}$ = 8.8 Hz, 1 H, NH), 2.71 (d, $J_{CH3,C3'}$ = 0.9 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -80.38 (d, $J_{CF3,CH}$ = 4.7 Hz, $CHCF_3$) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.56 (C2), 148.34 (C6), 137.95 (C4), 136.25 (C8′a), 133.31 (C4′a), 132.02 (C4′), 129.29 (d, $J_{C,F}$ = 1.0 Hz, C1′), 126.93 (C7′), 126.39 (C3′), 126.23 (C6′), 126.11 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 125.31 (C5′), 124.88 (q, $J_{C,F}$ = 1.8 Hz, C2′), 123.94 (d, $J_{C,F}$ = 0.9 Hz, C8′), 114.88 (C5), 108.70 (C3), 51.67 (q, $J_{C,F}$ = 30.6 Hz, CH), 20.04 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{18}H_{16}F_3N_2^+$ $[M+H]^+$ 317.1260, found 317.1262. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 12.09 min, λ = 214 nm.

***N*-(1-(2,4-Dimethoxypyrimidin-5-yl)-2,2,2-trifluoroethyl)pyridin-2-amine (2l)**

(2,4-Dimethoxypyrimidin-5-yl)magnesium chloride was prepared according to **TP3** from 5-bromo-2,4-dimethoxypyrimidine (110 mg, 0.50 mmol) in 1 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2l** as a light yellow oil (120 mg, 85%).



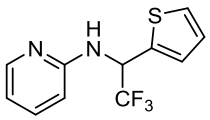
R_f (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.40.**^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, H6′), 8.11 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.8 Hz, $J_{H6,H3}$ = 0.8 Hz, 1 H, H6), 7.43 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.66 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.49 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3), 6.07 (dqd, $J_{CH,NH}$ = 9.7 Hz, $J_{CH,CF3}$ = 8.0 Hz, $J_{CH,H5}$ = 0.5 Hz, H, CH), 5.34 (d, $J_{NH,CH}$ = 9.6 Hz, 1 H, NH), 4.07 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -74.27 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.61 (C4′), 165.72 (C2′), 159.12 (q, $J_{C,F}$ = 1.1 Hz, C6′), 156.22 (C2), 148.20 (C6), 137.99 (*C*4), 125.29 (q, $J_{C,F}$ = 282.6 Hz, CF_3), 115.08 (C5), 109.07 (C3), 108.68 (d, $J_{C,F}$ = 1.2 Hz, C5′), 55.29 (OCH_3), 54.82 (OCH_3), 50.95 (q, $J_{C,F}$ = 32.4 Hz,

*C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{11}N_3F_3^+$ $[M+H]^+$ 315.1063, found 315.1064. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.46 min, λ = 214 nm.

N-(2,2,2-Trifluoro-1-(thiophen-2-yl)ethyl)pyridin-2-amine (2m)

Thiophen-2-ylmagnesium chloride was prepared according to **TP3** from 2-bromothiophene (0.05 mL, 0.50 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2m** as a colorless oil (84 mg, 72%).

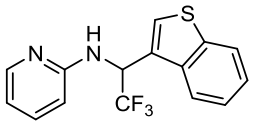


R$_f$ (cyclohexane/ethyl acetate 10:1) = 0.60. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.15 (dddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.8 Hz, $J_{H6,H3}$ = 0.8 Hz, $J_{H6,NH}$ = 0.3 Hz, 1 H, H6), 7.45 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 7.30 (dd, $J_{H5',H4'}$ = 5.1, $J_{H5',H3'}$ = 1.2 Hz, 1 H, H5′), 7.21 (ddt, $J_{H3',H4'}$ = 3.6 Hz, $J_{H3',H5'}$ = 1.3 Hz, $J_{H3',CH}$ = 0.7 Hz, 1 H, H3′), 7.02 (dd, $J_{H4',H5'}$ = 5.1 Hz, $J_{H4',H3'}$ = 3.6 Hz, 1 H, H4′), 6.70 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3), 6.30 (dqd, $J_{CH,NH}$ = 9.5 Hz, $J_{CH,CF3}$ = 7.6 Hz, J = 0.8 Hz, 1 H, CH), 4.87 (d, $J_{NH,CH}$ = 9.5 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -74.72 (d, $J_{CF3,CH}$ = 7.7 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.04 (C2), 148.07 (C6), 137.98 (C4), 137.13 – 137.08 (m, C2′), 127.43 (C4′), 127.21 (q, $J_{C,F}$ = 1.3 Hz, C3′), 126.15 (C5′), 124.95 (q, $J_{C,F}$ = 281.9 Hz, CF_3), 115.22 (C5), 109.07 (C3), 52.28 (q, $J_{C,F}$ = 32.2 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_{10}N_2F_3^+$ $[M+H]^+$ 259.0517, found 259.05113. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.10 min, λ = 214 nm.

N-(1-(Benz[*b*]thiophen-3-yl)-2,2,2-trifluoroethyl)pyridin-2-amine (2n)

Benzo[*b*]thiophen-3-ylmagnesium chloride was prepared according to **TP3** from 3-bromobenz[*b*]thiophene (107 mg, 0.50 mmol) in 3 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) at -30 °C in 3 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 50:1:0.1 → 15:1:0.1) furnished **2n** as a yellow oil (115 mg, 83%).

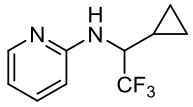


R$_f$ (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.40. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.22 (ddd, $J_{H6,H5}$ = 5.0 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.86 (dddd, $J_{H4',H5'} = J_{H7',H6'}$ = 6.8 Hz, $J_{H4',H6'} = J_{H7',H5'}$ = 5.4 Hz, $J_{H4',H7'} = J_{H7',H4'}$ = 3.3 Hz, $J_{H4',H2'} = J_{H7',H2'}$ = 0.7 Hz, 2 H, H4′, H7′), 7.62 (dd, $J_{H2',CH}$ = 1.5 Hz, $J_{H2',H4'} = J_{H2',H7'}$ = 0.7 Hz, 1 H, H2′), 7.43 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 7.40 – 7.35 (m, 2 H, H5′, H6′), 6.71 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.44 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3), 6.54 (dqd, $J_{CH,NH}$ = 9.9 Hz, $J_{CH,CF3}$ = 7.6 Hz, $J_{CH,H2'}$ = 0.8 Hz, 1 H, CH), 4.79 (d, $J_{NH,CH}$ =

9.3 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.10 (d, $J_{CF3,CH}$ = 7.6 Hz, $J_{CF3,NH}$ = 1.1 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 156.09 (C2), 147.85 (C6), 139.97 (C7′a), 137.90 (C3′a), 137.69 (C4), 129.24 (d, $J_{C,F}$ = 1.1 Hz, C3′), 125.43 (q, $J_{C,F}$ = 282.6 Hz, CF_3), 124.94 (C2′), 124.89 (C5′), 124.61 (C6′), 122.77 (C4′), 121.94 (C7′), 114.73 (C5), 108.62 (C3), 50.20 (q, $J_{C,F}$ = 31.8 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{15}H_{12}F_3N_3S^+$ $[M+H]^+$ 309.0668, found 309.0667. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 11.71 min, λ = 214 nm.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)pyridin-2-amine (2o)

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (100 mg, 0.45 mmol) and cyclopropylmagnesium bromide (1.0 M, 0.55 mL, 0.55 mmol) at 0 °C in 2 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 50:1:0.1 → 10:1:0.1) furnished **2o** as a white solid (83 mg, 85%).

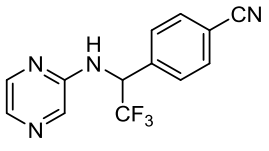


R$_f$ (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.45. mp 77 °C, **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.07 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.42 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.63 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.44 (dt, $J_{H3,H4}$ = 8.4 Hz, $J_{H3,H5}$ = $J_{H3,H6}$ = 0.9 Hz, 1 H, H3), 4.47 (d, $J_{NH,CH}$ = 9.5 Hz, 1 H, NH), 4.36 – 4.17 (m, 1 H, CH), 1.17 – 1.04 (m, 1 H, C*H*(CH$_2$)$_2$), 0.76 – 0.63 (m, 1 H, CH$_2$), 0.61 – 0.49 (m, 2 H, CH$_2$), 0.46 – 0.32 (m, 1 H, CH$_2$) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -75.58 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 157.26 (C2), 147.98 (C6), 137.81 (C4), 126.26 (q, $J_{C,F}$ = 283 Hz, CF_3), 114.47 (C5), 108.50 (C3), 55.82 (q, $J_{C,F}$ = 29.3 Hz, *C*HCF$_3$), 10.86 (q, $J_{C,F}$ = 2.3 Hz, *C*H(CH$_2$)$_2$), 3.82 (d, $J_{C,F}$ = 0.9 Hz, CH$_2$), 1.91 (CH$_2$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{10}H_{12}F_3N_2^+$ $[M+H]^+$ 217.0953, found 217.0946. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.14 min, λ = 214 nm.

4-(2,2,2-Trifluoro-1-(pyrazin-2-ylamino)ethyl)benzonitrile (2p)

(4-Cyanophenyl)magnesium chloride was prepared according to **TP3** from 4-bromobenzonitrile (91 mg, 0.50 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluorethyl)pyrazin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate 10:1 → 3:1) furnished **2p** as a light yellow oil (70 mg, 56%).



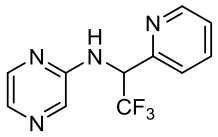
R$_f$ (cyclohexane/ethyl acetate 1:1) = 0.37. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.07 (d, $J_{H3',H6'}$ = 1.5 Hz, 1 H, H3′), 8.00 (dd, $J_{H6',H5'}$ = 2.7 Hz, $J_{H6',H3'}$ = 1.5 Hz, 1 H, H6′), 7.93 (d, $J_{H5',H6'}$ = 2.7 Hz, 1 H, H5′), 7.72 – 7.67 (m, 2 H, H3, H5), 7.61 (d, J = 8.1 Hz, 2 H, H2, H6), 5.97 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.0 Hz, 1 H, CH), 5.48 (d, $J_{NH,CH}$ = 8.8 Hz, 1 H, NH) ppm. **^{19}F NMR** (280 MHz, $CDCl_3$): δ = -73.33 (d, $J_{CF3,CH}$ = 7.7 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz,

$CDCl_3$): δ = 152.18 (C2′), 141.71 (C6′), 139.01 (C1), 135.19 (C5′), 133.32 (C3′), 132.77 (C3, C5), 128.98 (C2, C6), 124.41 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 118.27 (CN), 113.32 (C4) , 55.48 (q, $J_{C,F}$ = 31.0 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{13}H_{10}F_3N_4^+$ $[M+H]^+$ 279.0852, found 279.0852. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 13.16 min, λ = 214 nm.

N-(2,2,2-Trifluoro-1-(pyridin-2-yl)ethyl)pyrazin-2-amine (2q)

Pyridin-2-ylmagnesium chloride was prepared according to **TP3** from 2-bromopyridine (50 µL, 0.55 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2q** as a light yellow oil (65 mg, 56%).

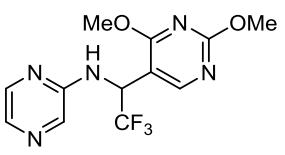


R$_f$(cyclohexane/ethyl acetate 1:1) = 0.48. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.68 – 8.62 (m, 1 H, H6′), 8.13 – 8.10 (m, 1 H, H3), 8.03 (ddd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, J = 0.5 Hz, 1 H, H6), 7.89 (dt, $J_{H5,H6}$ = 2.7 Hz, J = 0.5 Hz, 1 H, H5), 7.75 (tdd, $J_{H4',H3'}$ = $J_{H4',H5'}$ = 7.7 Hz, J = 1.8 Hz, J = 0.5 Hz, 1 H, H4′), 7.46 (dd, $J_{H3',H4'}$ = 8.1 Hz, $J_{H3',H5'}$ = 1.3 Hz, 1 H, H3′), 7.39 – 7.31 (m, 1 H, H5′), 6.51 (d, $J_{NH,CH}$ = 8.2 Hz, 1 H, NH), 6.00 (m, 1 H, CH) ppm. **^{19}F NMR** (280 MHz, $CDCl_3$): δ = -74.15 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 153.08 (C2), 151.21 (C2′), 149.52 (C6′), 141.53 (C6), 137.08 (C4′), 134.46 (C5), 134.03 (C3), 124.78 (q, $J_{C,F}$ = 283.3 Hz, CF_3), 124.33 (C3′/C5′), 124.29 (C3′/C5′), 55.16 (q, $J_{C,F}$ = 31.1 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_{10}F_3N_4^+$ $[M+H]^+$ 255.0852, found 255.0852. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.98 min, λ = 214 nm.

N-(1-(2,4-Dimethoxypyrimidin-5-yl)-2,2,2-trifluoroethyl)pyrazine-2-amine (2r)

(2,4-Dimethoxypyrimidin-5-yl)magnesium chloride was prepared according to **TP3** from 5-bromo-2,4-dimethoxypyrimidine (77 mg, 0.35 mmol) in 1 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (66 mg, 0.3 mmol) at -30 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2r** as a light yellow oil (75 mg, 79%).



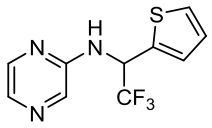
R$_f$ (cyclohexane/ethyl acetate/NEt_3 6:4:0.1) = 0.24. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.30 (s, 1 H, H6′), 8.05 – 8.00 (m, 2 H, H3, H5), 7.92 (d, $J_{H6,H5}$ = 2.6 Hz, 1 H, H6), 6.04 (dq, $J_{CH,NH}$ = 9.6 Hz, $J_{CH,CF3}$ = 7.9 Hz, 1 H, CH), 5.60 (d, $J_{NH,CH}$ = 9.6 Hz, 1 H, NH), 4.09 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -74.21 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 169.38 (C4′), 165.71 (C2′), 159.08 (C6′), 152.39 (C2), 141.69 (C6), 134.94 (C5), 133.29 (C3), 124.84 (q, $J_{C,F}$

= 282.6 Hz, CF_3), 107.71 (C5′), 55.28 (OCH_3), 54.74 (OCH_3), 50.41 (q, $J_{C,F}$ = 33.0 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{12}H_{13}F_3N_5O_2^+$ $[M+H]^+$ 316.1016, found 316.1014.

***N*-(2,2,2-Trifluoro-1-(thiophen-2-yl)ethyl)pyrazin-2-amine (2s)**:

Thiophen-2-ylmagnesium chloride was prepared according to **TP3** from 2-bromothiophene (0.07 mL, 0.70 mmol) in 2 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazine-2-amine (100 mg, 0.45 mmol) at -30 °C in 8 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 8:1:0.1) furnished **2s** as a light red oil (64 mg, 55%).

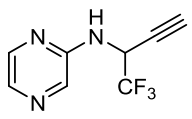


R_f (cyclohexane/ethyl acetate/NEt_3 4:2:0.1) = 0.38. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.06 (ddd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, J = 0.4 Hz, 1 H, H6), 8.03 (dd, $J_{H3,H6}$ = 1.5 Hz, J = 0.4 Hz, 1 H, H3), 7.95 (dd, $J_{H5,H6}$ = 2.8 Hz, J = 0.4 Hz, 1 H, H5), 7.33 (dd, $J_{H5',H4'}$ = 5.1 Hz, $J_{H5',H3'}$ = 1.2 Hz, 1 H, H5′), 7.22 (ddt, $J_{H3',H4'}$ = 3.6 Hz, $J_{H3',H5'}$ = 1.3 Hz, $J_{H3',CH}$ = 0.7 Hz, 1 H, H3′), 7.04 (dd, $J_{H4',H5'}$ = 5.1 Hz, $J_{H4',H3'}$ = 3.6 Hz, 1 H, H4′), 6.27 (dqd, $J_{CH,NH}$ = 9.4 Hz, $J_{CH,CF3}$ = 7.4 Hz, $J_{CH,H3'}$ = 0.8 Hz, 1 H, CH), 5.11 (d, $J_{NH,CH}$ = 9.4 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -74.67 (d, $J_{CF3,CH}$ = 7.6 Hz, CF_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 152.28 (C2), 141.73 (C6), 135.84 (C2′), 135.12 (C5), 133.21 (C3), 127.51 (q, $J_{C,F}$ = 1.3 Hz, C3′), 127.45 (C4′), 126.44 (C5′), 124.58 (q, $J_{C,F}$ = 281.9 Hz, CF_3), 51.60 (q, $J_{C,F}$ = 32.7 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_{10}N_2F_3^+$ $[M+H]^+$ 260.0464, found 260.0463. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 13.50 min, λ = 214 nm.

***N*-(1-(Benz[*b*]thiophen-3-yl)-2,2,2-trifluoroethyl)pyrazine-2-amine (2t)**

Benzo[*b*]thiophen-3-ylmagnesium chloride was prepared according to **TP3** from 3-bromobenz[*b*]thiophene (192 mg, 0.90 mmol) in 3 h at 0 °C.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) at 0 °C in 6 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 20:1:0.1 → 8:1:0.1) furnished **2t** as a yellow oil (120 mg, 86%).

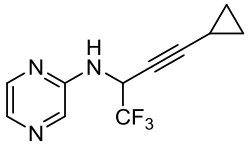


R_f (cyclohexane/ethyl acetate/NEt_3 2:1:0.05) = 0.38. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.13 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.96 (d, $J_{H5,H6}$ = 2.8 Hz, 2 H, H3, H5), 7.92 – 7.85 (m, 1 H, H5′), 7.82 – 7.75 (m, 1 H, H8′), 7.67 – 7.62 (m, 1 H, H2′), 7.46 – 7.32 (m, 2 H, H6′, H7′), 6.59 – 6.42 (m, 1 H, CH), 5.02 (d, $J_{NH,CH}$ = 9.1 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -73.06 (dd, $J_{CF3,CH}$ = 7.5 Hz, $J_{CF3,NH}$ = 1.2 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 152.58 (C2), 141.76 (C6), 140.14 (C4′, C9′), 137.84 (C3′), 134.94 (C5), 133.13 (C3), 125.53 (C2′), 125.32 (q, $J_{C,F}$ = 282.5 Hz, CF_3), 125.24 (C6′/C7′), 124.93 (C6′/C7′), 123.07 (C5′), 121.76, 49.69

(q, $J_{C,F}$ = 32.3 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_{10}N_2F_3^+$ $[M+H]^+$ 310.0620, found 310.0619, **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 15.13 min, λ = 214 nm.

N-(1,1,1-Trifluoro-but-3-yn-2-yl)pyrazin-2-amine (2u)

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) and ethynylmagnesium bromide (0.5 M, 1.4 mL, 0.67 mmol) at -78 °C in 2 h. Flash column chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 10:1:0.1) furnished **2u** as a light yellow oil (88 mg, 96%).

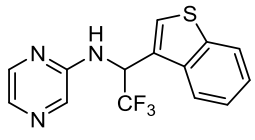


R$_f$ (cyclohexane/ethyl acetate/NEt_3 8:1:0.1) = 0.46. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.07 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 8.04 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 7.99 (d, $J_{H5,H6}$ = 2.7 Hz, 1 H, H5), 5.82 (dqd, $J_{CH,NH}$ = 9.1 Hz, $J_{CH,CF3}$ = 6.6 Hz, $J_{CH,C\equiv CH}$ = 2.5 Hz, 1 H, CH), 4.93 (d, $J_{NH,CH}$ = 9.2 Hz, 1 H, NH), 2.46 (d, $J_{C\equiv CH,CH}$ = 2.5 Hz, 1 H, C≡CH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -76.14 (d, $J_{CF3,CH}$ = 6.5 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 151.74 (C2), 141.62 (C6), 135.60 (C5), 133.34 (C3), 123.36 (q, $J_{C,F}$ = 281.8 Hz, CF_3), 75.30 (C≡*C*H), 74.45 (*C*≡CH), 44.83 (q, $J_{C,F}$ = 35.8 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_8H_7F_3N_3^+$ $[M+H]^+$ 202.0587, found 202.0586. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 11.99 min, λ = 214 nm.

N-(2,2,2-Trifluoro-1-(perfluorophenyl)ethyl)pyrazin-2-amine (2v)

(Perfluorophenyl)magnesium chloride was prepared from 1-bromo-2,3,4,5,6-pentafluorobenzene (90 µL, 0.70 mmol) solved in THF (0.50 mL). *i*PrMgCl (2 M, 0.39 mL, 0.77 mL) was added dropwise at -78 °C and the reaction was stirred for 45 min.

The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) at -78 °C in 5 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate 30:1 → 8:1) furnished **2v** as a colorless oil (143 mg, 92%).

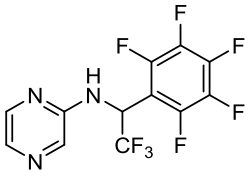


R$_f$ (cyclohexane/ethyl acetate/NEt_3 2:1:0.05) = 0.58. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.09 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 8.06 (dd, $J_{H6,H5}$ = 2.8, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.99 (d, $J_{H5,H6}$ = 2.7 Hz, 1 H, H5), 6.56 (dq, $J_{CH,NH}$ = 10.2 Hz, $J_{CH,CF3}$ = 7.8 Hz, 1 H, CH), 5.48 (d, $J_{NH,CH}$ = 10.4 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -74.56 (d, $J_{CF3,CH}$ = 7.8 Hz, CF_3), -141.10 (s, F2′, F6′), -151.01 (tt, $J_{F4',F3'} = J_{F4',F5'}$ = 20.9 Hz, $J_{F4',F2'} = J_{F4',F6'}$ = 2.9 Hz, F4′), -159.73 – -160.77 (m, F5′, F3′) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 151.71 (C2), 147.95 – 144.10 (m, C2′, C6′) , 143.95 – 140.22 (m, C3′, C5′), 141.66 (C6), 139.91 – 135.96 (m, C4′), 135.71 (C5), 133.45 (C3), 124.04 (q, $J_{C,F}$ = 281.9 Hz, CF_3), 108.30 – 107.72 (m, C1′), 47.60 (q, $J_{C,F}$ = 34.3 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_{10}N_2F_3^+$ $[M+H]^+$ 344.0428, found 344.0427. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 15.72 min, λ = 214 nm.

_N_-(4-Cyclopropyl-1,1,1-trifluorobut-3-yn-2-yl)pyrazin-2-amine (2w)

(Cyclopropylethynyl)magnesium chloride was prepared from ethynylcyclopropane (45 µL, 0.54 mmol) in THF (1 mL), which was reacted with *n*BuMgBr (2.0 M in Et_2O, 0.27 mL, 0.54 mmol) for 2 h at 0 °C.

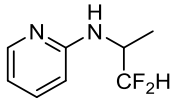
The addition reaction was performed according to **TP4** with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (100 mg, 0.45 mmol) and (cyclopropylethynyl)magnesium chloride at -20 °C in 2 h. Flash column chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 10:1:0.1 → 4:1:0.05) furnished **2w** as a colorless oil (87 mg, 80%).



R_f (cyclohexane/ethyl acetate/NEt_3 2:1:0.05) = 0.38. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.05 (ddd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, J = 0.4 Hz, 1 H, H6), 8.00 (dd, $J_{H3,H6}$ = 1.5 Hz, J = 0.4 Hz, 1 H, H3), 7.95 (dd, $J_{H5,H6}$ = 2.8 Hz, J = 0.4 Hz, 1 H, H5), 5.74 – 5.62 (m, 1 H, NHC*H*), 4.81 (d, $J_{NH,CH}$ = 9.2 Hz, 1 H, NH), 1.32 – 1.20 (m, 1 H, CH), 0.85 – 0.77 (m, 2 H, CH_2), 0.75 – 0.69 (m, 2 H, CH_2) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -76.45 (d, $J_{CF3,CH}$ = 6.6 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 152.04 (C2), 141.65 (C6), 135.10 (C5), 133.20 (C3), 123.66 (q, $J_{C,F}$ = 281.7 Hz, CF_3), 90.12 (C≡*C*-CH$(CH_2)_2$), 66.43 (*C*≡C-CH$(CH_2)_2$), 45.15 (q, $J_{C,F}$ = 35.4 Hz, *C*HCF$_3$) , 8.42 (2 × CH_2), -0.58 (C≡C-*C*H$(CH_2)_2$) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_{11}F_3N_3^+$ $[M+H]^+$ 242.0900, found 242.0898. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 13.83 min, λ = 214 nm.

_N_-(1,1-Difluoropropan-2-yl)pyridine-2-amine (3a)

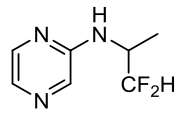
Following **TP5**, the hemiaminal ether **1b** (100 mg, 0.50 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.78 mL, 1.09 mmol) in dry THF (5 mL) for 2 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 100:10:1) to give the desired amine **3a** (61 mg, 72%) as an orange, amorphous solid.



R_f (cyclohexane/ethyl acetate 1:1) = 0.70. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.09 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.41 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.61 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.42 (dt, $J_{H3,H4}$ = 8.4 Hz, $J_{H3,H6}$ = $J_{H3,H5}$ = 0.9 Hz, 1 H, H3), 5.90 (ddd, $J_{F,H}$ = 57.7 Hz, $J_{F,H}$ = 55.7 Hz, $J_{CHF2,CH}$ = 2.0 Hz, 1 H, CHF_2), 4.54 – 4.36 (m, 1 H, CH), 4.32 (s, br, 1 H, NH), 1.30 (dt, $J_{CH3,CH}$ = 6.7 Hz, J = 1.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -125.78 (ddd, $J_{F,F}$ = 280.1 Hz, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 6.8 Hz, CHF_2), -134.19 (ddt, $J_{F,F}$ = 280.2 Hz, $J_{F,H}$ = 57.9 Hz, $J_{CHF2,CH}$ = 20.4 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.28 (C2), 148.10 (C6), 137.57 (C4), 115.65 (dd, $J_{C,F}$ = 245.4 Hz, $J_{C,F}$ = 244.2 Hz, CHF_2), 113.92 (C5) 108.47 (C3), 48.23 (dd, $J_{C,F}$ = 26.1 Hz, $J_{C,F}$ = 21.7 Hz, CH), 12.79 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_8H_{11}F_2N_2^+$ $[M+H]^+$ 173.0885, found 173.0885. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 3.55 min, λ = 214 nm.

***N*-(1,1-difluoropropan-2-yl)pyrazin-2-amine (3b)**

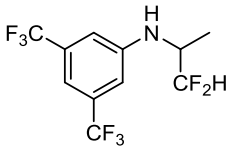
Following **TP5**, the hemiaminal ether **1d** (100 mg, 0.49 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.77 mL, 1.08 mmol) in dry THF (5 mL) for 1.5 h at 0 °C. The crude product was purified by preparative **HPLC** (0.1% TFA. 0 min: 4% MeCN (B) → 15 min: 100% B, flow: 20 mL/min, t_R = 16.51 min) to give the desired amine **3b** (80 mg, 94%) as colorless oil.



R$_f$ (cyclohexane/ethyl acetate 1:1) = 0.36. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.01 – 7.91 (m, 2 H, H3, H6), 7.85 (d, $J_{H5,H6}$ = 2.8 Hz, 1 H, H5), 5.89 (ddd, $J_{H,F}$ = 57.4 Hz, $J_{H,F}$ = 55.4 Hz, $J_{CHF2,CH}$ = 2.0 Hz, 1 H, CHF_2), 4.61 (s, br, 1 H, NH), 4.55 – 4.39 (m, 1 H, CH), 1.32 (d, $J_{CH3,CH2}$ = 6.9 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -126.59 (ddd, $J_{F,F}$ = 281.4 Hz, $J_{F,H}$ = 55.4 Hz, $J_{CHF2,CH}$ = 7.8 Hz, CHF_2), -133.24 (ddd, $J_{F,F}$ = 281.5 Hz, $J_{F,H}$ = 57.4 Hz, $J_{CHF2,CH}$ = 19.3 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 153.52 (C2), 141.78 (C6), 133.82 (C5), 133.13 (C3), 115.17 (t, $J_{C,F}$ = 244.8 Hz, CHF_2), 47.83 (dd, $J_{C,F}$ = 26.2 Hz, $J_{C,F}$ = 21.8 Hz, CH), 12.84 (dd, $J_{C,F}$ = 5.7 Hz, $J_{C,F}$ = 2.1 Hz, CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_7H_{10}F_2N_3^+$ $[M+H]^+$ 174.0837, found 174.0837. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.16 min, λ = 214 nm.

***N*-(1,1-Difluoropropan-2-yl)-3,5-*bis*(trifluoromethyl)aniline (3c)**

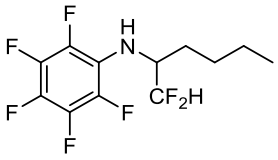
Following **TP5**, the hemiaminal ether **1f** (101 mg, 0.30 mmol) was reacted with MeMgBr (1.4 M in toluene/THF 3:1, 0.47 mL, 0.69 mmol) in dry THF (5 mL) for 3 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 100:5:1) to give the desired amine **3c** (65 mg, 71%) as a colorless oil.



R$_f$ (cyclohexane/ethyl acetate 5:1) = 0.64. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.21 (s, 1 H, H4), 7.00 (s, 2 H, H2, H6), 5.79 (ddd, $J_{H,F}$ = 56.2 Hz, $J_{H,F}$ = 55.5 Hz, $J_{CHF2,CH}$ = 2.6 Hz, 1 H, CHF_2), 4.06 (d, $J_{NH,CH}$ = 9.0 Hz, 1 H, NH), 3.98 – 3.79 (m, 1 H, CH), 1.34 (dt, $J_{CH3,CH2}$ = 6.7 Hz, $J_{CH3,CH}$ = 1.1 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = 63.30 (2 × CF_3), -127.08 (ddd, $J_{F,F}$ = 282.9 Hz, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 9.9 Hz, CHF_2), -128.03 (ddd, $J_{F,F}$ = 282.9 Hz, $J_{F,H}$ = 56.2 Hz, $J_{CHF2,CH}$ = 14.0 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.31 (C1), 132.87 (q, $J_{C,F}$ = 33.0 Hz, C3, C5), 123.53 (q, $J_{C,F}$ = 272.7 Hz, 2 × CF_3), 115.69 (t, $J_{C,F}$ = 245.8 Hz, CHF_2), 112.62 (m, C2, C6), 111.57 (dq, J= 3.9 Hz, C4), 50.63 (dd, $J_{C,F}$ = 24.0 Hz, $J_{C,F}$ = 22.6 Hz, CH), 13.81 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_8F_8N^-$ $[M-H]^-$ 306.0534, found 306.0538. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 19.89 min, λ = 214 nm.

***N*-(1,1-Difluorohexan-2-yl)-2,3,4,5,6-pentafluoroaniline (3d)**

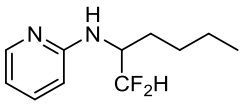
According **TP5**, the hemiaminal ether **1g** (113 mg, 0.39 mmol) was reacted with *n*BuMgBr (2.0 M in Et_2O, 0.43 mL, 0.85 mmol) in dry THF (5 mL) for 1.5 h at 0 °C. The desired amine **3d** (108 mg, 92%) was isolated after workup as a yellow liquid without further purification.



R_f (cyclohexane/ethyl acetate 7:1) = 0.80. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 5.79 (td, $J_{H,F}$ = 55.7 Hz, $J_{CHF2,CH}$ = 2.1 Hz, 1 H, CHF_2), 3.88 – 3.70 (m, 1 H, CH), 3.46 (d, $J_{NH,CH}$ = 10.7 Hz, 1 H, NH), 1.82 – 1.68 (m, 1 H, CH_2), 1.60 – 1.45 (m, 2 H, CH_2), 1.42 – 1.33 (m, 2 H, CH_2), 0.93 (t, $J_{CH3,CH2}$ = 7.2 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -127.32 (ddd, $J_{F,F}$ = 282.6 Hz, $J_{F,H}$ = 55.8 Hz, $J_{CHF2,CH}$ = 13.0 Hz, CHF_2), -129.96 (ddt, $J_{F,F}$ = 282.6 Hz, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 13.0 Hz, CHF_2), -158.23 (d, $J_{F2,F3}$ = $J_{F6,F5}$ = 21.8 Hz, F2, F6), -163.86 (td, $J_{F5,F4}$ = $J_{F5,F6}$ = $J_{F3,F2}$ = $J_{F3,F4}$ = 21.8 Hz, $J_{F5,F3}$ = $J_{F3,F5}$ = 6.4 Hz, F3, F5), -169.88 (td, $J_{F4,F3}$ = $J_{F4,F5}$ = 21.9 Hz, J = 6.0 Hz, F4) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.07 – 137.12 (m), 136.10 – 132.99 (m), 123.47 – 122.92 (m), 116.28 (t, $J_{C,F}$ = 245.1 Hz, CHF_2), 57.35 (ddt, $J_{C,F}$ = 24.0 Hz, $J_{C,F}$ = 20.4 Hz, $J_{C,F}$ = 3.6 Hz, CH), 29.21 (CH_2), 27.79 (CH_2), 22.55 (CH_2), 13.99 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{12}H_{11}F_7N^-$ $[M-H]^-$ 302.0785, found 302.0787. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 21.58 min, λ = 214 nm.

N-(1,1-Difluorohexan-2-yl)pyridine-2-amine (3e)

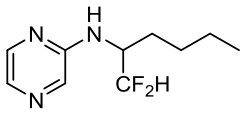
According **TP5**, the hemiaminal ether **1b** (100 mg, 0.50 mmol) was reacted with *n*BuMgBr (2.0 M in Et_2O, 0.54 mL, 1.08 mmol) in dry THF (5 mL) for 2.5 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 100:10:1) to give the desired amine **3e** (72 mg, 68%) as a white solid.



R_f (cyclohexane/ethyl acetate 1:1) = 0.88. mp 30 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.07 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.40 (ddd, $J_{H4,H3}$ = 8.4 Hz, $J_{H4,H5}$ = 7.1 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.60 (ddd, $J_{H5,H4}$ = 7.1 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.43 (dt, $J_{H3,H4}$ = 8.4 Hz, $J_{H3,H6}$ = $J_{H3,H5}$ = 1.0 Hz, 1 H, H3), 5.87 (ddd, $J_{H,F}$ = 57.3 Hz, $J_{H,F}$ = 55.9 Hz, $J_{CHF2,CH}$ = 1.9 Hz, 1 H, CHF_2), 4.42 – 4.19 (m, 2 H, CH, NH), 1.92 – 1.75 (m, 1 H, CH_2), 1.58 – 1.40 (m, 2 H, CH_2), 1.42 – 1.28 (m, 3 H, CH_2), 0.89 (t, $J_{CH3,CH}$ = 7.2 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -126.07 (ddd, $J_{F,F}$ = 279.8 Hz, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 8.6 Hz, CHF_2), -131.59 (ddt, $J_{F,F}$ = 280.0 Hz, $J_{F,H}$ = 57.2 Hz, $J_{CHF2,CH}$ = 18.4 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.87 (C2), 148.07 (C6), 137.58 (C4), 115.86 (t, $J_{C,F}$ = 244.6 Hz, CHF_2), 113.74 (C5) 108.16 (C3), 52.45 (dd, $J_{C,F}$ = 24.4 Hz, $J_{C,F}$ = 21.1 Hz, CH), 27.91 (CH_2), 27.48 (CH_2), 22.70 (CH_2), 14.02 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_{17}F_2N_2^+$ $[M+H]^+$ 215.1354, found 215.1354. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.96 min, λ = 214 nm.

N-(1,1-Difluorohexan-2-yl)pyrazin-2-amine (3f)

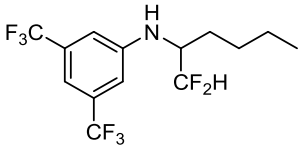
According **TP5**, the hemiaminal ether **1d** (100 mg, 0.49 mmol) was reacted with *n*BuMgBr (2.0 M in Et_2O, 0.54 mL, 1.08 mmol) in dry THF (5 mL) for 1.5 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 100:10:1 → 100:15:1) to give the desired amine **3f** (112 mg, quant.) as a yellow oil.



R_f (cyclohexane/ethyl acetate 1:1) = 0.61. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.97 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.94 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 7.84 (d, $J_{H5,H6}$ = 2.8 Hz, 1 H, H5), 5.86 (ddd, $J_{H,F}$ = 56.9 Hz, $J_{H,F}$ = 55.6 Hz, $J_{CHF2,CH}$ = 2.0 Hz, $J_{CHF2,NH}$ = 1.3 Hz, 1 H, CHF_2), 4.56 (d, $J_{NH,CH}$ = 8.9 Hz, 1 H, NH), 4.48 – 4.30 (m, 1 H, CH), 1.90 – 1.77 (m, 2 H, CH_2), 1.62 – 1.24 (m, 4 H, 2 × CH_2), 0.89 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -126.96 (ddd, $J_{F,F}$ = 281.2 Hz, $J_{F,H}$ = 55.6 Hz, $J_{CHF2,CH}$ = 10.6 Hz, CHF_2), -130.63 (ddt, $J_{F,F}$ = 281.1 Hz, $J_{F,H}$ = 56.9 Hz, $J_{CHF2,CH}$ = 17.4 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 154.14 (C2), 141.78 (C6), 133.69 (C5), 132.93 (C3), 115.43 (t, $J_{C,F}$ = 244.8 Hz, CHF_2), 51.93 (dd, $J_{C,F}$ = 24.1 Hz, $J_{C,F}$ = 21.0 Hz, CH), 27.82 (CH_2), 27.45 (CH_2), 22.59 (CH_2), 13.97 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{10}H_{16}F_2N_3^+$ $[M+H]^+$ 216.1307, found 216.1307. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 14.57 min, λ = 214 nm.

N-(1,1-Difluorohexan-2-yl)-3,5-bis(trifluoromethyl)aniline (3g)

According **TP5**, the hemiaminal ether **1f** (100 mg, 0.30 mmol) was reacted with *n*BuMgBr (2.0 M in Et_2O, 0.33 mL, 0.65 mmol) in dry THF (5 mL) for 2 h at 0 °C. The desired amine **3g** (100 mg, 96%) was isolated after workup as an orange liquid without further purification.

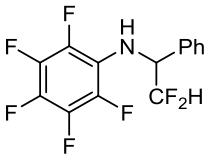


^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.20 (s, 1 H, H4), 7.00 (s, 2 H, H2, H6), 5.79 (td, $J_{H,F}$ = 55.7 Hz, $J_{CHF2,CH}$ = 2.5 Hz, 1 H, CHF_2), 3.99 (d, $J_{NH,CH}$ = 9.3 Hz, 1 H, NH), 3.78 – 3.66 (m, 1 H, CH), 1.86 – 1.77 (m, 1 H, CH_2), 1.58 – 1.46 (m, 2 H, CH_2), 1.43 – 1.30 (m, 3 H, CH_2), 0.96 – 0.89 (m, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -63.33 (2 × CF_3), -126.33 (ddd, $J_{F,F}$ = 282.7 Hz, $J_{F,H}$ = 55.8 Hz, $J_{CHF2,CH}$ = 12.3 Hz, CHF_2), -128.03 (ddd, $J_{F,F}$ = 282.7 Hz, $J_{F,H}$ = 55.7 Hz, $J_{CHF2,CH}$ = 12.3 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 148.08 (C1), 132.83 (q, $J_{C,F}$ = 32.9 Hz, C3, C5), 123.56 (q, $J_{C,F}$ = 272.6 Hz, 2 × CF_3), 115.80 (t, $J_{C,F}$ = 245.7 Hz, CHF_2), 112.40 (m, C2, C6), 111.35 (C4), 55.12 (t, $J_{C,F}$ = 21.8 Hz, CH), 28.76 (CH_2), 27.86 (CH_2), 22.65 (CH_2), 13.94 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{14}F_8N^-$ $[M-H]^-$ 348.1004, found 348.1010. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 21.70 min, λ = 214 nm.

N-(1,1-Difluoro-1-phenylethyl)-2,3,4,5,6-pentafluoroaniline (3h)

According to **TP5**, the hemiaminal ether **1g** (91 mg, 0.31 mmol) was reacted with PhMgBr (3 M in Et_2O, 0.23 mL, 0.69 mmol) in dry THF (5 mL) for 4 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/NEt_3 100:1) to give the desired amine **3h** (51 mg, 50%) as a yellow oil.

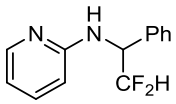
R_f (cyclohexane/ethyl acetate 7:1) = 0.56. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.42 – 7.31 (m, 5 H, 5 × H_{Phenyl}), 6.07 (ddd, $J_{H,F}$ = 55.8 Hz, $J_{H,F}$ = 55.0 Hz, $J_{CHF2,CH}$ = 2.3 Hz, 1 H, CHF_2), 4.96 (tdd, $J_{CH,F}$ = 13.5 Hz, $J_{CH,NH}$ = 10.6 Hz, $J_{CH,CHF2}$ = 2.2 Hz, 1 H, CH), 4.33 (d, $J_{NH,CH}$ = 10.5 Hz, 1 H, NH) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -125.23 (ddd, $J_{F,F}$ = 282.4 Hz, $J_{F,H}$ = 55.9 Hz, $J_{CHF2,CH}$ = 14.0 Hz, CHF_2), -129.32 (ddt, $J_{F,F}$ = 282.2 Hz, $J_{F,H}$ = 55.0 Hz, $J_{CHF2,CH}$ = 13.6 Hz, CHF_2), -157.21 (dd, $J_{F2,F3}$ = $J_{F6,F5}$ = 21.0 Hz, $J_{F2,F4}$ = $J_{F6,F4}$ = 4.0 Hz F2, F6), -



163.40 (td, $J_{F5,F4} = J_{F5,F6} = J_{F3,F2} = J_{F3,F4} = 21.6$ Hz, $J_{F5,F3} = J_{F3,F5} = 4.4$ Hz, 2 F, F3, F5), -168.14 (td, $J_{F4,F3} = J_{F4,F5} = 21.9$ Hz, $J = 4.8$ Hz, F4) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 140.06 – 137.38 (m), 139.48 – 136.64 (m), 136.26 – 133.48 (m), 134.41 ($C1_{Phenyl}$), 129.08 (C_{Phenyl}), 129.02 (C_{Phenyl}), 127.48 (C_{Phenyl}), 121.68 – 121.40 (m, C_{Phenyl}), 115.22 (dd, $J_{C,F}$ = 248.1 Hz, $J_{C,F}$ = 246.1 Hz CHF_2), 61.17 (tt, $J_{C,F}$ = 21.5 Hz, $J_{C,F}$ = 4.1 Hz, CH) ppm. **HRMS** (ESI-): m/z calcd. for $C_{14}H_7F_7N^-$ $[M-H]^-$ 322.0472, found 322.0474. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 19.82 min, λ = 214 nm.

N-(1,1-Difluoro-1-phenylethyl)pyridine-2-amine (3i)

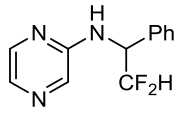
According to the **TP5**, the hemiaminal ether **1b** (100 mg, 0.49 mmol) was reacted with PhMgBr (3 M in Et_2O, 0.36 mL, 1.07 mmol) in dry THF (5 mL) for 2 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate/NEt_3 100:10:1) to give the desired amine **3i** (118 mg, quant.) as a colorless oil.



R_f (cyclohexane/ethyl acetate 1:1) = 0.83. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.10 (ddd, $J_{H6,H5}$ = 5.0 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.47 – 7.43 (m, 2 H, 2 × H_{Phenyl}), 7.43 – 7.32 (m, 4 H, 3 × H_{Phenyl}, H4), 6.63 (ddd, $J_{H5,H4}$ = 7.1 Hz, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.43 (dt, $J_{H3,H4}$ = 8.4 Hz, $J_{H3,H6} = J_{H3,H5}$ = 1.0 Hz, 1 H, H3), 6.12 (td, $J_{H,F}$ = 55.9 Hz, $J_{CHF2,CH}$ = 2.4 Hz, 1 H, CHF_2), 5.48 – 5.33 (m, 1 H, CH), 5.07 (d, $J_{NH,CH}$ = 7.9 Hz, 1 H, NH) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -126.42 (ddd, $J_{F,H}$ = 56.0 Hz, $J_{F,H}$ = 33.8 Hz, $J_{CHF2,CH}$ = 14.7 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.13 (C2), 148.17 (C6), 137.66 (C4), 135.43 ($C1_{Phenyl}$), 128.91 (C_{Phenyl}), 128.61 (C_{Phenyl}), 128.06 (C_{Phenyl}), 115.51 (t, $J_{C,F}$ = 246.6 Hz, CHF_2), 114.34 (C5) 108.43 (C3), 57.15 (t, $J_{C,F}$ = 22.1 Hz, CH) ppm. **HRMS** (ESI+): m/z calcd. for $C_{13}H_{13}F_2N_2^+$ $[M+H]^+$ 235.1041, found 235.1041. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 8.77 min, λ = 214 nm.

N-(1,1-difluoro-1-phenylethyl)pyrazin-2-amine (3j)

According to **TP5**, hemiaminal ether **1d** (100 mg, 0.49 mmol) was reacted with PhMgBr (3 M in Et_2O, 0.39 mL, 1.08 mmol) in dry THF (5 mL) for 1.5 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 100:6:1 → 100:25:1) to give the desired slightly unpurified amine **3j** (145 mg, quant.). A fraction of the product was further purified by preparative **HPLC** (0.1% TFA. 0 min: 4% MeCN (B) → 30 min: 100% B, flow: 20 mL/min, t_R = 19.37 min) to give the desired amine as a colorless oil.



R_f (cyclohexane/ethyl acetate 1:1) = 0.55. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.99 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.98 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 7.86 (d, $J_{H5,H6}$ = 2.7 Hz, 1 H, H5), 7.45 – 7.33 (m, 5 H, 5 × H_{Phenyl}), 6.11 (ddd, $J_{H,F}$ = 56.0 Hz, $J_{H,F}$ = 55.2 Hz, $J_{CHF2,CH}$ = 2.3 Hz, 1 H, CHF_2), 5.52 – 5.42 (m, 1 H, CH), 5.35 (d, $J_{NH,CH}$ = 8.2 Hz, 1 H, NH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -125.38 (ddd, $J_{F,F}$ = 280.3 Hz, $J_{F,H}$ = 56.1 Hz, $J_{CHF2,CH}$ = 15.3 Hz, CHF_2), -127.47 (ddd,

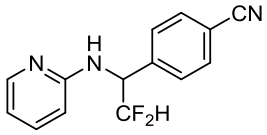
$J_{F,F}$ = 280.3 Hz, $J_{F,H}$ = 55.2 Hz, $J_{CHF2,CH}$ = 13.7 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 153.21 (C2), 141.73 (C6), 134.68 ($C1_{Phenyl}$) 134.12 (C5), 132.90 (C3), 128.90 (C_{Phenyl}), 128.72 (C_{Phenyl}), 127.80 (C_{Phenyl}), 115.08 (t, $J_{C,F}$ = 246.2 Hz, CHF_2), 56.35 (dd, $J_{C,F}$ = 22.6 Hz, $J_{C,F}$ = 21.3 Hz, CH) ppm. **HRMS** (ESI+): m/z calcd. for $C_{12}H_{12}F_2N_3^+$ $[M+H]^+$ 236.0994, found 236.0994. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 13.59 min, λ = 214 nm.

4-(2,2-Difluoro-1-(pyridin-2-ylamino)ethyl)benzonitrile (3k)

(4-Cyanophenyl)magnesium chloride was prepared from 4-bromobenzonitrile (82 mg, 0.45 mmol) and *i*PrMgCl·LiCl (1.25 M in THF, 0.36 mL, 0.45 mmol) according to **TP3** within 3 h at 0 °C.

Following **TP4**, a solution of *N*-(1-ethoxy-2,2-difluoroethyl)pyridine-2-amine **1b** (76 mg, 0.38 mmol) in dry THF (5 mL) was treated with LiHMDS (1 M in THF, 0.38 mL, 0.38 mmol) at -78 °C. The *Grignard* reagent was added after 15 min and the solution was stirred at -30 °C for 4 h. After workup and flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate 20:1 → 5:1) the desired amine **3k** (60 mg, 56%) was furnished as a light yellow oil.

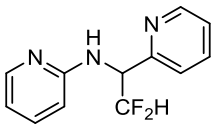
R_f (cyclohexane/ethyl acetate 2:1) = 0.47. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.06 (d, $J_{H6',H5'}$ = 5.1 Hz, 1 H, H6'), 7.74 – 7.63 (d, $J_{H3,H2}$ = $J_{H5,H6}$ = 8.4 Hz, 2 H, H3, H5), 7.58 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 7.9 Hz, 2 H, H2, H6), 7.48 – 7.38 (t, $J_{H4',H3'}$ = $J_{H4',H5'}$ = 7.7 Hz, 1 H, H4'), 6.66 (dd, $J_{H5',H4'}$ = 7.2 Hz, $J_{H5',H6'}$ = 5.2 Hz, 1 H, H5'), 6.48 (d, $J_{H3',H4'}$ = 8.3 Hz, 1 H, H3'), 6.12 (td, $J_{H,F}$ = 55.7 Hz, $J_{CHF2,CH}$ = 2.4 Hz, 1 H, CHF_2), 5.67 – 5.48 (m, 1 H, CH), 5.11 (d, $J_{NH,CH}$ = 8.2 Hz, 1 H, NH) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -124.67 (ddd, $J_{F,F}$ = 282.9 Hz, $J_{F,H}$ = 55.1 Hz, $J_{CHF2,CH}$ = 11.2 Hz, CHF_2), -127.41 (ddd, $J_{F,F}$ = 282.8 Hz, $J_{F,H}$ = 56.2 Hz, $J_{CHF2,CH}$ = 18.2 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.39 (C2'), 148.05 (C6'), 140.97 (C1), 137.85 (C4'), 132.54 (C3, C5), 129.00 (C2, C6), 118.60 (CN), 114.96 (t, $J_{C,F}$ = 247.0 Hz, CHF_2), 114.85 (C5'), 112.51 (C4), 108.86 (C3'), 56.61 (dd, $J_{C,F}$ = 23.7 Hz, $J_{C,F}$ = 21.1 Hz, CH) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{12}F_2N_3^+$ $[M+H]^+$ 260.0994, found 260.0996. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.56 min, λ = 214 nm.



***N*-(2,2-Difluoro-1-(pyridin-2-yl)ethyl)pyridin-2-amine (3l)**

Pyridin-2-ylmagnesium chloride was prepared from 2-bromopyridine (43 µL, 0.45 mmol) and *i*PrMgCl·LiCl (1.25 M in THF, 0.36 mL, 0.45 mmol) according to **TP3** within 2 h at 0 °C.

Following **TP4**, a solution of *N*-(1-ethoxy-2,2-difluoroethyl)pyridine-2-amine **1b** (76 mg, 0.38 mmol) in dry THF (5 mL) was treated with LiHMDS (1 M in THF, 0.38 mL, 0.38 mmol) at -78 °C. The *Grignard* reagent was added after 15 min and the solution was stirred at -30 °C for 4 h. After workup and flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate 10:1 → 5:1) the desired amine **3l** (39 mg, 44%) was furnished as a light yellow oil.

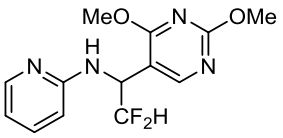


R_f (cyclohexane/ethyl acetate 3:1) = 0.26. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.56 (d, $J_{H6',H5'}$ = 4.7 Hz, 1 H, H6'), 8.04 (d, $J_{H6,H5}$ = 4.9 Hz, 1 H, H6), 7.63 (td, $J_{H4',H3'}$ = $J_{H4',H5'}$ = 7.7 Hz, $J_{H4',H6'}$ = 1.7 Hz, 1 H, H4'), 7.35 (m, 2 H, H4, H3'), 7.24 – 7.19 (m, 1 H, H5'), 6.56 (dd, $J_{H5,H4}$ = 7.1 Hz, $J_{H5,H6}$ = 5.1 Hz, 1 H, H5), 6.51 (d, $J_{H3,H4}$ = 8.3 Hz, 1 H, H3), 6.34 – 6.00 (m, 1 H, CHF_2), 5.96 (d, $J_{NH,CH}$ = 7.3 Hz, 1 H, NH), 5.61 – 5.48 (m, 1 H, CH) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -124.85 (ddd, $J_{F,F}$ = 278.5 Hz, $J_{F,H}$ = 55.5 Hz, $J_{CHF2,CH}$ = 9.6 Hz, CHF_2), -129.09 (ddd, $J_{F,F}$ = 278.6 Hz, $J_{F,H}$ = 56.6 Hz, $J_{CHF2,CH}$ = 17.3 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 157.24 (C2), 153.85 (C2'), 149.31 (C6'), 147.96 (C6), 137.54 (C4), 136.76 (C4'), 123.86 (C3'), 123.41 (C5'), 115.43 (t, $J_{C,F}$ = 246.8 Hz, CHF_2), 114.03 (C5), 109.28 (C3) , 56.93 (dd, $J_{C,F}$ = 24.1 Hz, $J_{C,F}$ = 22.7 Hz, CH) ppm. **HRMS** (ESI+): m/z calcd. for $C_{12}H_{12}F_2N_3^+$ $[M+H]^+$ 236.0994, found 236.0997. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 7.48 min, λ = 214 nm.

***N*-(1-(2,4-Dimethoxypyrimidin-5-yl)-2,2-difluoroethyl)pyridin-2-amine (3m)**

(2,4-Dimethoxypyrimidin-5-yl)magnesium chloride was prepared from 5-bromo-2,4-dimethoxypyrimidine (99 mg, 0.45 mmol) and *i*PrMgCl·LiCl (1.25 M in THF, 0.36 mL, 0.45 mmol) according to **TP3** within 3 h at 0 °C.

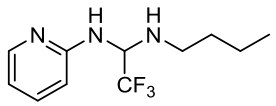
Following **TP4**, a solution of *N*-(1-ethoxy-2,2-difluoroethyl)pyridine-2-amine **1b** (76 mg, 0.38 mmol) in dry THF (5 mL) was treated with LiHMDS (1 M in THF, 0.38 mL, 0.38 mmol) at -78 °C. The *Grignard* reagent was added after 15 min and the solution was stirred at -30 °C for 4 h. After workup and flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate 10:1 → 5:1) the desired amine **3m** (85 mg, 75%) was furnished as a light yellow oil.



R_f (cyclohexane/ethyl acetate 2:1) = 0.36. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.26 (s, 1 H, H6'), 8.11 – 8.03 (d, $J_{H6,H5}$ = 4.0 Hz, 1 H, H6), 7.39 (ddd, $J_{H4,H3}$ = 8.6 Hz, $J_{H4,H5}$ = 7.2 Hz, J = 1.9 Hz, 1 H, H4), 6.61 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz, J = 0.9 Hz, 1 H, H5), 6.46 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 1.0 Hz, 1 H, H3), 6.09 (td, $J_{H,F}$ = 56.1 Hz, $J_{CHF2,CH}$ = 3.1 Hz, 1 H, CHF_2), 5.68 – 5.52 (m, 1 H, CH), 5.26 (d, $J_{NH,CH}$ = 9.1 Hz, 1 H, NH), 4.04 (s, 3 H. OCH_3), 3.96 (s, 3 H, OCH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -125.00 (ddd, $J_{F,F}$ = 279.0 Hz, $J_{F,H}$ = 56.1 Hz, $J_{CHF2,CH}$ = 13.8 Hz, CHF_2), -126.88 (ddd, $J_{F,F}$ = 279.0 Hz, $J_{F,H}$ = 56.0 Hz, $J_{CHF2,CH}$ = 13.8 Hz, CHF_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.13 (C4'), 165.33(C2'), 158.45 (C6'), 156.70 (C2), 148.01 (C6), 137.65 (C4), 114.47 (t, $J_{C,F}$ = 246.0 Hz, CHF_2), 114.40 (C5), 109.28 (C5'), 108.63 (C3), 55.02 (OCH_3), 54.42 (OCH_3), 51.16 (t, $J_{C,F}$ = 23.6 Hz, CH) ppm. **HRMS** (ESI+): m/z calcd. for $C_{13}H_{15}F_2N_4O_2^+$ $[M+H]^+$ 297.1158, found 297.1160. **HPLC** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 8.61 min, λ = 214 nm.

_N_-Butyl-2,2,2-trifluoro-_N'_-phenylethan-1,1-diamine (4a)

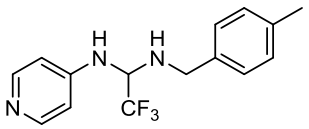
In a dry, argon-flushed Schlenk-flask *n*-BuLi (2.48 M in hexane, 0.36 mL, 0.90 mmol) was slowly added to a solution of *n*-butylamine (0.10 mL, 0.90 mmol) in dry *n*-hexane (3 mL) at 0 °C. The suspension was stirred at 0 °C for 30 min. A solution of *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine **1a** (100 mg, 0.45 mmol) in dry THF (3 mL) was added to the reaction mixture. After stirring the reaction mixture for 2 h, the solution was quenched with sat. NH_4Cl-solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. Purification by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate/NEt_3 100:20:1 → 100:50:1) furnished the desired diamine **4a** (84 mg, 75%) as a light yellow oil.



R_f (cyclohexane/ethyl acetate/NEt_3 2:1:0.05) = 0.56. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.13 – 8.08 (d, $J_{H6,H5}$ = 5.0 Hz, 1 H, H6), 7.45 (dddd, $J_{H4,H3}$ = 8.2 Hz, $J_{H4,H5}$ = 7.2 Hz, J = 1.9 Hz, J = 1.0 Hz, 1 H, H4), 6.68 (ddt, $J_{H5,H4}$ = 7.0 Hz, $J_{H5,H6}$ = 4.9 Hz, J = 0.9 Hz, 1 H, H5), 6.47 (dt, $J_{H3,H4}$ = 8.4 Hz, J = 1.0 Hz, 1 H, H3), 5.49 (m, 1 H, CH), 4.57 (d, $J_{NH,CH}$ = 9.4 Hz, 1 H, NH), 2.72 (m, 2 H, CH_2), 1.53 – 1.40 (m, 2 H, CH_2), 1.37 – 1.24 (m, 2 H, CH_2), 0.88 (td, $J_{CH3,CH2}$ = 7.3 Hz, J = 1.1 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -78.80 (d, $J_{CF3,CH}$ = 6.1 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 156.90 (C2), 148.04 (C6), 137.81 (C4), 124.61 (q, $J_{C,F}$ = 282.6 Hz, CF_3), 114.76 (C5), 108.54 (C3), 65.57 (q, $J_{C,F}$ = 31.4 Hz, *C*HCF_3), 45.29 (CH_2), 32.21 (CH_2), 20.33 (CH_2), 14.00 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{11}H_{18}F_3N_3^+$ $[M+H]^+$ 248.1369, found 248.1368. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 3.82 min, λ = 214 nm.

2,2,2-Trifluoro-_N_-(4-methylbenzyl)-_N'_-(pyridin-4-yl)ethane-1,1-diamine (4b)

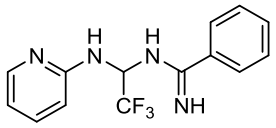
In a dry, argon-flushed Schlenk-flask *n*-BuLi (1.7 M in hexane, 0.53 mL, 0.90 mmol) was slowly added to a solution of 4-methylbenzylamine (0.12 mL, 0.90 mmol) in dry *n*-hexane (4 mL) at 0 °C. The white suspension was stirred at 0 °C for 3 h. A solution of *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-4-amine **1h** (100 mg, 0.45 mmol) in dry THF (2 mL) was added to the reaction mixture. After stirring the reaction mixture for 2 h at 0 °C, the solution was quenched with sat. NH_4Cl-solution (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. Purification by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate 10:1 → 5:1) furnished the desired diamine **4b** (116 mg, 87%) as a light yellow oil.



R_f (ethyl acetate/MeOH 10:1) = 0.12. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.24 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 5.5 Hz, 2 H, H2, H6), 7.13 (m, 4 H, H2', H3', H5', H6'), 6.47 – 6.39 (m, 2 H, H3, H5), 4.67 (dq, $J_{CH,NH}$ = 10.0 Hz, $J_{CH,CF3}$ = 5.1 Hz, 1 H, CH), 4.29 (d, $J_{NH,CH}$ = 9.3 Hz, 1 H, NH), 3.98 – 3.78 (m, 2 H, CH_2), 2.35 (s, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -78.91 (d, $J_{CF3,CH}$ = 5.1 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 151.39 (C4), 150.37 (C2, C6), 137.48 (C4'), 134.97 (C1'), 129.40 (C3', C5'), 128.19 (C2', C6'), 108.40 (C3, C5), 66.22 (q, $J_{C,F}$ = 32.1 Hz, *C*HCF_3), 48.92 (CH_2), 21.11 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{15}H_{17}F_3N_3^+$ $[M+H]^+$ 296.1369, found 296.13696.

_N_-(2,2,2-Trifluoro-1-(pyridin-2-ylamino)ethyl)benzimidamide (4c)

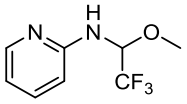
A dry microwave vial equipped with a magnetic stirrer was charged with *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine **1a** (50 mg, 0.23 mmol) and benzamidine (27 mg, 0.23 mmol) in toluene (2 mL). The reaction mixture was stirred at 160 °C in a CEM microwave reactor operating at 200 W (maximum power) for 1 h. After removal of the solvent using rotary evaporation, purification by flash column chromatography (SiO_2, cyclohexane/ethyl acetate 4:1 → 1:1) afforded the desired product **4c** (58 mg, 86%) as a white solid.



R$_f$ (cyclohexane/ethyl acetate 4:1) = 0.18. mp 99 – 105 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ = 8.09 (dd, $J_{H6',H5'}$ = 5.2 Hz, $J_{H6',H4'}$ = 1.8 Hz, 1 H, H6'), 7.75 (d, $J_{H2,H3} = J_{H6,H5}$ = 7.4 Hz. 2 H, H2, H6), 7.48-7.31 (m, 4 H, H4', H3, H4, H5), 6.68 (ddd, $J_{H5',H4'}$ = 7.2 Hz, $J_{H5',H6'}$ = 5.1 Hz, $J_{H5',H3'}$ = 1.0 Hz, 1 H, H5'), 6.49 (d, $J_{H3',H4'}$ = 8.3 Hz, 1 H, H3'), 6.20 (s, 2 H, NH) 6.12 (dq, $J_{CH,NH}$ = 10.0 Hz, $J_{CH,CF3}$ = 6.2 Hz, 1 H, CH), 5.05 (d, $J_{NH,CH}$ = 10.0 Hz, 1 H, NH) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$) δ = -79.59 (d, $J_{CF3,CH}$ = 6.2 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ = 160.68 (C=NH), 156.73 (C2'), 147.24 (C6'), 138.28 (C4'), 136.54 (C1), 130.69 (C4), 128.59 (C3, C5), 127.07 (C2, C6), 124.79 (q, $J_{C,F}$ = 280.8 Hz, CF_3), 114.64 (C5'), 110.06 (C3'), 63.82 (q, $J_{C,F}$ = 31.9 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{14}F_3N_4^+$ $[M+H]^+$ 295.1165, found 295.11646. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.78 min, λ = 214 nm.

_N_-(2,2,2-Trifluoro-1-methoxyethyl)pyridin-2-amine (4d)

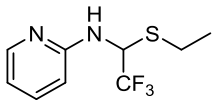
In a dry, argon-flushed Schlenk-flask *n*-BuLi (2.48 M in hexane, 2.00 mL, 5.00 mmol) was slowly added to a solution of MeOH (0.20 mL, 5.00 mmol) in dry *n*-hexane (5 mL) at 0 °C. The suspension was stirred at 0 °C for 1 h. *N*-(1-Ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine **1a** (220 mg, 1.00 mmol) was added and the reaction mixture was allowed to warm up to room temperature. After stirring the reaction mixture for 48 h the solvent was evaporated *in vacuo*. Purification by flash chromatography (SiO_2, gradient: cyclohexane/ethyl acetate 10:1 → 2:1) furnished the desired hemiaminal ether **4d** (100 mg, 49%) as a yellow solid.



R$_f$ (cyclohexane/ethyl acetate/NEt_3 2:1:0.05) = 0.51. mp 63-64 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.16 (d, $J_{H6,H5}$ = 5.1 Hz, 1 H, H6), 7.55 – 7.46 (m, 1 H, H4), 6.76 (ddd, $J_{H5,H4}$ = 7.3 Hz, $J_{H5,H6}$ = 5.1 Hz, J = 0.9 Hz, 1 H, H5), 6.59 – 6.51 (m, 1 H, H3), 5.87 (dq, $J_{CH,NH}$ = 10.1 Hz, $J_{CH,CF3}$ = 5.0 Hz, 1 H, CH), 5.08 (d, $J_{NH,CH}$ = 7.6 Hz, 1 H, NH), 3.52 (s, 3 H, OCH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -80.37 (d, $J_{CF3,CH}$ = 5.0 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 156.14 (C2), 147.91 (C6), 138.34 (C4), 123.06 (q, $J_{C,F}$ = 282.5 Hz, CF_3), 115.76 (C5), 109.18 (C3), 79.97 (q, $J_{C,F}$ = 33.9 Hz, *C*HCF_3), 56.85 (OCH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_8H_9F_3N_2O^*$ $[M^*]$ 206.0667, found 206.0661. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 8.25 min, λ = 214 nm.

_N_-(1-(Ethylthio)-2,2,2-trifluoroethyl)pyridin-2-amine (4e)

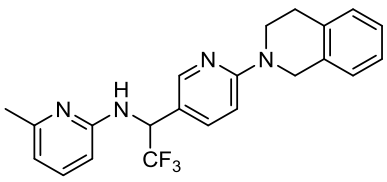
In a dry, argon-flushed Schlenk-flask *n*-BuLi (1.7 M in hexane, 1.32 mL, 2.25 mmol) was slowly added to a solution of EtSH (0.17 mL, 2.25 mmol) in dry *n*-hexane (6 mL) at 0 °C. The white suspension was stirred at 0 °C for 1 h. *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine **1a** (100 mg, 0.45 mmol) was added to the reaction mixture and the reaction was allowed to warm up to room temperature. After stirring for 3 d, the solution was quenched with sat. NH_4Cl-solution (10 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The desired product **4e** (160 mg, quant.) was obtained as a light yellow solid without further purification.



R_f (cyclohexane/ethyl acetate 3:1) = 0.60. mp 54 °C. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.15 (ddd, $J_{H6,H5}$ = 5.0 Hz, $J_{H6,H4}$ = 1.9 Hz, J = 0.9 Hz, 1 H, H6), 7.47 (ddd, $J_{H4,H3}$ = 8.3 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.72 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.51 (dt, $J_{H3,H4}$ = 8.3 Hz, J = 0.9 Hz, 1 H, H3), 6.03 (dq, $J_{CH,NH}$ = 10.3 Hz, $J_{CH,CF3}$ = 7.4 Hz, 1 H, CH), 4.63 (d, $J_{NH,CH}$ = 10.4 Hz, 1 H, NH), 2.74 (tdd, $J_{CH2,CH3}$ = 7.7 Hz, $J_{CH2,CH3}$ = 6.9 , J = 1.7 Hz, 2 H, CH_2), 1.29 (t, $J_{CH3,CH2}$ = 7.4 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ = -74.24 (d, $J_{CF3,CH}$ = 7.5 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 155.62 (C2), 148.04 (C6), 137.94 (C4), 115.37 (C5), 109.22 (C3), 56.55 (q, $J_{C,F}$ = 33.0 Hz, *C*HCF$_3$), 25.38 (CH_2), 14.97 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_9H_{12}F_3N_2S^+$ $[M+H]^+$ 237.0668, found 237.06672. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.33 min, λ = 214 nm.

_N_-(1-(6-(3,4-Dihydroisoquinolin-2(1*H*)-yl)pyridin-3-yl)-2,2,2-trifluoroethyl)-6-methylpyridin-2-amine (5)

N-(1-(6-Chloropyridin-3-yl)-2,2,2-trifluoroethyl)-6-methylpyridin-2-amine **2i** (1.01 g, 3.35 mmol) and tetrahydroisoquinolin (1.76 g, 13.2 mol) were refluxed in 2-propanol (40 mL) for 48 h. After removal of the solvent the crude product was purified by preparative **HPLC** (0 min: 4% MeCN (B) → 30 min: 100% B, flow: 20 mL/min, t_R = 26.28 min) to give the desired DIMN bioisostere **5** (438 mg, 33%) as colorless oil.

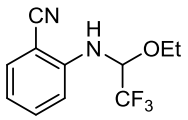


R_f (cyclohexane/ethyl acetate/NEt_3 4:1:0.1) = 0.35. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.29 (d, $J_{H2'',H4''}$ = 2.4 Hz, 1 H, H2''), 7.59 (dd, $J_{H4'',H5''}$ = 8.9 Hz, $J_{H4'',H2''}$ = 2.3 Hz, 1 H, H4''), 7.31 (t, $J_{H4,\ H3,H5}$ = 7.7 Hz, 1 H, H4), 7.22 – 7.14 (m, 4 H, H5', H6', H7', H8'), 6.66 (d, $J_{H5'',H4''}$ = 8.9 Hz, 1 H, H5''), 6.52 (d, $J_{H5,H4}$ = 7.3 Hz, 1 H, H5), 6.25 (d, $J_{H3,H4}$ = 8.3 Hz, 1 H, H3), 5.59 (p, $J_{CH,CF3}$ = $J_{CH,NH}$ = 8.1 Hz, 1 H, CH), 5.12 (s, 1 H, NH), 4.70 (s, 2 H. 2 × H1'), 3.84 (t, $J_{H3',H4'}$ = 5.9 Hz, 2 H, 2 × H3'), 2.96 (t, $J_{H4',H3'}$ = 6.0 Hz, 2 H, 2 × H4'), 2.38 (s, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -74.15 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 158.82 (C6''), 157.02 (C6), 155.82 (C2), 148.12 (C2''), 138.26 (C4), 136.71 (C4''), 135.43 (C5a'/C8a'), 134.21 (C5a'/C8a'), 128.48 (C5'/C6'/C7'/C8'), 126.66 (C5'/C6'/C7'/C8'), 126.41 (C5'/C6'/C7'/C8'), 125.37 (q, $J_{C,F}$ = 281.6 Hz, CF_3), 118.23 (H3''), 114.06 (H5), 106.49 (H5''), 104.85 (H3), 54.83 (q, $J_{C,F}$ = 30.9 Hz, *C*HCF$_3$), 47.15 (C1'), 42.59 (C3'),

29.10 (C4'), 24.30 (CH_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{22}H_{22}F_3N_4^+$ $[M+H]^+$ 399.1791, found 399.1787. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.06 min, λ = 214 nm.

2-((1-Ethoxy-2,2,2-trifluoroethyl)amino)benzonitrile (1i)

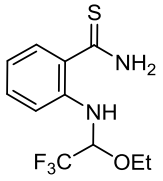
According to **TP2**, 2-aminobenzonitril (2.00 g, 17.0 mmol), TFAE (2.58 mL, 22.0 mmol) and *p*TSA·H_2O (160 mg, 0.86 mmol) were solved in EtOH (20 mL) and the reaction mixture was refluxed for 6 h until no further conversion was observed. After removal of the solvent using rotary evaporation, flash column chromatography (SiO_2, cyclohexane/ethyl acetate 20:1) furnished the hemiaminal ether **1i** (1.46 g, 35%) as a colorless oil.



R_f (cyclohexane/ethyl acetate 10:1) = 0.29. mp 31 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.52 – 7.43 (m, 2 H, H4, H6), 6.90 (m, 2 H, H3, H6), 5.16 – 5.06 (m, 1 H, CH), 4.99 (d, $J_{NH,CH}$ = 9.5 Hz, 1 H, NH), 3.85 – 3.59 (m, 2 H, CH_2), 1.25 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -80.14 (d, $J_{CF3,CH}$ = 4.2 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 147.13 (C2), 134.53 (C4), 133.25 (C6), 122.60 (q, $J_{C,F}$ = 283.7 Hz, CF_3), 120.01 (C5), 116.90 (C≡N), 112.93 (C3), 98.68 (C1), 81.76 (q, $J_{C,F}$ = 34.4 Hz, *C*HCF_3), 64.93 (CH_2), 15.03 (CH_3) ppm. **HRMS** (ESI-): m/z calcd. for $C_{11}H_{10}F_3N_2O^-$ $[M-H]^-$ 243.0751, found 243.07511. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 17.69 min, λ = 214 nm.

2-((1-Ethoxy-2,2,2-trifluoroethyl)amino)benzothioamide (8)

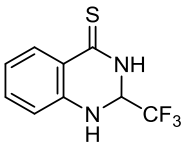
Following a literature procedure,[213] 2-((1-ethoxy-2,2,2-trifluoroethyl)amino)benzonitrile **1i** (448 mg, 2.00 mmol), $MgCl_2$ (190 mg, 2.00 mmol) and NaHS·H_2O (296 mg, 4.00 mmol) were solved in dry DMF (8 mL). The reaction mixture was stirred at room temperature for 1.5 h. After complete conversion, the reaction was quenched with distilled water and extracted with ethyl acetate (3 × 30 mL). The aqueous phase was acidified (pH 6.5) with an aqueous solution of HCl (1 N) and extracted with ethyl acetate (3 × 30 mL) again. The combined organic phases were dried over $MgSO_4$. After filtration and removal of the solvent the desired thioamid **8** (570 mg, quant.) was obtained as a yellow oil without further purification.



R_f (cyclohexane/ethyl acetate 3:1) = 0.34. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 9.83 (d, J = 158.6 Hz, 2 H, NH_2), 7.71 (d, $J_{NH,CH}$ = 10.1 Hz, 1 H, NH), 7.30 (t, $J_{H4,H3}$ = $J_{H4,H5}$ = 7.8 Hz, 1 H, H4), 7.24 (d, $J_{H6,H5}$ = 7.7 Hz, 1 H, H6), 7.10 (d, $J_{H3,H4}$ = 8.3 Hz, 1 H, H3), 6.80 (t, $J_{H5,H4}$ = $J_{H5,H6}$ = 7.5 Hz, 1 H, H5), 5.73 (dq, $J_{CH,NH}$ = 10.0 Hz, $J_{CH,CF3}$ = 4.8 Hz, 1 H, CH), 3.78 – 3.55 (m, 2 H, CH_2), 1.11 (t, $J_{CH2,CH3}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = -79.31 (d, $J_{CF3,CH}$ = 4.8 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 199.51 (C=S), 143.21 (C2), 131.09 (C4), 127.12 (C6), 126.49 (C1), 123.38 (q, $J_{C,F}$ = 283.8 Hz, CF_3), 118.20 (C5), 113.59 (C3), 80.12 (q, $J_{C,F}$ = 32.3 Hz, *C*HCF_3), 63.51 (CH_2), 15.08 (CH_3) ppm. **HRMS** (ESI-): m/z calcd. for $C_{11}H_{12}F_3N_2OS^-$ $[M-H]^-$ 277.0628, found 277.06283. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 16.29 min, λ = 214 nm.

2-(Trifluoromethyl)-2,3-dihydroquinazoline-4(1*H*)-thione (7)

2-((1-Ethoxy-2,2,2-trifluoroethyl)amino)benzothioamide **8** (40 mg, 0.14 mmol) was solved in dry THF (2 mL) with molecular sieve (4 Å) and cooled to 0 °C. KO^{t}Bu (16 mg, 0.14 mmol) was added and the reaction was stirred at room temperature for 48 h. After complete conversion of the starting material, the reaction was quenched with distilled water, extracted with diethyl ether (3 × 20 mL) and dried with $MgSO_4$. After filtration and removal of the solvent the desired dihydroquinalzoline thione **7** (28 mg, 86%) was furnished by crystallization from CH_2Cl_2/cyclcohexane as yellow crystals.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.67 (d, $J_{NH,CH}$ = 5.0 Hz, 1 H, NH), 8.07 (dd, $J_{H5,H6}$ = 8.1 Hz, $J_{H5,H7}$ = 1.6 Hz, 1 H, H5), 7.81 (d, $J_{NH,CH}$ = 4.0 Hz, 1 H, NH), 7.33 (ddd, $J_{H7,H8}$ = 8.5 Hz, $J_{H7,H6}$ = 7.2 Hz, $J_{H7,H5}$ = 1.6 Hz, 1 H, H7), 6.82 (dd, $J_{H8,H7}$ = 8.2 Hz, $J_{H8,H6}$ = 1.1 Hz, 1 H, H8), 6.73 (ddd, $J_{H6,H5}$ = 8.1 Hz, $J_{H6,H7}$ = 7.2 Hz, $J_{H6,H8}$ = 1.1 Hz, 1 H, H6), 5.43 (dt, $J_{CH,CF3}$ = 6.7 Hz, $J_{CH,NH}$ = 4.7 Hz, 1 H, CH) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = -80.74 (d, $J_{CF3,CH}$ = 6.6 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 190.73 (C=S), 141.12 (C8a), 134.53 (C7), 131.24 (C5), 123.33 (q, $J_{C,F}$ = 291.7 Hz, CF_3), 118.77 (C4a), 118.02 (C6), 114.51 (C8), 61.55 (q, $J_{C,F}$ = 33.4 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): m/z calcd. for $C_9H_8F_3N_2S^+$ $[M+H]^+$ 233.0355, found 233.03556. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 14.43 min, λ = 214 nm.

4. Experimental Procedures and Analytical Data: *One-Pot Synthesis of Functionalized β-Fluoroalkylated Mannich-Type Products from N-Aryl N,O-Acetals*

The complete supporting information including the NMR spectra of all compounds is available on the *Synthesis* website (DOI: 10.1055/s-0035-1561324) and on the CD in the book cover of this thesis. The compounds are numbered according to the publication.

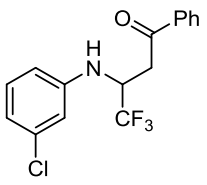
4.1 General procedure for the addition of ketones to *N*-aryl *N*,*O*-acetals 1a-i

N-aryl hemiaminal ether **1** was placed in a dry Schlenk flask equipped with a magnetic stirrer and a septum, and dissolved in dry CH_2Cl_2 (ca. 0.06 M). The solution was flushed with argon and cooled to −78 °C before lithium *bis*(trimethylsilylamide) (LiHMDS, 1.0 M solution in toluene, 2.0−3.3 equiv) was added dropwise. Stirring was continued at −78 °C for 10 min, the ketone (1.5−2.5 equiv) was added, the reaction mixture was allowed to warm up to room temperature and stirred for 1−2 h (TLC and LC-MS control). After complete consumption of the starting material the solution was quenched with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash- or column chromatography and optional subsequent crystallization from cyclohexane/ethyl acetate furnished the desired *β*-amino *β*-fluoroalkylated carbonyl compounds **2a**−**2i** and **3a**−**3o**.

4.2 Experimental data

3-((3-Chlorophenyl)amino)-4,4,4-trifluoro-1-phenylbutan-1-one (2a)

According to the general procedure, 3-Chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline **1a** (150 mg, 0.59 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.18 mL, 1.18 mmol) and reacted with acetophenone (0.10 mL, 0.89 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (cyclohexane → cyclohexane/ethyl acetate 9:1) and recrystallization (cyclohexane) the *β*-amino ketone **2a** (138 mg, 0.42 mmol, 71%) was obtained as a colorless crystalline solid.

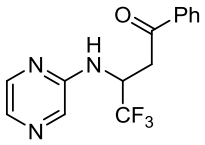


^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 – 7.93 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.73 – 7.62 (m, 1H, $H4_{ph}$), 7.55 (m, 2H, $H3_{ph}$, $H5_{ph}$), 7.11 (t, $J_{H5,H4/H6}$ = 8.1 Hz, 1H, H5), 6.77 (br s, 1H, H2), 6.65 (m, 2H, H4, H6), 6.30 (d, $J_{NH,CH}$ = 8.4 Hz, 1H, NH), 4.87 – 4.76 (m, 1H, CH), 3.62 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 10.0 Hz, 1H, CH_2), 3.44 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 2.5 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 194.97 (C=O), 148.96 (C1), 136.13($C1_{ph}$), 133.55 (C3), 133.52 ($C4_{ph}$) 130.34 (C5), 128.73 ($C3_{ph}$, $C5_{ph}$), 128.09 ($C2_{ph}$, $C6_{ph}$), 126.58 (q, $^1J_{C,F}$ = 283.8 Hz, CF_3), 116.47 (C4), 111.93 (C2), 111.35 (C6), 50.16 (q, $^2J_{C,F}$ = 29.7 Hz, CH), 37.54 (CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.25 (d, $J_{CF3,CH}$ = 7.4 Hz, CF_3) ppm. **HRMS** (EI): *m/z*

calcd. for $C_{16}H_{13}ClF_3NO^+$ $[M]^+$ 327.0638; found 327.0641. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.98 min, λ = 220 nm. **mp** 98 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 2:1) = 0.61.

4,4,4-Trifluoro-1-phenyl-3-(pyrazin-2-ylamino)butan-1-one (2b)

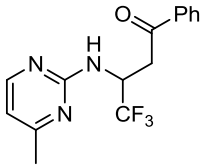
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with acetophenone (0.08 mL, 0.68 mmol). After stirring at rt (1h), aqueous workup, flash chromatography (cyclohexane → cyclohexane/ethyl acetate 4:1) and recrystallization (cyclohexane) the *β*-amino ketone **2b** (123 mg, 0.42 mmol, 92%) was obtained as a colorless crystalline solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.04 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 8.01 – 7.94 (m, 3H, H3, $H2_{ph}$, $H6_{ph}$), 7.82 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.70 – 7.63 (m, 1H, $H4_{ph}$), 7.58 – 7.51 (m, 2H, $H3_{ph}$, $H5_{ph}$), 7.48 (d, $J_{NH,CH}$ = 8.2 Hz, 1H, NH), 5.50 – 5.38 (m, 1H, CH), 3.65 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 9.8 Hz, 1H, CH_2), 3.52 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 3.3 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 195.03 (C=O), 153.90 (C2), 141.26 (C6), 136.08 ($C1_{ph}$), 133.55 (C5), 133.02 ($C4_{ph}$), 132.91 (C3), 128.74 ($C3_{ph}$, $C5_{ph}$), 128.07 ($C2_{ph}$, $C6_{ph}$), 126.22 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3) 47.17 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 37.12 (CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.37 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{14}H_{12}F_3N_3O^+$ $[M]^+$ 295.0932; found 295.0931. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.59 min, λ = 220 nm. **mp** 128 °C. $\mathbf{R}_f$ (hex/ethyl acetate 2:1) = 0.20.

4,4,4-Trifluoro-3-(4-methylpyrimidin-2-ylamino)-1-phenylbutan-1-one (2c)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-methylpyrimidin-2-amine **1c** (100 mg, 0.43 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.98 mL, 0.98 mmol) and reacted with acetophenone (0.08 mL, 0.64 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (cyclohexane → cyclohexane/ethyl acetate 4:1) and recrystallization (cyclohexane) the *β*-amino ketone **2c** (97 mg, 0.31 mmol, 72%) was obtained as a colorless crystalline solid.

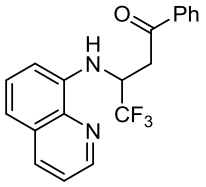


^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.19 (br s, 1H, H6), 8.00 – 7.91 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.65 (tt, $J_{H4ph,H3ph/H5ph}$ = 7.4 Hz, $J_{H4ph,H2ph/H6ph}$ = 1.1 Hz, $H4_{ph}$), 7.53 (m, 3H, NH, $H3_{ph}$, $H5_{ph}$), 6.60 (d, $J_{H5,H6}$ = 5.0 Hz, 1H, H5), 5.54 – 5.39 (m, 1H), 3.74 (dd, $J_{CH2,CH2}$ = 17.7 Hz, $J_{CH2,CH}$ = 10.3 Hz, 1H, CH_2), 3.39 (dd, $J_{CH2,CH2}$ = 17.6 Hz, $J_{CH2,CH}$ = 2.9 Hz, 1H, CH_2), 2.25 (s, 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 195.89 (C=O), 167.89 (C4), 162.05 (C2), 157.85 (C6), 136.70 ($C1_{ph}$), 134.02 ($C4_{ph}$), 129.24 ($C2_{ph}$, $C6_{ph}$), 128.19 ($C3_{ph}$, $C5_{ph}$), 126.78 (q, $^1J_{C,F}$ = 283.1 Hz, CF_3), 111.53 (C5), 48.51 (q, $^2J_{C,F}$ = 30.2 Hz, CH), 37.21 (CH_2), 24.00 (CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.48 (br s, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{15}H_{15}F_3N_3O^+$

$[M+H]^+$ 310.1162; found 310.1162. **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 13.93 min, λ = 214 nm. **mp** 109 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 2:1) = 0.35.

4,4,4-Trifluoro-1-phenyl-3-(quinolin-8-ylamino)butan-1-one (2d)

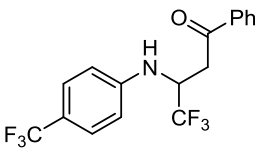
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)quinolin-8-amine **1d** (100 mg, 0.37 mmol) was dissolved in 5 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.85 mL, 0.85 mmol) and reacted with acetophenone (0.65 mL, 0.56 mmol). After stirring at rt (20 min), aqueous workup and flash chromatography (cyclohexane → cyclohexane/ethyl acetate 9:1) the *β*-amino ketone **2d** (117 mg, 0.34 mmol, 92%) was obtained as a light yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 (dd, $J_{H2,H3}$ = 4.2 Hz, $J_{H2,H4}$ = 1.7 Hz, 1H, H2), 8.06 (dd, $J_{H4,H3}$ = 8.2 Hz, $J_{H4,H2}$ = 1.7 Hz, 1H, H4), 7.99 – 7.93 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.62 – 7.54 (m, 1H, $H4_{ph}$), 7.51 – 7.40 (m, 3H, H6, $H3_{ph}$, $H5_{ph}$), 7.36 (dd, $J_{H3,H4}$ = 8.2 Hz, $J_{H3,H2}$ = 4.2 Hz, 1H, H3), 7.16 (dd, $J_{H5,H6}$ = 8.2 Hz, $J_{H5,H7}$ = 1.1 Hz, 1H, H5), 7.07 (d, $J_{H7,H6}$ = 7.6 Hz, 1H, H7), 6.44 (d, $J_{NH,CH}$ = 9.9 Hz, 1H, NH), 5.10 (dtd, $J_{CH,NH}$ = 9.9 Hz, $J_{CH,CF3}$ = 7.2 Hz, $J_{CH,CH2}$ = 4.7 Hz, 1H, CH), 3.63 – 3.49 (m, 2H, CH_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.05 (C=O), 147.32 (C2), 142.75 (C4a), 138.16 (C8a), 136.42 ($C1_{ph}$), 136.20 (C4), 133.82 ($C4_{ph}$), 128.91 ($C3_{ph}$, $C5_{ph}$), 128.73 (C8), 128.34 ($C2_{ph}$, $C6_{ph}$), 127.71 (C6), 126.40 (q, $J_{C,F}$ = 283.3 Hz, CF_3), 121.61 (C3), 116.12 (C5), 106.54 (C7), 51.40 (q, $J_{C,F}$ = 30.5 Hz, $C$$CF_3$), 39.06 ($CH_2$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = − 75.63 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{19}H_{16}F_3N_2O^+$ $[M+H]^+$ 345.1209; found 345.1210. **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 18.93 min, λ = 214 nm**.** $\mathbf{R}_f$ (cyclohexane/ethyl acetate 3:1) = 0.50.

4,4,4-Trifluoro-1-phenyl-3-((4-(trifluoromethyl)phenyl)amino)butan-1-one (2e)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline **1e** (50 mg, 0.17 mmol) was dissolved in 5 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.40 mL, 0.40 mmol) and reacted with acetophenone (0.03 mL, 0.26 mmol). After stirring at rt (1 h), aqueous workup and flash chromatography (cyclohexane → cyclohexane/ethyl acetate 5:1) the *β*-amino ketone **2e** (33 mg, 0.09 mmol, 52%) was obtained as a light brown solid.

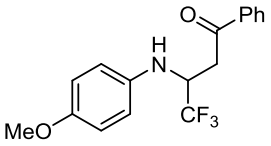


^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 – 7.92 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.65 – 7.59 (m, 1H, $H4_{ph}$), 7.50 (dd, J = 8.3 Hz, J = 7.1 Hz, 2H, $H3_{ph}$, $H5_{ph}$), 7.44 (d, $J_{H3,H2}$ = $J_{H5,H6}$ = 8.5 Hz, 2H, H3, H5), 6.79 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 8.4 Hz, 2H, H2, H6), 4.87 (dtd, $J_{CH,NH}$ = 9.6 Hz, $J_{CH,CF3}$ = 7.2 Hz, $J_{CH,CH2}$ = 4.3 Hz, 1H, CH), 4.14 (d, $J_{NH,CH}$ = 9.9 Hz, 1H, NH), 3.45 – 3.37 (m, 2H, CH_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 194.90 (C=O), 148.67 (C1), 136.16 ($C1_{ph}$), 134.14 ($C4_{ph}$), 129.05 ($C3_{ph}$, $C5_{ph}$), 128.31 ($C2_{ph}$, $C6_{ph}$), 126.92 (q, $J_{C,F}$ = 3.8 Hz, C3, C5), 125.97 (q, $J_{C,F}$ = 283.2 Hz, CF_3), 124.77 (d, $J_{C,F}$ = 270.6 Hz, CF_3), 121.15 (q, $J_{C,F}$ = 32.8 Hz, C4), 113.19 (C2, C6), 51.80 (q, $^2J_{C,F}$ = 30.7 Hz, $C$$CF_3$), 38.34 ($CH_2$) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = − 61.40 (CF_3), − 75.66 (d,

$J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. **HRMS** (ESI-): m/z calcd. for $C_{17}H_{12}F_6NO^-$ $[M-H]^-$ 360.0828; found 360.0835. **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 19.85 min, λ = 214 nm. **mp** 127 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 3:1) = 0.46.

4,4,4-Trifluoro-3-((4-methoxyphenyl)amino)-1-phenylbutan-1-one (2f)

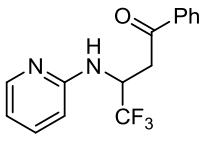
Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-methoxyaniline **1f** (170 mg, 0.68 mmol) was dissolved in 10 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with acetophenone (0.12 mL, 1.02 mmol). After stirring at rt (2 h), aqueous workup and flash chromatography (cyclohexane → cyclohexane/ethyl acetate 4:1) and recrystallization (cyclohexane) the *β*-amino ketone **2f** (140 mg, 0.43 mmol, 64%) was obtained as a colorless crystalline solid.



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.95 (m, 1H, $H2_{ph}$/$H6_{ph}$), 7.94 (m, 1H, $H2_{ph}$/$H6_{ph}$), 7.60 (m, 1H, $H4_{ph}$), 7.51 – 7.46 (m, 2H, $H3_{ph}$, $H5_{ph}$), 6.80 – 6.76 (m, 2H, H2, H6), 6.76 – 6.72 (m, 2H, H3, H5), 4.69 (m, 1H, CH), 3.74 (s, 3H, OMe), 3.40 – 3.29 (m, 2H, CH_2) ppm. **^{13}C NMR** (151 MHz, $CDCl_3$): δ = 195.53 (C=O), 153.58 (C4), 139.93 (C1), 136.48 ($C1_{ph}$), 133.85 ($C4_{ph}$), 129.94 ($C2_{ph}$, $C6_{ph}$), 128.29 ($C3_{ph}$, $C5_{ph}$), 126.34 (q, $J_{C,F}$ = 283.5 Hz, CF_3), 116.13 ($C3_{ph}$, $C5_{ph}$), 114.98 ($C2_{ph,}$ $C1_{ph}$), 55.79 (OMe), 53.97 (q, $^2J_{C,F}$ = 29.5 Hz, *C*CF_3), 38.47 (CH_2) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = − 75.48 (CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{17}H_{17}F_3NO_2^+$ $[M+H]^+$ 324.1206; found 324.1210. **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 18.43 min, λ = 214 nm**. mp** 90 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 4:1) = 0.53.

4,4,4-Trifluoro-1-phenyl-3-(pyridin-2-ylamino)butan-1-one (2g)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine **1g** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with acetophenone (0.08 mL, 0.68 mmol). After stirring at rt (1 h), aqueous workup, flash chromatography (cyclohexane → cyclohexane/ethyl acetate 4:1) and recrystallization (cyclohexane) the *β*-amino ketone **2g** (104 mg, 0.35 mmol, 78%) was obtained as a colorless crystalline solid.

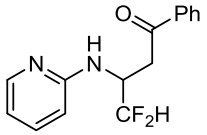


^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (dd, $J_{H6,H5}$ = 5.0 Hz, $J_{H6,H4}$ = 1.2 Hz, 1H, H6), 8.00 – 7.95 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.69 – 7.63 (m, 1H, $H4_{ph}$), 7.56 – 7.51 (m, 2H, $H3_{ph}$, $H5_{ph}$), 7.41 (ddd, $J_{H4,H3}$ = 8.8 Hz, $J_{H4,H5}$ = 7.1 Hz, $J_{H4,H6}$ = 1.9 Hz, 1H, H4), 6.94 (d, $J_{NH,CH}$ = 8.4 Hz, 1H, NH), 6.59 (ddd, $J_{H5,H4}$ = 7.0 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.8 Hz, 1 H, H5), 6.51 (d, $J_{H3,H4}$ = 8.4 Hz, 1H, H3), 5.60 – 5.44 (m, 1H, CH), 3.60 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 9.6 Hz, 1H, CH_2), 3.43 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 3.5 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 195.50 (C=O), 157.47 (C1), 147.33 (C6), 137.18 (C4), 136.34 ($C1_{ph}$), 133.67 ($C4_{ph}$), 128.92 ($C3_{ph}$, $C5_{ph}$), 128.21 ($C2_{ph}$, $C6_{ph}$), 126.59 (q, $J_{C,F}$ = 283.8 Hz, CF_3), 113.32 (C5), 108.74 (C3), 47.56 (q, $J_{C,F}$ = 30.0 Hz, CH), 37.55 (CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.34 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{15}H_{13}F_3N_2O^+$ $[M]^+$ 294.0980; found 294.0977. **HPLC-**

MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.25 min, λ = 220 nm. **mp** 124 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 2:1) = 0.46.

4,4-Difluoro-1-phenyl-3-(pyridin-2-ylamino)butan-1-one (2h)

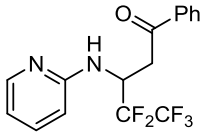
According to the general procedure, *N*-(1-ethoxy-2,2-difluoroethyl)pyridin-2-amine **1h** (100 mg, 0.49 mmol) was dissolved in 5 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.13 mL, 1.13 mmol) and reacted with acetophenone (0.09 mL, 0.74 mmol). After stirring at rt (2 h), aqueous workup and flash chromatography (cyclohexane → cyclohexane/ethyl acetate 4:1) the *β*-amino ketone **2h** (136 mg, 0.49 mmol, quant.) was obtained as a light brown solid.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1H, H6), 8.00 – 7.92 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.65 – 7.54 (m, 1H, $H4_{ph}$), 7.53 – 7.44 (m, 2H, $H3_{ph}$, $H5_{ph}$), 7.40 (ddd, $J_{H4,H3}$ = 8.4 Hz, $J_{H4,H5}$ = 7.1 Hz, $J_{H4,H6}$ = 1.9 Hz, 1H, H4), 6.62 (ddd, $J_{H5,H4}$ = 7.1 Hz, $J_{H5,H6}$ = 5.1 Hz, $J_{H5,H3}$ = 0.9 Hz, 1H, H5), 6.48 (dt, $J_{H3,H4}$ = 8.3 Hz, $J_{H3,H5}$ = 0.9 Hz, 1H, H3), 6.20 (td, $J_{CHF2,CHF2}$ = 56.7 Hz, $J_{CHF2,CH}$ = 3.1 Hz, 1H, CHF_2), 5.08 – 4.91 (m, 1H, CH), 4.89 (d, $J_{NH,CH}$ = 9.0 Hz, 1H, NH), 3.46 – 3.38 (m, 2H, CH_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 197.85 (C=O), 157.16 (C2), 147.97 (C6) , 137.61 (C4), 136.58 ($C1_{ph}$), 133.76 ($C4_{ph}$), 128.89 ($C3_{ph}$, $C5_{ph}$), 128.34 ($C2_{ph}$, $C6_{ph}$), 115.45 (t, $J_{CHF2,CHF2}$ = 244.9 Hz, CHF_2), 113.02 (C5), 108.87 (C3), 49.94 (dd, $J_{CH,CHF2}$ = 24.5 Hz, $J_{CH,CHF2}$ = 22.8 Hz, CH), 36.73 (CH_2) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = − 125.78 (ddd, $J_{CHF2,CHF2}$ = 281.1 Hz, $J_{CHF2,CHF2}$ = 56.4 Hz, $J_{CHF2,CH}$ = 10.4 Hz, CHF_2), − 128.96 (ddd, $J_{CHF2,CHF2}$ = 281.1 Hz, $J_{CHF2,CHF2}$ = 56.9 Hz, $J_{CHF2,CH}$ = 16.0 Hz, CHF_2) ppm. **HRMS** (ESI+): m/z calcd. for $C_{15}H_{15}F_2N_2O^+$ $[M+H]^+$ 277.1147; found 277.1146. **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 10.23 min, λ = 214 nm. **mp** 115 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 3:1) = 0.24.

4,4,5,5,5-Pentafluoro-1-phenyl-3-(pyrazin-2-ylamino)pentan-1-one (2i)

Following the general procedure, *N*-(1-ethoxy-2,2,3,3,3-pentafluoropropyl)pyrazin-2-amine **1i** (100 mg, 0.37 mmol) was dissolved in 5 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.85 mL, 0.85 mmol) and reacted with acetophenone (0.07 mL, 0.55 mmol). After stirring at rt (1 h), aqueous workup and flash chromatography (cyclohexane → cyclohexane/ethyl acetate 2:1) the *β*-amino ketone **2i** (130 mg, 0.37 mmol, quant.) was obtained as a light yellow solid.

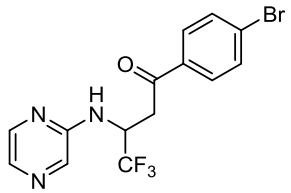


^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1 H, H6), 7.99 (d, $J_{H3,H6}$ = 1.5 Hz, 1 H, H3), 7.95 – 7.91 (m, 2 H, $H2_{ph}$; $H6_{ph}$), 7.90 (m, 1 H, H5), 7.60 (m, 1 H, $H4_{ph}$), 7.48 (m, 2 H, $H3_{ph}$; $H5_{ph}$), 5.73 (m, 1 H, CH), 5.06 (d, $J_{NH,CH}$ = 10.0 Hz, 1 H, NH), 3.51 – 3.46 (m, 2 H, CH_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 195.68 (C=O), 152.61 (C2), 141.68 (C6), 136.31 ($C1_{ph}$), 134.84 (C5), 134.01 ($C4_{ph}$), 132.96 (C3), 129.01 ($C3_{ph;}$ $C5_{ph}$), 128.27 ($C2_{ph;}$ $C6_{ph}$), 46.94 (dd, $^2J_{CH,CF2}$ = 27.1 Hz, $^2J_{CH,CF2}$ = 21.4 Hz, CH), 37.07 (CH_2) ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = − 81.84 (CF_3), − 118.54 (dd, $J_{CF2,CF2}$ = 273.6 Hz,

$J_{CF2,CF3}$ = 7.3 Hz, CF_2), − 124.82 (dd, $J_{CF2,CF2}$ = 273.6 Hz, $J_{CF2,CF3}$ = 19.8 Hz, CF_2) ppm. **HRMS** (ESI+): m/z calcd. for $C_{15}H_{13}F_5N_3O^+$ $[M+H]^+$ 346.0973; found 346.0973. . **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 16.28 min, λ = 214 nm. **mp** 105 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 2:1) = 0.23.

1-(4-Bromophenyl)-4,4,4-trifluoro-3-(pyrazin-2-ylamino)butan-1-one (3a)

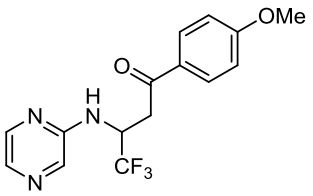
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with 4-bromoacetophenone (203 mg, 1.02 mmol). After stirring at 40 °C (2 h), aqueous workup, flash chromatography (cyclohexane/ethyl acetate 3:1 → 2:1) and recrystallization (cyclohexane/ethyl acetate 9:1) the *β*-amino ketone **3a** (157 mg, 0.42 mmol, 62%) was obtained as a colorless crystalline solid.



^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.04 (dd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.4 Hz, 1H, H6), 7.96 (d, $J_{H3,H6}$ = 1.4 Hz, 1H, H3), 7.94 – 7.89 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.82 (d, $J_{H5,H6}$ = 2.7 Hz, 1H, H5), 7.78 – 7.73 (m, 2H, $H3_{ph}$, $H5_{ph}$), 7.46 (d, $J_{NH,CH}$ = 8.2 Hz, 1H, NH), 5.48 – 5.35 (m, 1H, CH), 3.62 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 9.8 Hz, 1H, CH_2), 3.52 (dd, $J_{CH2,CH2}$ = 17.8 Hz, $J_{CH2,CH}$ = 3.3 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 194.57 (C=O), 154.01 (C2), 141.46 (C6), 135.19 (C1), 133.13 (C3), 133.09 (C5), 131.98 ($C3_{ph}$, $C5_{ph}$), 130.26 ($C2_{ph}$, $C6_{ph}$), 127.87 (C-Br), 126.29 (q, $J_{C,F}$ = 282.8 Hz, CF_3), 47.26 (q, $J_{C,F}$ = 30.3 Hz, CH), 37.28 (CH_2) ppm. **^{19}F NMR** (471 MHz, DMSO-d_6): δ = − 74.37 (d, $J_{CF3,CH}$ = 7.6 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_{12}BrF_3N_3O^+$ $[M+H]^+$ 374.0110; found 374.0112. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.74 min, λ = 220 nm. **mp** 112 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 2:1) = 0.24.

4,4,4-Trifluoro-1-(4-methoxyphenyl)-3-(pyrazin-2-ylamino)butan-1-one (3b)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with 4-methoxyacetophenone (153 mg, 1.02 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (cyclohexane/ethyl acetate 3:1 → 2:1) and recrystallization (cyclohexane/ethyl acetate 9:1) the *β*-amino ketone **3b** (199 mg, 0.61 mmol, 90%) was obtained as a colorless crystalline solid.

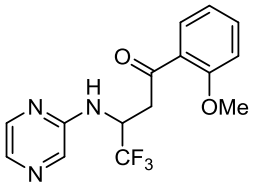


^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.03 (dd, $J_{H6,H5}$ = 2.6 Hz, $J_{H6,H3}$ = 1.4 Hz, 1H, H6), 7.99 – 7.93 (m, 3H, H3, $H2_{ph}$, $H6_{ph}$), 7.81 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.47 (d, $J_{NH,CH}$ = 8.3 Hz, 1H, NH), 7.05 (m, 2H, $H3_{ph}$, $H5_{ph}$), 5.52 – 5.34 (m, 1H, CH), 3.85 (s, 3H, OMe), 3.57 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 9.9 Hz, 1H, CH_2), 3.42 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 3.2 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 193.51 (C=O), 163.59 (C-OMe), 154.04 (C2), 141.47 (C6), 133.10 (C3), 133.01 (C5), 130.64 ($C2_{ph}$, $C6_{ph}$), 129.17 ($C1_{ph}$), 126.40 (q,

$^1J_{C,F}$ = 283.0 Hz, CF_3), 114.11 ($C3_{ph}$, $C5_{ph}$), 55.73 (OMe), 47.36 (q, $^2J_{C,F}$ = 30.3 Hz, CH), 36.84 (CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.34 (d, $J_{CF3,CH}$ = 7.8 Hz, CF_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{15}H_{14}F_3N_3O_2^+$ $[M]^+$ 325.1038; found 325.1043. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.60 min, λ = 220 nm. **mp** 135 °C. **R**$_f$ (cyclohexane/ethyl acetate 2:1) = 0.11.

4,4,4-Trifluoro-1-(2-methoxyphenyl)-3-(pyrazin-2-ylamino)butan-1-one (3c)

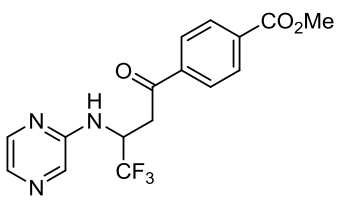
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with 2-methoxyacetophenone (0.14 mL, 1.02 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (cyclohexane/ethyl acetate 3:1 → 2:1) and recrystallization (cyclohexane/ethyl acetate 9:1) the *β*-amino ketone **3c** (194 mg, 0.59 mmol, 88%) was obtained as a colorless crystalline solid.



^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.97 (dd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.95 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.79 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.60 – 7.49 (m, 3H, $H2_{ph}$, $H4_{ph}$, $H5_{ph}$), 7.20 (d, $J_{NH,CH}$ = 8.2 Hz, 1H, NH), 7.03 – 6.97 (m, 1H, $H3_{ph}$), 5.47 – 5.37 (m, 1H, CH), 3.91 (s, 3H, OMe), 3.46 (dd, $J_{CH2,CH2}$ = 17.4 Hz, $J_{CH2,CH}$ = 4.2 Hz, 1H, CH_2), 3.40 (dd, $J_{CH2,CH2}$ = 17.4 Hz, $J_{CH2,CH}$ = 9.2 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 196.16 (C=O), 158.68 (C-OMe), 153.95 (C2), 141.39 (C6), 134.64 ($C4_{ph}$), 133.16 (C3), 132.95 (C5), 129.99 ($C2_{ph}$), 126.51 ($C1_{ph}$), 126.30 (q, $^1J_{C,F}$ = 282.9 Hz, CF_3) 120.71 ($C3_{ph}$), 112.68 ($C5_{ph}$), 55.97 (OMe), 47.31 (q, $^2J_{C,F}$ = 30.1 Hz, CH), 42.49 (CH_2) ppm. **^{19}F NMR** (471 MHz, DMSO-d_6): δ = − 74.52 (d, $J_{CF3,CH}$ = 7.7 Hz, CF_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{15}H_{14}F_3N_3O_2^+$ $[M]^+$ 325.1038; found 325.1044. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.62 min, λ = 220 nm. **mp** 134 °C. **R**$_f$ (cyclohexane/ethyl acetate 2:1) = 0.14.

Methyl 4-(4,4,4-trifluoro-3-(pyrazin-2-ylamino)butanoyl)benzoate (3d)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with methyl-4-acetylbenzoate (120 mg, 0.68 mmol). After stirring at rt (2.5 h), aqueous workup, flash chromatography (cyclohexane → cyclohexane/ethyl acetate 4:1) and recrystallization (cyclohexane) the desired *β*-amino ketone **3d** (130 mg, 0.37 mmol, 82%) was obtained as a colorless crystalline solid.



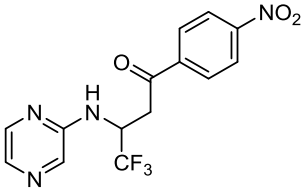
^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10 (d, $J_{H2ph,H3ph}$ = $J_{H5ph,H6ph}$ = 2.1 Hz, 4H, $H2_{ph}$, $H3_{ph}$, $H5_{ph}$, $H6_{ph}$), 8.04 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.96 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.82 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.46 (d, $J_{NH,CH}$ = 8.2 Hz, 1H, NH), 5.49 – 5.36 (m, 1H, CH), 3.69 (dd, $J_{CH2,CH2}$ = 17.9 Hz, $J_{CH2,CH}$ = 9.7 Hz, 1H, CH_2), 3.59 (dd, $J_{CH2,CH2}$ = 17.5 Hz, $J_{CH2,CH}$ = 3.1 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 194.84 (C=O), 165.46 (COOMe),

153.85 (C2), 141.22 (C6), 139.39 ($C1_{ph}$), 133.47 (C5), 133.00 ($C4_{ph}$), 132.96 (C3), 129.42 ($C3_{ph}$, $C5_{ph}$), 128.38 ($C2_{ph}$, $C6_{ph}$), 52.47 (CH_3), 47.12 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 37.50 (CH_2) ppm.* **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.38 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{16}H_{15}F_3N_3O_3^+$ $[M+H]^+$ 354.1060; found 354.1061. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.62 min, λ = 220 nm. **mp** 121 °C. **R**$_f$ (cyclohexane/ethyl acetate 2:1) = 0.17.

* Due to low intensity the signal of CF_3 could not be observed.

4,4,4-Trifluoro-1-(4-nitrophenyl)-3-(pyrazin-2-ylamino)butan-1-one (3e)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 4'-nitroacetophenone (111 mg, 0.68 mmol). After stirring at rt (1 h) followed by stirring at 40 °C (2 h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at −78 °C for 10 min, 4'-nitroacetophenone (75 mg, 0.45 mmol) was added and the reaction mixture was stirred at 40 °C (20 h). Subsequent aqueous workup, flash chromatography (cyclohexane → cyclohexane/ethyl acetate 4:1) and recrystallization (cyclohexane/ethyl acetate 9:1) furnished the *β*-amino ketone **3e** (115 mg, 0.34 mmol, 75%) as a yellow crystalline solid.

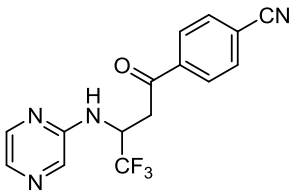


^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.41 – 8.30 (m, 2H, $H3_{ph}$, $H5_{ph}$), 8.26 – 8.18 (m, 2H, $H2_{ph}$, $H6_{ph}$), 8.04 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.96 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.83 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.47 (d, $J_{NH,CH}$ = 8.1 Hz, 1H, NH), 5.52 – 5.33 (m, 1H, CH), 3.77 – 3.60 (m, 2H, 2 × CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 194.63 (C=O), 154.01 (C2), 150.24 (C-NO_2), 141.46 (C6), 140.72 (C3), 133.17 (C5), 129.70 ($C2_{ph}$, $C6_{ph}$), 126.23 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3) 123.98 ($C3_{ph}$, $C5_{ph}$), 47.25 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 37.90 (CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.47 (d, $J_{CF3,CH}$ = 7.8 Hz, CF_3) **HRMS** (ESI+): m/z calcd. for $C_{14}H_{12}F_3N_4O_3^+$ $[M+H]^+$ 341.0856; found 341.0859. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.62 min, λ = 220 nm. **mp** 163 °C. **R**$_f$ (cyclohexane/ethyl acetate 2:1) = 0.14.

4-(4,4,4-Trifluoro-3-(pyrazin-2-ylamino)butanoyl)benzonitrile (3f)

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 4'-cyanoacetophenone (99 mg, 0.68 mmol). After stirring at rt (1 h) followed by stirring at 40 °C (1h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at −78 °C (10 min), 4'-cyanoacetophenone (65 mg, 0.45 mmol) was added and the reaction mixture was stirred at 40 °C (1 h). Subsequent aqueous workup, flash chromatography

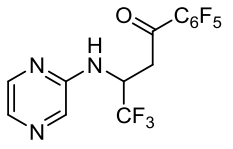
(cyclohexane → cyclohexane/ethyl acetate 4:1) and recrystallization (cyclohexane) furnished the *β*-amino ketone **3f** (131 mg, 0.41 mmol, 91%) as a colorless crystalline solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18 – 8.09 (m, 2H, $H3_{ph}$, $H5_{ph}$), 8.05 – 8.02 (m, 2H, $H2_{ph}$, $H6_{ph}$), 8.01 (m, 1H, H6), 7.96 (d, $J_{H3,H6}$ = 1.4 Hz, 1H, H3), 7.82 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.46 (d, $J_{NH,CH}$ = 8.1 Hz, 1H, NH), 5.53 – 5.28 (m, 1H, CH), 3.68 (dd, $J_{CH2,CH2}$ = 18.1 Hz, $J_{CH2,CH}$ = 9.3 Hz, 1H, CH_2), 3.61 (dd, $J_{CH2,CH2}$ = 18.0 Hz, $J_{CH2,CH}$ = 3.9 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 194.84 (C=O), 154.01 (C2), 141.45 (C6), 139.30 ($C1_{ph}$), 133.16 (C3), 133.15 (C5), 132.94 ($C2_{ph}$, $C6_{ph}$), 128.88 ($C3_{ph}$, $C5_{ph}$), 126.24 (q, $^1J_{C,F}$ = 282.7 Hz, CF_3), 118.22 (C≡N), 115.61 (C-CN), 47.24 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 37.69 (CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.37 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{15}H_{12}F_3N_4O^+$ $[M+H]^+$ 321.0958; found 321.0959. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.56 min, λ = 220 nm. **mp** 185 °C. **R**$_f$ (cyclohexane/ethyl acetate 1:1) = 0.37.

4,4,4-Trifluoro-1-(perfluorophenyl)-3-(pyrazin-2-ylamino)butan-1-one (3g)

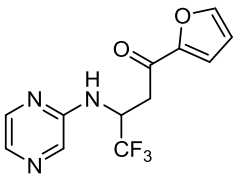
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 2',3',4',5',6'-pentafluoroacetophenone (0.10 mL, 0.68 mmol). After stirring at rt (1 h) followed by stirring at 40 °C (2 h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at −78 °C (10 min), 2',3',4',5',6'-pentafluoroacetophenone (0.07 mL, 0.45 mmol) was added and the reaction mixture was stirred at 40 °C (20 h). Subsequent aqueous workup, flash chromatography (cyclohexane → cyclohexane/ethyl acetate 4:1) and recrystallization (cyclohexane/ethyl acetate 9:1) furnished the *β*-amino ketone **3g** (61 mg, 0.16 mmol, 35%) as a light yellow solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 – 7.97 (m, 2H, H6, H3), 7.84 (d, $J_{H5,H6}$ = 2.3 Hz, 1H, H5), 7.70 (d, $J_{NH,CH}$ = 8.8 Hz, 1H, NH), 5.51 – 5.37 (m, 1H, CH), 3.55 (dd, $J_{CH2,CH2}$ = 17.7 Hz, $J_{CH2,CH}$ = 4.0 Hz, 1H, CH_2), 3.40 (dd, $J_{CH2,CH2}$ = 17.7 Hz, $J_{CH2,CH}$ = 9.7 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 189.83 (C=O), 153.88 (C2), 146.07 – 145.78 (m, C-F), 144.42 – 144.10 (m, C-F), 143.55 - 143.31 (m, C-F), 141.56 (C6), 139.00 - 138.65 (m, C-F), 136.52 - 136.16 (m, C-F), 133.64 (C5), 133.49 (C3), 126.01 (q, $^1J_{C,F}$ = 283.0 Hz, CF_3), 113.99 - 113.63 (m, C-F), 47.15 (q, $^2J_{C,F}$ = 30.8 Hz, CH), 43.49 (CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.68 (d, $J_{CF3,CH}$ = 7.8 Hz, CF_3), − 140.87 – −141.17 (m, F2, F6), − 149.30 (tt, $J_{F4,F3}$ = $J_{F4,F5}$ = 22.2 Hz, $J_{F4,F2}$ = $J_{F4,F6}$ = 4.4 Hz, F4), − 160.93 – −161.21 (m, F3, F5) ppm. **HRMS** (ESI+): m/z calcd. for $C_{14}H_8F_8N_3O^+$ $[M+H]^+$ 386.0534; found 386.0534. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.74 min, λ = 220 nm. **mp** 115 °C. **R**$_f$ (cyclohexane/ethyl acetate 2:1) = 0.30.

4,4,4-Trifluoro-1-(furan-2-yl)-3-(pyrazin-2-ylamino)butan-1-one (3h)

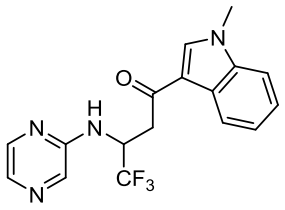
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMSD (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 2-acetylfuran (75 mg, 0.68 mmol). After stirring at rt (2 h), aqueous workup and column chromatography (cyclohexane/ethyl acetate 5:1 → 1:1) the *β*-amino ketone **3h** (75 mg, 0.26 mmol, 58%) was obtained as a light yellow oil.



^{1}H NMR (800 MHz, DMSO-d_6): δ = 8.02 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 8.00 (dd, $J_{H5furan,H4furan}$ = 1.7 Hz, $J_{H5furan,H3furan}$ = 0.7 Hz, 1H, $H5_{furan}$), 7.95 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.80 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.57 (d, $J_{NH,CH}$ = 8.5 Hz, 1H, NH), 7.52 (dd, $J_{H3furan,H4furan}$ = 3.6 Hz, $J_{H3furan,H5furan}$ = 0.7 Hz 1H, $H3_{furan}$), 6.73 (dd, $J_{H4furan,H3furan}$ = 3.6 Hz, $J_{H4furan,H5furan}$ = 1.7 Hz, 1H, $H4_{furan}$), 5.47 – 5.29 (m, 1H, CH), 3.43 – 3.37 (m, 1H, CH_2), 3.31 (dd, $J_{CH2,CH2}$ = 17.1 Hz, $J_{CH2,CH}$ = 3.8 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 183.44 (C=O), 153.91 (C2), 151.57 ($C2_{furan}$), 148.36 ($C5_{furan}$), 141.45 (C6), 133.15 (C3, C5), 129.19 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3), 119.42 ($C3_{furan}$), 112.92 ($C4_{furan}$), 47.02 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 36.95 (CH_2) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.52 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{12}H_{11}F_3N_3O_2^+$ $[M+H]^+$ 286.0798; found 286.0797 **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 12.68 min, λ = 214 nm. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 1:1) = 0.32.

4,4,4-Trifluoro-1-(1-methyl-1*H*-indol-3-yl)-3-(pyrazin-2-ylamino)butan-1-one (3i)

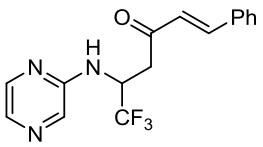
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 1-(1-methyl-1*H*-indol-3-yl)ethan-1-one (117 mg, 0.68 mmol). After stirring at rt (2 h), aqueous workup, flash chromatography (CH_2Cl_2 → CH_2Cl_2/MeOH 10:1) and recrystallization (cyclohexane) the *β*-amino ketone (105 mg, 0.30 mmol, 67%) was obtained as a colorless solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.46 (s, 1H, $H2_{in}$), 8.12 (d, $J_{H7in,H6in}$ = 7.6 Hz, 1H, $H7_{in}$), 8.03 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.98 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.79 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.54 (m, 2H, NH, $H4_{in}$), 7.32 – 7.25 (m, 1H, $H5_{in}$), 7.21 (td, $J_{H6in,H7in/H5in}$ = 7.6 Hz, $J_{H6in,H4in}$ = 1.0 Hz, 1H, $H6_{in}$), 5.59 – 5.41 (m, 1H, CH), 3.89 (s, 3H, NCH_3), 3.45 (dd, $J_{CH2,CH2}$ = 16.5 Hz, $J_{CH2,CH}$ = 9.8 Hz, 1H, CH_2), 3.26 (dd, $J_{CH2,CH2}$ = 16.5 Hz, $J_{CH2,CH}$ = 3.5 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 188.98 (C=O), 154.06 (C2), 141.51 (C6), 138.37 ($C2_{in}$), 137.39 (C_{quart}-N), 133.11 (C3), 132.92 (C5), 126.53 (q, $^1J_{C,F}$ = 283.0 Hz, CF_3) 125.75 ($C3_{in}$), 123.21 ($C5_{in}$), 122.46 ($C6_{in}$), 121.47 ($C7_{in}$), 115.00 (C_{quart}), 110.81 ($C4_{in}$), 47.42 (q, $^2J_{C,F}$ = 30.1 Hz, CH), 37.64 (CH_2), 33.35 (CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.34 (d, $J_{CF3,CH}$ = 8.0 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{17}H_{16}F_3N_4O^+$ $[M+H]^+$ 349.1271; found 349.1273. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.60 min, λ = 220 nm. **mp** 198 °C. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 1:1) = 0.17.

(*E*)-6,6,6-trifluoro-1-phenyl-5-(pyrazin-2-ylamino)hex-1-en-3-one (3j)

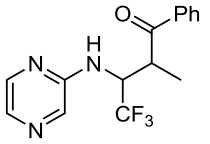
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with (*E*)-4-phenylbut-3-en-2-one (99 mg, 0.68 mmol). After stirring at rt (2 h), aqueous workup and column chromatography (cyclohexane/ethyl acetate 3:1 → 1:1) the *β*-amino ketone (92 mg, 0.29 mmol, 64%) was obtained as a yellow oil.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.99 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 7.80 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.74 – 7.70 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.67 (d, $J_{Ha,Hb}$ = 16.3 Hz, 1H, H_a), 7.53 (d, $J_{NH,CH}$ = 8.5 Hz, 1H, NH), 7.47 – 7.42 (m, 3H, $H3_{ph}$, $H4_{ph}$, $H5_{ph}$,), 6.96 (d, $J_{Hb,Ha}$ = 16.3 Hz, 1H, H_b), 5.48 – 5.31 (m, 1H, CH), 3.32 – 3.24 (m, 1H, CH_2), 3.19 (dd, $J_{CH2,CH2}$ = 17.3 Hz, $J_{CH2,CH}$ = 3.6 Hz, 1H, CH_2) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 195.11 (C=O), 154.02 (C2), 143.33 (C_a), 141.45 (C6), 134.32 ($C1_{ph}$), 133.18 (C3), 133.05 (C5), 130.88 ($C4_{ph}$), 129.16 ($C3_{ph}$, $C5_{ph}$), 128.68 ($C2_{ph}$, $C6_{ph}$), 126.31 (q, $^1J_{C,F}$ = 282.8 Hz, CF_3) 126.10 (C_b), , 47.20 (q, $^2J_{C,F}$ = 30.3 Hz, CH) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.50 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{16}H_{15}F_3N_3O^+$ $[M+H]^+$ 322.1162; found 322.1160. **R**$_f$ (cyclohexane/ethyl acetate 1:1) = 0.55.

4,4,4-Trifluoro-2-methyl-1-phenyl-3-(pyrazin-2-ylamino)butan-1-one (3k)

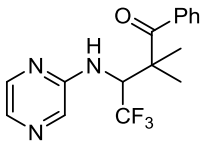
Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with propiophenone (0.09 mL, 0.68 mmol). After stirring at rt (2 h), aqueous workup and column chromatography (cyclohexane/ethyl acetate 3:1 → 2:1) the *β*-amino ketone **3k** (95 mg, 0.31 mmol, 68%) was obtained as a colorless solid (mixture of diastereomeres).



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 – 7.98 (m, 4H, H6, H3, $H2_{ph}$, $H6_{ph}$), 7.80 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.71 – 7.65 (m, 1H, $H4_{ph}$), 7.60 – 7.53 (m, 3H, $H3_{ph}$, $H5_{ph}$, NH), 5.36 – 5.23 (m, 1H, CH), 4.17 (dq, $J_{CH}CH3,CH$ = 14.2 Hz, $J_{CH}CH3,CH3$ = 7.0 Hz 1H, C*H*CH_3), 1.25 (dd, $J_{CH3,CH}CH3$ = 7.0 Hz, $J_{CH3,CF3}$ = 1.1 Hz 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 199.81 (C=O), 153.69 (C2), 141.17 (C6), 135.21 ($C1_{ph}$), 133.65 (C5), 133.12 ($C4_{ph}$), 132.96 (C3), 128.90 ($C3_{ph}$, $C5_{ph}$), 128.43 ($C2_{ph}$, $C6_{ph}$), 126.13 (q, $^1J_{C,F}$ = 284.3 Hz, CF_3), 52.21 (q, $^2J_{C,F}$ = 28.8 Hz, CH), 26.32 (*C*HCH_3), 14.60 (d, $^4J_{C,F}$ = 1.9 Hz, CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 69.65 (dd, $J_{CF3,CH}$ = 8.4 Hz, $J_{CF3,CH3}$ = 1.1 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{15}H_{15}F_3N_3O^+$ $[M+H]^+$ 310.1162; found 310.1160. **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 15.79 min, 15.97 min, λ = 214 nm. **mp** 95 °C. **R**$_f$ (cyclohexane/ethyl acetate 2:1) = 0.37.

4,4,4-Trifluoro-2,2-dimethyl-1-phenyl-3-(pyrazin-2-ylamino)butan-1-one (3l)

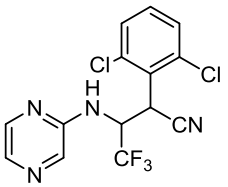
Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (100 mg, 0.45 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol) and reacted with 2-methyl-1-phenylpropan-1-one (0.1 mL, 0.68 mmol). After stirring at rt (3 h), aqueous workup and column chromatography (cyclohexane/ethyl acetate 3:1 → 2:1) the *β*-amino ketone **3l** (32 mg, 0.10 mmol, 22%) was obtained as a light yellow solid.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.20 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 8.00 (dd, $J_{H6,H5}$ = 2.8 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.82 (d, $J_{H5,H6}$ = 2.8 Hz, 1H, H5), 7.75 – 7.68 (m, 1H, $H4_{ph}$), 7.67 – 7.61 (m, 2H, $H2_{ph}$, $H6_{ph}$), 7.58 – 7.51 (m, 1H, NH), 7.47 (m, 2H, $H3_{ph}$, $H5_{ph}$), 6.01 (m, 1H, CH), 1.40 (s, 3H, CH_3), 1.27 (s, 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 206.17 (C=O), 154.05 (C2), 141.02 (C6), 137.80 ($C1_{ph}$), 133.52 (C5), 133.14 ($C4_{ph}$), 131.20 (C3), 128.36 ($C3_{ph}$, $C5_{ph}$), 127.29 ($C2_{ph}$, $C6_{ph}$), 125.73 (q, $^1J_{C,F}$ = 284.7 Hz, CF_3), 54.13 (q, $^2J_{C,F}$ = 27.6 Hz, CH), 49.48 ($C(CH_3)_2$), 24.02 (CH_3), 20.37 (d, $^4J_{C,F}$ = 1.1 Hz, CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 67.66 (d, $J_{CF3,CH}$ = 8.9 Hz, CF_3) ppm. **HRMS** (ESI+): m/z calcd. for $C_{16}H_{17}F_3N_3O^+$ $[M+H]^+$ 324.1318; found 324.1318. **HPLC** (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 15.83 min, λ = 214 nm. **mp** 130 °C. **R**$_f$ (cyclohexane/ethyl acetate 2:1) = 0.29.

2-(2,6-Dichlorophenyl)-4,4,4-trifluoro-3-(pyrazin-2-ylamino)butane-nitrile (3m)

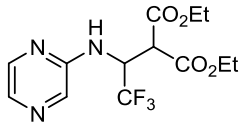
Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol) and reacted with 2,6-dichlorphenylacetonitrile (202 mg, 1.09 mmol). After stirring at rt (2.5 h), aqueous workup, column chromatography (cyclohexane/ethyl acetate 5:1 → 3:1) and washing with toluene the *β*-amino ketone **3m** (148 mg, 0.41 mmol, 60%) was obtained as a colorless solid (mixture of diastereomeres).



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (d, $J_{H3ar,H4ar}$ = 9.6 Hz, 1H, $H3_{ar}$), 8.18 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 8.09 (dd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.94 (d, $J_{H5,H6}$ = 2.7 Hz, 1H, H5), 7.65 (s, 2H, NH, $H5_{ar}$), 7.53 (t, $J_{H4ar,H3ar/H5ar}$ = 8.1 Hz, 1H, $H4_{ar}$), 6.22 – 6.07 (m, 1H, CH), 5.51 (d, $J_{CHCN,CH}$ = 10.5 Hz, 1H, CHCN) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ = 152.60 (C2), 140.63 (C6), 135.21 ($C1_{ph}$), 133.83 (C5), 132.89 (C3), 131.79 ($C2_{ph}$, $C6_{ph}$), 129.30 ($C4_{ph}$), 128,21 (q, $^1J_{C,F}$ = 283.9 Hz, CF_3), 126.23 ($C3_{ph}$, $C5_{ph}$), 114.98 (C≡N), 50.71 (q, $^2J_{C,F}$ = 30.2 Hz, *C*-CF_3), 32.00 (*C*-CN). **^{19}F NMR** (471 MHz, DMSO-d_6): δ = − 71.63 (br s, CF_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{14}H_9Cl_2F_3N_4^+$ $[M]^+$ 360.0156; found 360.0177. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.68 min, 1.73, λ = 220 nm.

Diethyl 2-(2,2,2-trifluoro-1-(pyrazin-2-ylamino)ethyl)malonate (3n)

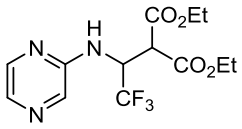
According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (150 mg, 0.68 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 1.42 mL, 1.42 mmol) and reacted with diethyl malonate (0.16 mL, 1.02 mmol). After stirring at rt (2 h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.68 mL, 0.68 mmol) was added. Stirring was continued at −78 °C (10 min), diethyl malonate (0.1 mL, 0.68 mmol) was added and the reaction mixture was stirred at 40 °C (2 h). Subsequent aqueous workup and column chromatography (cyclohexane/ethyl acetate 3:1) furnished the desired *β*-amino ketone **3n** (134 mg, 0.40 mmol, 59%) as a light yellow oil.



^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.09 (d, $J_{H3,H6}$ = 1.5 Hz, 1H, H3), 8.07 (dd, $J_{H6,H5}$ = 2.7 Hz, $J_{H6,H3}$ = 1.5 Hz, 1H, H6), 7.87 (d, $J_{H5,H6}$ = 2.7 Hz, 1H, H5), 7.71 (d, $J_{NH,CH}$ = 9.5 Hz, 1H, NH), 5.73 – 5.59 (m, 1H, CH), 4.23 – 3.94 (m, 4H, 2 × CH_2), 1.16 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3H, CH_3), 1.01 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3H, CH_3) ppm. **^{13}C NMR** (75 MHz, DMSO-d_6): δ = 165.19 (C=O), 164.99 (C=O), 153.23 (C2), 141.06 (C6), 133.57 (C5), 133.31 (C3), 124.90 (q, $^1J_{C,F}$ = 283.5 Hz, CF_3), 61.97 (CH_2), 61.70 (CH_2), 51.66 ($CH(CO_2Et)_2$), 49.70 (q, $^2J_{C,F}$ = 30.5 Hz, CH), 13.63 (CH_3), 13.51 (CH_3) ppm. **^{19}F NMR** (282 MHz, DMSO-d_6): δ = − 72.79 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{13}H_{16}F_3N_3O_4^+$ $[M]^+$ 335.1093; found 335.1104. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.62 min, λ = 220 nm. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 2:1) = 0.31.

Ethyl 4,4,4-trifluoro-3-(pyrazin-2-ylamino)butanoate (3o)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine **1b** (90 mg, 0.41 mmol) was dissolved in 7 mL dry CH_2Cl_2, treated with LHMDS (1.0 M solution in toluene, 0.94 mL, 0.94 mmol) and reacted with ethylacetate (0.06 mL, 0.62 mmol). After stirring at rt (1 h), aqueous workup and flash chromatography (cyclohexane → cyclohexane/ethyl acetate 3:1) the *β*-amino ester **3o** (27 mg, 0.10 mmol, 25%) was obtained as a light yellow oil.



^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.12 – 7.91 (m, 2H, H6, H3), 7.82 (d, $J_{H5,H6}$ = 2.3 Hz, 1H, H5), 7.65 (d, $J_{NH,CH}$ = 8.9 Hz, 1H, NH), 5.40 – 5.18 (m, 1H, CH), 4.03 (m, 2H, OCH_2), 2.92 (dd, $J_{CH2,CH2}$ = 16.2 Hz, $J_{CH2,CH}$ = 4.2 Hz, 1H, CH_2), 2.72 (dd, $J_{CH2,CH2}$ = 16.2 Hz, $J_{CH2,CH}$ = 10.0 Hz, 1H, CH_2), 1.06 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3H, CH_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 168.76 (C=O), 153.64 (C2), 141.15 (C6), 133.11 (C5), 133.06 (C3), 125.57 (q, $^1J_{C,F}$ = 283.2 Hz, CF_3), 60.47 (OCH_2), 47.83 (q, $^2J_{C,F}$ = 30.7 Hz, CH), 33.58 (CH_2), 13.76 (CH_3). **^{19}F NMR** (376 MHz, DMSO-d_6): δ = − 74.89 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{10}H_{12}F_3N_3O_2^+$ $[M]^+$ 263.0882; found 263.0898. **HPLC-MS** (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.43 min, λ = 220 nm. $\mathbf{R}_f$ (cyclohexane/ethyl acetate 2:1) = 0.15.

5. Experimental Procedures and Analytical Data: *Strategy toward a Stereoselective Synthesis of Trifluoroethylamines*

5.1 General procedures

Typical procedure for the conversion of hemiaminal ethers with RMgCl, Typical Procedure TPI

The hemiaminal ether **20** (1 equiv) was solved in freshly distilled THF in a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum and cooled to −15 °C. The *Grignard* reagent (2 equiv) was added dropwise with a syringe and the solution was stirred until TLC-analysis showed complete conversion. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated and the crude product was purified by flash chromatography (SiO_2).

Typical procedure for the conversion of hemiaminal ethers with Et_2Zn and $Cu(OTf)_2$, Typical procedure TPII

A suspension of $Cu(OTf)_2$ (0.1 equiv) and MeDuPHOS monooxide (0.1 equiv) in dry toluene (5 mL) was stirred at r.t. for 1 h. Et_2Zn (3 equiv) was added dropwise and the reaction mixture was stirred further for 20 min and then cooled to 0 °C. The hemiaminal ether **20** (1 equiv) was then added and the reaction was stirred for 18 h at 0 °C. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated and the crude product was purified by flash chromatography (SiO_2).

Typical procedure for the preparation of CuCN·2LiCl solution, Typical procedure TPIII

CuCN·2LiCl solution (1.00 M) was prepared by drying CuCN (20.0 mmol, 1.80 g) and LiCl (40 mmol, 1.70 g) in a Schlenk-flask under vacuum at 140 °C for 5 h. After cooling, 20 mL dry THF were added and stirring was continued until the salts were dissolved.

Typical procedure for the conversion of hemiaminal ethers with organocopper reagents, Typical procedure TPIV

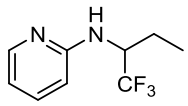
A solution of a *Grignard* reagent (2.5 equiv) in dry THF (5 mL) was cooled to -30 °C and a solution of CuCN·2LiCl (1.00 M, 3.1 equiv) was added dropwise. After stirring the reaction mixture for 30 min, the chiral ligand (0.1 equiv) added. The mixture was stirred for 1 h, before the hemiaminal ether **20** (1 equiv) was added and the reaction was stirred for 18 h at 0 °C. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated and the crude product was purified by flash chromatography (SiO_2).

5.2 Experimental data

_N_-(1,1,1-Trifluorbutan-2-yl)pyridin-2-amine 21

Reaction conditions without addition of a chiral ligand:

Following TPII, hemiaminal ether **20** (100 mg, 0.45 mmol) was reacted with Et_2Zn (1.0 M, 1.35 mL, 1.35 mmol) and $Cu(OTf)_2$ (17.0 mg, 0.05 mmol) in toluene (5 mL) at 0 °C for 16 h. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated. The crude product was purified by flash chromatography (SiO_2, cyclocyclohexaneane/ethyl acetate/NEt_3 8:1:0.1) to give the desired amine **21** (74 mg, 80%) as a colorless oil.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.43 (ddd, $J_{H4,H3}$ = 8.4 Hz, $J_{H4,H5}$ = 7.2 Hz, $J_{H4,H6}$ = 1.9 Hz, 1 H, H4), 6.64 (ddd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.0 Hz, $J_{H5,H3}$ = 0.9 Hz, 1 H, H5), 6.46 (dt, $J_{H3,H4}$ = 8.4 Hz, $J_{H3,H5.NH}$ = 0.9 Hz, 1 H, H3), 4.74 – 4.54 (m, 1 H, CH), 4.35 (d, $J_{NH,CH}$ = 9.6 Hz, 1 H, NH), 1.95 (dtq, $J_{CH2,CH2}$ = 18.8 Hz, $J_{CH2,CH3}$ = 7.5 Hz, $J_{CH2,CF3}$ = 3.9 Hz, 1 H, CH_2), 1.58 (ddq, $J_{CH2,CH2}$ = 14.6 Hz, $J_{CH2,CF3}$ = 10.0 Hz, $J_{CH2,CH3}$ = 7.4 Hz, 1 H, CH_2), 1.03 (td, $J_{CH3,CH2}$ = 7.6 Hz, $J_{CH3,CH}$ = 0.9 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = -76.12 (d, $J_{CF3,CH}$ = 7.4 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 157.83 (C2), 148.21 (C6), 137.94 (d, $J_{C,F}$ = 0.8 Hz, C4), 126.41 (q, $J_{C,F}$ = 282.8 Hz, CF_3), 114.49 (C5), 108.20 (C3), 53.87 (q, $J_{C,F}$ = 29.4 Hz, CH), 22.85 (q, $J_{C,F}$ = 1.7 Hz, CH_2), 10.24 (CH_3) ppm. **HRMS** (EI+): *m/z* calcd. for $C_{13}H_{11}N_2F_3^+$ [M^+] 204.0869, found 204.0881. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 8.68 min, λ = 214 nm.

Reaction conditions under addition of a chiral ligand:

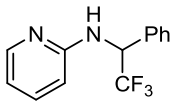
Following TPII, hemiaminal ether **20** (100 mg, 0.45 mmol) was reacted with Et_2Zn (1.0 M, 1.35 mL, 1.35 mmol), $Cu(OTf)_2$ (17.0 mg, 0.05 mmol) and MeDuPHOS monoxide (16.0 mg, 0.05 mmol) in toluene (5 mL) at 0 °C for 16 h. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated. The crude product was purified by flash chromatography (SiO_2, cyclocyclohexaneane/ethyl acetate/NEt_3 8:1:0.1) to give the desired amine **21** (74 mg, 80%) as a colorless oil.

The product was analyzed *via* chiral **HPLC** to determine the ratio of enantiomers.

_N_-(2,2,2-Trifluoro-1-phenylethyl)pyridin-2-amine 23

*Synthesis of **23** using PhMgCl:*

According to TPI, *N*-(1-Ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine **20** (100 mg, 0.45 mmol) was reacted with PhMgCl (3.0 M in Et_2O, 0.45 mL, 1.36 mmol) in dry THF (6 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane /ethyl acetate 10:1) to give the desired amine **23** (115 mg, quant.) as colorless oil.



^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.52 – 7.34 (m, 6 H, H4, H2', H3', H4', H5', H6'), 6.66 (dd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.1 Hz, 1 H, H5), 6.47 (dt, $J_{H3,H4}$ = 8.3 Hz, $J_{H3,H4}$ = 0.9 Hz, 1 H, H3), 5.86 (p, $J_{CH,NH} = J_{CH,CF3}$ = 8.1 Hz, 1 H, $CHCF_3$), 5.04 (d, $J_{NH,CH}$ = 9.1 Hz, 1 H, NH) ppm. **^{19}F NMR** (280 MHz, $CDCl_3$): δ = -73.88 (d, $J_{CF3,CH}$ = 7.9 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 156.42 (C2), 148.08 (C6), 137.77 (C4), 134.49 (q, J(C,F) = 1.0 Hz, C1'), 129.06 (C3', C5'), 128.96 (C4'), 128.07 (C2', C6'), 125.35 (q, $J_{C,F}$ = 281.9 Hz, CF_3), 114.79 (C5), 108.62 (C3), 56.52 (q, $J_{C,F}$ = 30.5 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{13}H_{12}F_3N_2^+$ $[M+H]^+$ 253.0953, found 253.0945. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 6.28 min, λ = 214 nm.

*Synthesis of **23** using organocopper reagents:*

Following TPIV, PhMgCl (3.0 M, 0.38 mL, 1.13 mmol) and CuCN·2LiCl (1.0 M, 1.13 mL, 1.13 mmol) were reacted in dry THF (6 mL) for 20 min. Then, the hemiaminal ether **20** (100 mg, 0.45 mmol) was added to the reaction mixture, which was stirred for further 8 h. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 10:1) to give the desired amine **23** (102 mg, 90%) as colorless oil.

*Synthesis of **23** using an external base and organocopper reagents:*

Similar to TPIV, PhMgCl (3.0 M, 0.38 mL, 1.13 mmol) and CuCN·2LiCl (1.0 M, 1.13 mL, 1.13 mmol) were reacted in dry THF (6 mL) for 20 min. In a second *Schlenk*-flask, the hemiaminal ether **20** (100 mg, 0.45 mmol) was solved in dry THF (3 mL). After the solution was cooled to -78 °C, LiHMDS (1.0 M, 0.45 mL, 0.45 mmol) was added dropwise and the reaction mixture was stirred for 15 min. The phenylcopper(I)-solution was added to the reaction mixture and the reaction mixture was allowed to warm up to -20 °C and was stirred at this temperature for 8 h. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 10:1) to give the desired amine **23** (100 mg, 88%) as colorless oil.

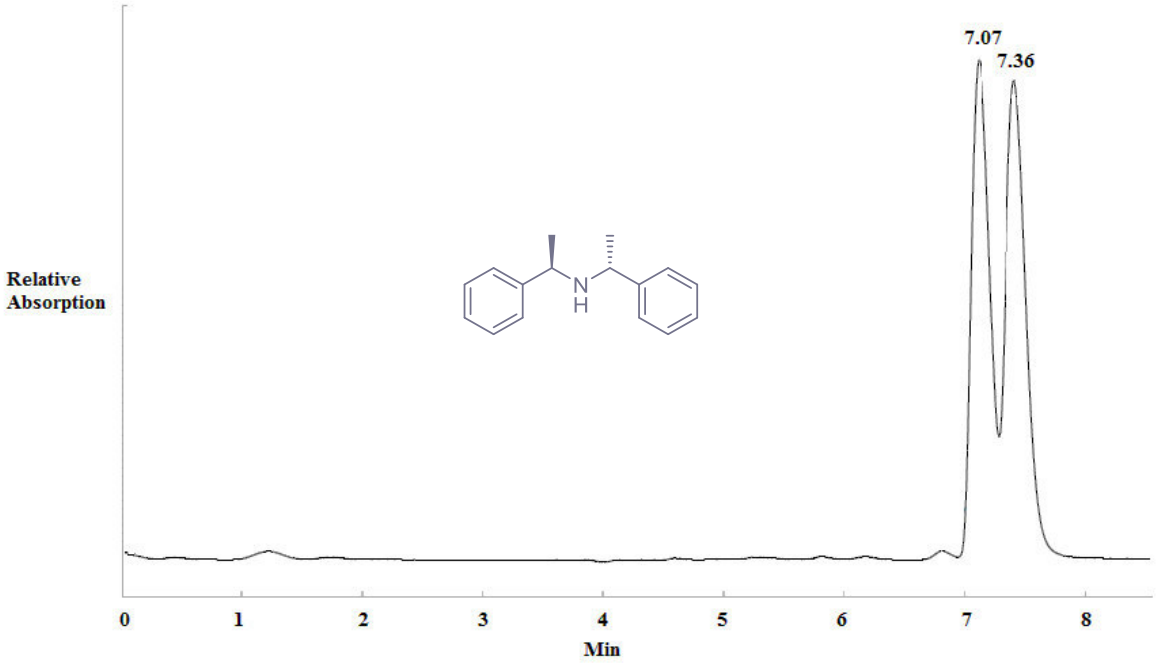
*Synthesis of **23** using organocopper reagents and chiral ligands:*

Following TPIII, PhMgCl (3.0 M, 0.38 mL, 1.13 mmol) and CuCN·2LiCl (1.0 M, 1.13 mL, 1.13 mmol) were reacted in dry THF (6 mL) for 20 min before the chiral ligand (0.05 mmol) was added. After stirring the reaction mixture for 1 h, the hemiaminal ether **20** (100 mg, 0.45 mmol) was added to the reaction mixture, which was stirred for further 8 h. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 10:1) to give the desired amine **23** as colorless oil.

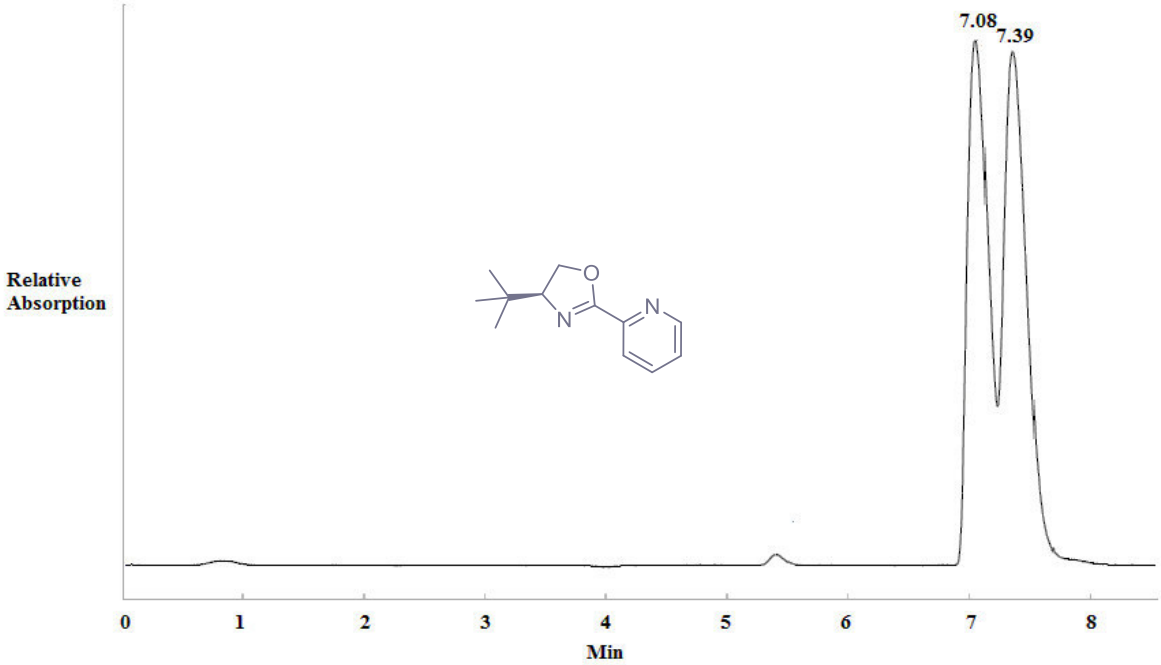
The product was analyzed *via* chiral **HPLC** to determine the ratio of enantiomers.

HPLC spectra and added chiral ligands

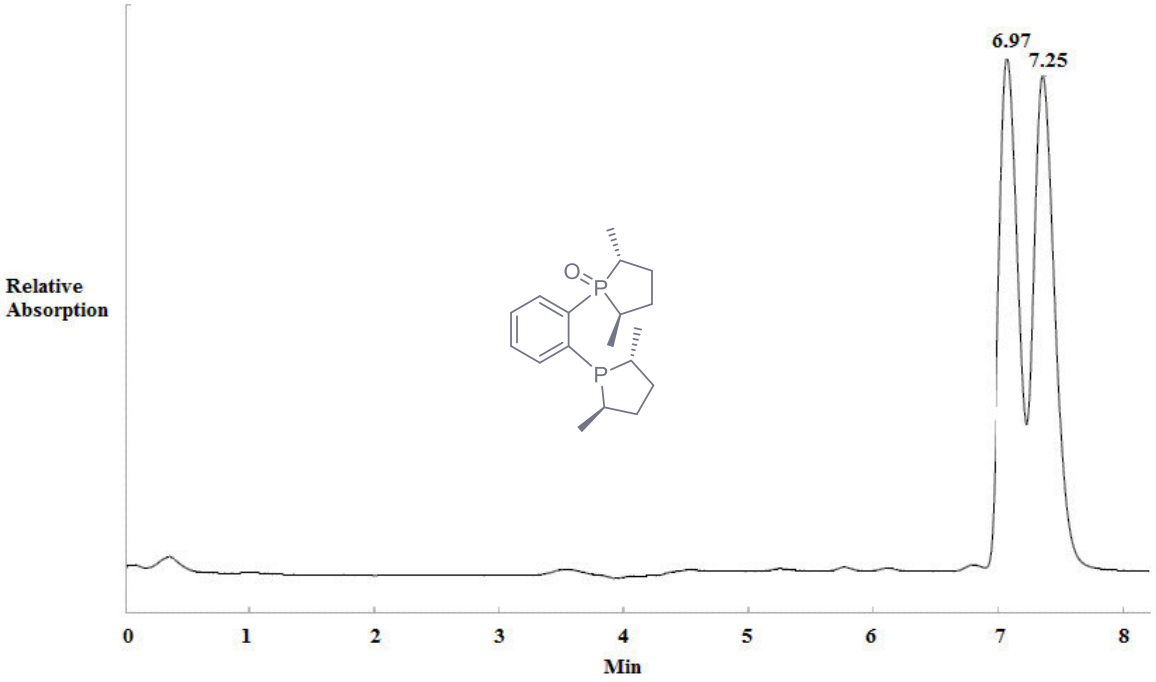
(+)-Bis[(R)-1-phenylethyl]amine (ChiPros):



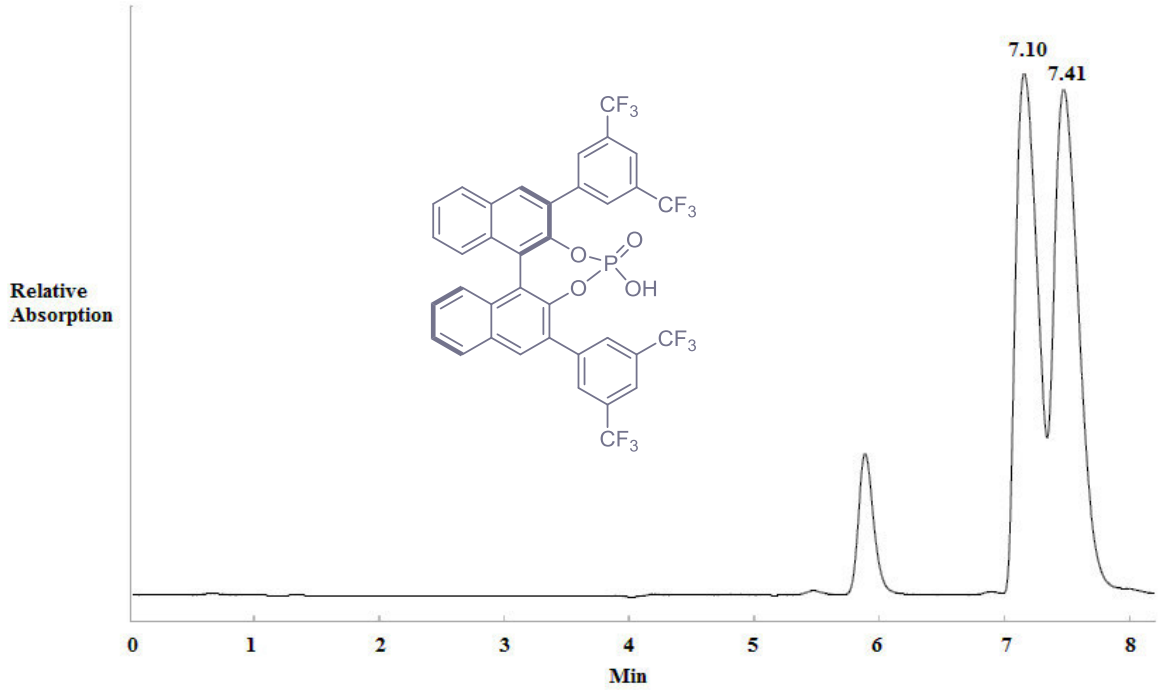
(S)-4-tert-Butyl-2-(2-pyridyl)oxazoline:



1,2-Bis[(2R,5R)-2,5-dimethylphospholano]benzene monooxide:



(R,R-MeBozPhos)(R)-3,3'-Bis[3,5-bis(trifluoromethyl)phenyl]-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate:



6. Experimenal procedures and analytical data: *Novel One-Pot Synthesis of Highly Substituted Trifluoromethylated Imidazoles*

The complete supporting information including the experimental procedures and NMR spectra of all compounds is available on the *Organic Letters* website (DOI: 10.1021/acs.orglett.6b01672) and on the CD in the book cover of this thesis. The synthesized compounds are numbered according to the publication.

6.1 Typical Procedures

Typical procedure for the synthesis of CF_3-imidazole derivatives 2, Typical Procedure TPI

The hemiaminal ether **1** (1 equiv) was solved in freshly distilled THF in a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum and cooled to −15 °C. The *Grignard* reagent (3 equiv) was added dropwise with a syringe and the solution was stirred until TLC-analysis showed complete conversion. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated and the crude product was purified by flash chromatography (SiO_2).

Typical Procedure for the magnesium insertion, Typical procedure TPII

A dry and argon flushed 10 mL flask, equipped with a magnetic stirrer and a septum, was charged with *i*PrMgCl·LiCl (1.25 M in THF, 1.1 equiv). The neat aryl bromide (1 equiv) was added at the appropriate temperature. The reaction mixture was stirred at the stated temperature, while the completion of the Br/Mg exchange was monitored by GC-analysis.

Typical procedure for the synthesis of CF_3-imidazole derivatives 2 with nBuLi, Typical Procedure TPIII

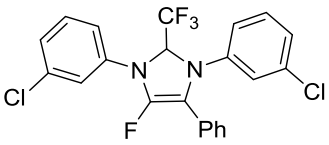
The hemiaminal ether **1** (1 equiv) and trifluoroethylamine **3** (1 equiv) were solved in freshly distilled THF in a dry and argon flushed *Schlenk*-flask, equipped with a magnetic stirrer and a septum and cooled to −60 °C. *n*BuLi (3 equiv) was added dropwise with a syringe, the solution was stirred at −60 °C for 30 min, warmed up to −30 °C and stirred until no further conversion was observed. Subsequently, sat. NH_4Cl solution was added and the mixture was extracted three times with Et_2O. The organic solvent was dried with $MgSO_4$, filtrated and evaporated and the crude product was purified by flash chromatography (SiO_2).

6.2 Synthesis of CF_3-imidazole derivatives

1,3-*bis*(3-Chlorophenyl)-4-fluoro-5-phenyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-imidazole 2a and 3-chloro-*N*-(2,2,2-trifluoro-1-phenylethyl)aniline 3a

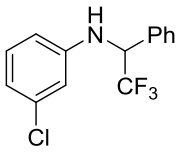
According to the TPI, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline 1a (200 mg, 0.79 mmol) was reacted with PhMgCl (1.0 M in MeTHF, 2.37 mL, 2.37 mmol) in dry THF (12 mL) for 3 h at 0 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/DCM 20:1) to give the desired imidazole derivative 2a (125 mg, 70%) as a yellow solid and 3-chloro-*N*-(2,2,2-trifluoro-1-phenylethyl)aniline 3a (36 mg, 16%) as a light yellow liquid.

1,3-*bis*(3-Chlorophenyl)-4-fluoro-5-phenyl-2-(trifluoromethyl)-2,3-dihydro-1*H*-imidazole 2a



R_f (cyclohexane/ethyl acetate 10:1) = 0.60. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.51 – 7.46 (m, 2 H, H2", H6"), 7.38 – 7.33 (m, 2 H, H3", H5"), 7.31 – 7.24 (m, 2 H, H4", H5'), 7.15 (tdd, $J_{H2',H4'} = J_{H2',H6'}$ = 1.9 Hz, $J_{H2',H5'} = J_{H2',CH}$ = 0.4 Hz, 1 H, H2'), 7.12 (ddd, $J_{H4',H5'}$ = 8.0 Hz, $J_{H4',H2'}$ = 1.9 Hz, $J_{H4',H6'}$ = 0.9 Hz, 1 H, H4'), 7.12 (ddd, $J_{H5,H6}$ = 8.1 Hz, $J_{H5,H4}$ = 7.7 Hz, $J_{H5,H2}$ = 0.7 Hz, 1 H, H5), 7.05 (dtd, $J_{H6',H5'}$ = 8.1 Hz, $J_{H6',H2'}$ = 2.3 Hz, $J_{H6',H4'}$ = 0.9 Hz, 1 H, H6'), 7.03 – 6.99 (m, 2 H, H2, H4), 6.88 (ddd, $J_{H6,H5}$ = 8.1 Hz, $J_{H6,H2}$ = 2.2 Hz, $J_{H6,H4}$ = 1.1 Hz, 1 H, H6), 5.11 – 5.03 (m, 1 H, CH) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$): δ = −83.32 (d, $J_{CF_3,CH}$ = 4.9 Hz, CF_3), −135.19 (dt, $J_{CF,CH}$ = 4.5 Hz, J = 2.2 Hz, CF) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 149.11 (d, $J_{C,F}$ = 1.5 Hz, C1), 147.25 (d, $J_{C,F}$ = 277.5 Hz, CF), 145.46 (d, $J_{C,F}$ = 6.0 Hz, C1'), 135.81 (C3'), 135.46 (C3), 131.11 (C5'), 130.71 (C5), 129.16 (d, $J_{C,F}$ = 0.9 Hz, C3", C5"), 128.67 (d, $J_{C,F}$ = 7.0 Hz, C1"), 128.12 (d, $J_{C,F}$ = 2.0 Hz, C4"), 126.51 (d, $J_{C,F}$ = 5.1 Hz, C2", C6"), 125.37 (C4'), 124.91 (C4), 122.69 (q, $J_{C,F}$ = 282.9 Hz, CF_3), 121.46 (C2), 120.08 (d, $J_{C,F}$ = 2.4 Hz, C2'), 119.30 (C6), 117.87 (d, $J_{C,F}$ = 1.9 Hz, C6'), 110.52 (d, $J_{C,F}$ = 21.8 Hz, FC*C*N), 85.10 (qd, $J_{C,F}$ = 34.7 Hz, $J_{C,F}$ = 5.4 Hz, CH) ppm. **HRMS** (EI): *m/z* calcd. for $C_{22}H_{14}Cl_2F_4N_2^{\cdot}$ [$M^{\cdot}$] 452.0470, found 452.0467. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 17.20 min, λ = 214 nm. **mp** 93 °C.

3-Chloro-*N*-(2,2,2-trifluoro-1-phenylethyl)aniline 3a

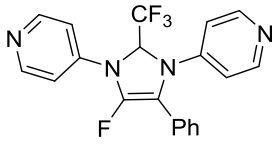


^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 – 7.36 (m, 5 H, 5 × H_{phenyl}), 7.07 (t, $J_{H5,H4} = J_{H5,H6}$ = 8.1 Hz, 1 H, H5), 6.75 (ddd, $J_{H4,H5}$ = 7.9 Hz, $J_{H4,H2}$ = 1.9 Hz, $J_{H4,H6}$ = 0.9 Hz, 1 H, H4), 6.65 (t, $J_{H2,H4} = J_{H2,H6}$ = 2.1 Hz, 1 H, H2), 6.51 (ddd, $J_{H6,H5}$ = 8.2 Hz, $J_{H6,H2}$ = 2.3 Hz, $J_{H6,H4}$ = 0.8 Hz, 1 H, H6), 4.89 (q, $J_{CH,CF3}$ = 7.2 Hz, 1 H, CH), 4.40 (s, 1 H, NH) ppm. **^{19}F NMR** (280 MHz, $CDCl_3$): δ = -74.02 (d, $J_{CF_3,CH}$ = 7.2 Hz, CF_3) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 146.62 (C1), 135.08 (C3), 133.48 ($C1_{phenyl}$), 130.32 (C5), 129.31 ($C4_{phenyl}$), 129.01 ($C3_{phenyl}$, $C5_{phenyl}$), 127.80 ($C2_{phenyl}$, $C6_{phenyl}$), 124.84 (q, $J_{C,F}$ = 282.1 Hz, CF_3), 119.24 (C4), 113.81 (C2), 112.05 (C6), 60.34 (q, $J_{C,F}$ = 30.1 Hz, *C*CF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{14}H_{13}ClF_3N^+$ $[M+H]^+$ 286.0605, found

286.0608. **HPLC-MS** (0.1% TFA, 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.52 min, λ = 220 nm.

N,*N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2b

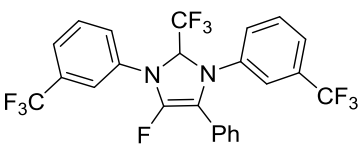
According to the TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine 1b (200 mg, 0.91 mmol) was reacted with PhMgCl (1.0 M in MeTHF, 2.72 mL, 2.72 mmol) in dry THF (12 mL) for 1.5 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, DCM → DCM/MeOH 20:1) to give the desired imidazole derivative 2b (163 mg, 93%) as a light yellow solid.



R$_f$ (ethyl acetate/MeOH 10:1) = 0.19. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.50 (d, $J_{H2,H3} = J_{H6,H5}$ = 6.5 Hz, 2 H, H2, H6), 8.34 (d, $J_{H2',H3'} = J_{H6',H5'}$ = 6.5 Hz, 2 H, H2', H6'), 7.50 – 7.42 (m, 4 H, H2", H3", H5", H6"), 7.37 (tt, $J_{H4",H3"} = J_{H4",H5"}$ = 6.7 Hz, $J_{H4",H2"} = J_{H4",H6"}$ = 2.1 Hz, 1 H, H4"), 7.25 (d, $J_{H3,H2} = J_{H5,H6}$ = 4.7 Hz, 2 H, H3, H5), 6.87 (d, $J_{H3',H2'} = J_{H5',H6'}$ = 6.4 Hz, 2 H, H3', H5'), 6.68 (q, $J_{CH,CF3}$ = 4.9 Hz, 1 H, CH) ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −82.32 (d, $J_{CF3,CH}$ = 4.9 Hz, CF_3), −133.83 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 152.42 (C4'), 150.79 (C2, C6), 150.22 (C2', C6'), 148.85 (d, $J_{C,F}$ = 6.2 Hz, C4), 146.59 (d, $J_{C,F}$ = 279.7 Hz, CF), 129.27 (C3", C5"), 128.48 (C4"), 127.57 (d, $J_{C,F}$ = 6.7 Hz, C1"), 125.71 (C2", C6"), 122.74 (q, $J_{C,F}$ = 284.6 Hz, CF_3), 114.06 (C3', C5'), 111.85 (C3, C5), 110.08 (d, $J_{C,F}$ = 24.0 Hz, FC*C*N), 79.20 (q, $J_{C,F}$ = 35.1 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{20}H_{15}F_4N_4^+$ $[M+H]^+$ 387.1233, found 387.1233. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.16 min, λ = 214 nm. **mp** 159 °C.

N,*N'*-1,3-(3-Trifluoromethylphenyl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2c

According to the TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-3-(trifluoromethyl)aniline 1c (200 mg, 0.69 mmol) was reacted with PhMgBr (3.0 M in THF, 0.69 mL, 2.06 mmol) in dry THF (10 mL) for 4 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 100:1) to give the desired imidazole derivative 2c (100 mg, 56%) as a colorless oil.

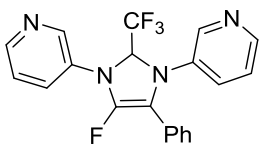


R$_f$ (ethyl acetate/MeOH 10:1) = 0.48. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.77 (d, $J_{H3,H2} = J_{H5,H6}$ = 6.4 Hz, 2 H, H3, H5), 8.62 (d, $J_{H3',H2'} = J_{H5',H6'}$ = 6.5 Hz, 2 H, H3', H5'), 7.65 (m, 2 H, H2, H6), 7.58 – 7.55 (m, 3 H, H4", H5", H6"), 7.38 – 7.33 (m, 2 H, $CHCF_3$, H2"), 7.18 (d, $J_{H2',H3'} = J_{H6',H5'}$ = 7.2 Hz, 2 H, H2', H6') ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −81.14 (d, $J_{CF3,CH}$ = 4.2 Hz, CF_3), −130.91 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 156.66 (C1'), 152.09 (d, $J_{C,F}$ = 5.9 Hz, C1), 147.28 (d, $J_{C,F}$ = 284.4 Hz, CF), 144.33 (C3, C5), 142.93 (C3', C5'), 134.30 (C3"), 131.60 (C5"), 129.24 (C4"), 128.20 (d, $J_{C,F}$ = 6.4 Hz, C1"), 125.41 (C6"), 124.42 (C2"), 114.01 (C2', C6'), 112.43 (C2,

C6), 109.17 (d, $J_{C,F}$ = 26.0 Hz, FC*C*N), 77.16 (q, $J_{C,F}$ = 35.1 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI-): *m/z* calcd. for $C_{25}H_{14}F_{10}N_2O_2^-$ [M+HCOO$^-$]$^-$ 564.0901, found 565.0980. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 19.25 min, λ = 214 nm.

N,*N'*-1,3-(Pyridin-3-yl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2d

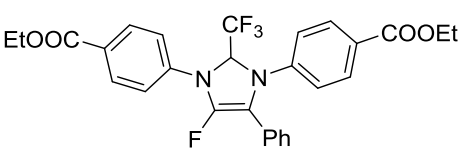
According to the TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-3-amine 1d (200 mg, 0.91 mmol) was reacted with PhMgBr (3.0 M in THF, 0.76 mL, 2.28 mmol) in dry THF (10 mL) for 3 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 1:2→ ethyl acetate/MeOH 100:1) to give the desired imidazole derivative 2d (158 mg, 90%) as a light yellow solid.



R$_f$ (ethyl acetate/MeOH 10:1) = 0.32. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.56 (t, $J_{H2,H4}$ = $J_{H2,H6}$ = 2.2 Hz, 1 H, H2), 8.39 (dd, $J_{H4,H5}$ = 4.7 Hz, $J_{H4,H6}$ = 1.4 Hz, 1 H, H4), 8.35 (dd, $J_{H2',H6'}$ = 2.8 Hz, $J_{H2',H4'}$ = 0.7 Hz, 1 H, H2'), 8.26 (dd, $J_{H4',H5'}$ = 4.7 Hz, $J_{H4',H6'}$ = 1.4 Hz, 1 H, H4'), 7.71 (ddd, $J_{H6,H5}$ = 8.3 Hz, $J_{H6,H2}$ = 2.5 Hz, $J_{H6,H4}$ = 1.4 Hz, 1 H, H6), 7.50 – 7.40 (m, 5 H, H6', H5, H2", H4", H6"), 7.34 – 7.25 (m, 2 H, H3", H5"), 7.28 (m, 3 H, H5', H3", H5"), 6.40 (q, $J_{CH,CF3}$ = 5.3 Hz, 1 H, CHCF$_3$) ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −82.81 (d, $J_{CF3,CH}$ = 5.4 Hz, CF$_3$), −136.81 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 146.66 (d, $J_{C,F}$ = 280.2 Hz, CF), 145.88 (C4), 145.32 (C4'), 143.29 (C2'), 142.60 (C1'), 141.60 (C2), 139.60 (d, $J_{C,F}$ = 5.9 Hz, C1), 129.04 (C4"), 128.69 (C6'), 128.04 (C3", C5"), 127.75 (d, $J_{C,F}$ = 6.8 Hz, C1"), 127.30 (C6), 126.05 (C2", C6"), 124.25 (C5), 123.80 (C5'), 122.78 (q, $J_{C,F}$ = 283.1 Hz, CF$_3$), 109.68 (d, $J_{C,F}$ = 22.5 Hz, FC*C*N), 81.28 (q, $J_{C,F}$ = 33.9 Hz, $J_{C,F}$ = 5.1 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{20}H_{15}F_4N_4^+$ [M+H]$^+$ 387.1233, found 387.1233. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.33 min, λ = 214 nm. **mp** 160 °C.

N,*N'*-1,3-(4-(Ethoxycarbonyl)phenyl)-2-(trifluoromethyl)-4-fluoro-5-phenyl-2,3-dihydro-1*H*-imidazole 2e

According to the TPI, ethyl-*N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-aminobenzoate 1e (200 mg, 0.69 mmol) was reacted with PhMgBr (3.0 M in THF, 0.69 mL, 2.06 mmol) in dry THF (10 mL) for 4 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 100:1→ 30:1) to give the desired imidazole derivative 2e (115 mg, 63%) as a yellow solid.

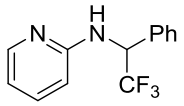


R$_f$ (cyclohexane/ethyl acetate 7:3) = 0.42. **^{1}H NMR** (600 MHz, DMSO-d_6): δ = 7.96 (d, $J_{H3,H4}$ = $J_{H5,H6}$ = 8.9 Hz, 2 H, H3, H5), 7.80 (d, $J_{H3',H4'}$ = $J_{H5',H6'}$ = 8.9 Hz, 2 H, H3', H5'), 7.47 – 7.41 (m, 4 H, H2", H3", H5", H6"), 7.36 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 8.9 Hz, 2 H, H2, H6), 7.35 – 7.31 (m, 1 H, H4") 7.08 (d, $J_{H2',H3'}$ = $J_{H6',H5'}$ = 8.8 Hz, 2 H, H2', H6'), 6.43 (q, $J_{CH,CF3}$ = 5.1 Hz, 1 H, CHCF$_3$), 4.28 (q, $J_{CH2,CH3}$ = 7.1 Hz, 2 H, CH$_2$), 4.22 (q, $J_{CH2,CH3}$ = 7.0 Hz, 2 H, CH$_2$), 1.28 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3 H, CH$_3$), 1.23 (t, $J_{CH3,CH2}$ = 7.1 Hz, 3 H, CH$_3$) ppm. **^{19}F NMR** (280 MHz, DMSO-d_6):

δ = −82.40 (d, $J_{CF_3,CH}$ = 5.1 Hz, CF_3), −134.39 (s, CF) ppm. **^{13}C NMR** (150 MHz, DMSO-d_6): δ = 165.01 (2×COOEt), 150.27 (C1'), 146.89 (d, $J_{C,F}$ = 5.6 Hz, C1), 146.87 (d, $J_{C,F}$ = 277.6 Hz, CF), 130.80 (C3, C5), 130.31 (C3', C5'), 129.11 (C3", C5"), 128.15 (C4"), 127.90 (d, $J_{C,F}$ = 6.7 Hz, C1"), 125.78 (C2", C6"), 125.45 (C4), 125.20 (C4'), 122.82 (q, $J_{C,F}$ = 283.5 Hz, CF_3), 120.27 (C2', C6'), 118.26 (C2, C6), 110.41 (d, $J_{C,F}$ = 22.9 Hz, FC*C*N), 81.32 (q, $J_{C,F}$ = 34.3 Hz, *C*HCF_3), 60.67 (CH_2), 60.51 (CH_2), 14.16 (CH_3), 14.13 (CH_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{28}H_{24}F_4N_2O_4^{\cdot}$ [$M^{\cdot}$] 528.1672, found 528.1676. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 20.30 min, λ = 214 nm. **mp** 67 – 74 °C.

N-(2,2,2-Trifluoro-1-phenylethyl)pyridin-2-amine 3f

According to TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridine-2-amine 1f (100 mg, 0.45 mmol) was reacted with PhMgBr (3.0 M in Et_2O, 0.45 mL, 1.36 mmol) in dry THF (6 mL). The crude product was purified by flash chromatography (SiO_2, cyclohexane /ethyl acetate 10:1) to give the amine 3f (115 mg, quant.) as yellow oil.

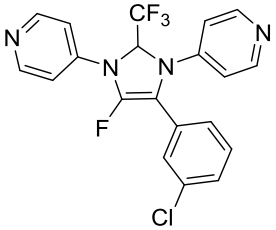


R_f (cyclohexane/ethyl acetate 19:1) = 0.14. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 8.12 (ddd, $J_{H6,H5}$ = 5.1 Hz, $J_{H6,H4}$ = 1.9 Hz, $J_{H6,H3}$ = 0.9 Hz, 1 H, H6), 7.52 – 7.34 (m, 6 H, H4, H2', H3', H4', H5', H6'), 6.66 (dd, $J_{H5,H4}$ = 7.2 Hz, $J_{H5,H6}$ = 5.1 Hz, 1 H, H5), 6.47 (dt, $J_{H3,H4}$ = 8.3 Hz, $J_{H3,H4}$ = 0.9 Hz, 1 H, H3), 5.86 (p, $J_{CH,NH}$ = J_{CH,CF_3} = 8.1 Hz, 1 H, $CHCF_3$), 5.04 (d, $J_{NH,CH}$ = 9.1 Hz, 1 H, NH) ppm. **^{19}F NMR** (280 MHz, $CDCl_3$): δ = -73.88 (d, $J_{CF_3,CH}$ = 7.9 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 156.42 (C2), 148.08 (C6), 137.77 (C4), 134.49 (q, *J*(C,F) = 1.0 Hz, C1'), 129.06 (C3', C5'), 128.96 (C4'), 128.07 (C2', C6'), 125.35 (q, *J*(C,F) = 281.9 Hz, CF_3), 114.79 (C5), 108.62 (C3), 56.52 (q, *J*(C,F) = 30.5 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{13}H_{12}F_3N_2^+$ $[M+H]^+$ 253.0953, found 253.0945. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B. Flow: 1 mL/min): t_R = 6.28 min, λ = 214 nm.

N,*N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(3-chlorophenyl)-2,3-dihydro-1*H*-imidazole 2g

The magnesium reagent was prepared from 3-bromo-1-chlorobenzene (0.16 mL, 1.36 mmol) and *i*PrMgCl·LiCl (1.2 M in THF, 1.14 mL, 1.40 mmol) according to TPII within 3.5 h at 0 °C.

According to the TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine 1b (100 mg, 0.45 mmol) was reacted with the *Grignard* reagent in dry THF (5 mL) for 3 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, ethyl acetate/MeOH 50:1 → 25:1) to give the desired imidazole derivative 2g (102 mg, quant.) as a yellow solid.



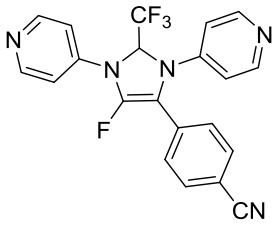
R_f (ethyl acetate/MeOH 10:1) = 0.19. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.77 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 6.4 Hz, 2 H, H2, H6), 8.62 (d, $J_{H2',H3'}$ = $J_{H6',H5'}$ = 6.5 Hz, 2 H, H2', H6'), 7.65 (d, $J_{H3,H2}$ = $J_{H5,H6}$ = 5.8 Hz, 2 H, H3, H5), 7.58 – 7.55 (m, 3 H, H4", H5", H6"), 7.38 – 7.33 (m, 2 H, $CHCF_3$, H2"), 7.18 (d, $J_{H3',H2'}$ = $J_{H5',H6'}$ = 7.2 Hz, 2 H, H3', H5') ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −81.14 (d, $J_{CF_3,CH}$ = 4.2 Hz, CF_3), −130.91 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6):

δ = 156.66 (C4'), 152.09 (d, $J_{C,F}$ = 5.9 Hz, C4), 147.28 (d, $J_{C,F}$ = 284.4 Hz, CF), 144.33 (C2, C6), 142.93 (C2', C6'), 134.30 (C3''), 131.60 (C5''), 129.24 (C4''), 128.20 (d, $J_{C,F}$ = 6.4 Hz, C1''), 125.41 (C6''), 124.42 (C2''), 114.01 (C3', C5'), 112.43 (C3, C5), 109.17 (d, $J_{C,F}$ = 26.0 Hz, FC*C*N), 77.16 (q, $J_{C,F}$ = 35.1 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{20}H_{14}ClF_4N_4^+$ [M+H]$^+$ 421.0843, found 421.0836. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.49 min, λ = 214 nm. **mp** 179 °C.

N,*N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(4-cyanophenyl)-2,3-dihydro-1*H*-imidazole 2h

The magnesium reagent was prepared from 4-bromobenzonitrile (373 mg, 2.05 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 1.90 mL, 2.25 mmol) according to TPII within 1.5 h at 0 °C.

According to the TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine 1b (135 mg, 0.61 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 2 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative 2h (95 mg, 76%) as a yellow oil.

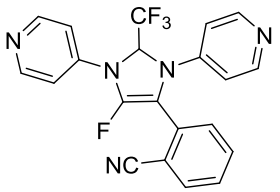


R$_f$ (ethyl acetate/MeOH 10:1) = 0.17 **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.77 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 6.5 Hz, 2 H, H2, H6), 8.63 (d, $J_{H2',H3'}$ = $J_{H6',H5'}$ = 6.0 Hz, 2 H, H2', H6'), 8.00 (d, $J_{H3'',H2''}$ = $J_{H5'',H6''}$ = 8.4 Hz, 1 H, H3'', H5''), 7.75 – 7.63 (m, 2 H, H3, H5), 7.61 (d, $J_{H6'',H5''}$ = $J_{H2'',H3''}$ = 8.4 Hz, 2 H, H2'', H6''), 7.46 – 7.31 (m, 1 H, CHCF$_3$), 7.21 – 7.12 (m, 2 H, H3', H5') ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −81.13 (m, CF$_3$), −128.03 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 156.53 (C4'), 151.56 (C4), 148.43 (d, $J_{C,F}$ = 287.0 Hz, CF), 144.72 (C2, C6), 143.20 (C2', C6'), 133.47 (C3'', C5''), 130.73 (C1''), 126.39 (C4'', C6''), 122.46 (q, $J_{C,F}$ = 286.4 Hz, CF$_3$), 118.37 (CN), 112.56 (C3', C5'), 111.18 (C3, C5), 108.79 (d, $J_{C,F}$ = 25.4 Hz, FC*C*N), 77.19 (qd, $J_{C,F}$ = 36.1 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{21}H_{14}F_4N_5^+$ [M+H]$^+$ 412.1185, found 412.1181. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.02 min, λ = 214 nm.

N,*N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(2-cyanophenyl)-2,3-dihydro-1*H*- imidazole 2i

The magnesium reagent was prepared from 2-bromobenzonitrile (491 mg, 2.70 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 2.50 mL, 3.00 mmol) according to TPII within 3 h at 0 °C.

According to the TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine 1b (200 mg, 0.91 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 3 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative 2i (151 mg, 81%) as a yellow solid.

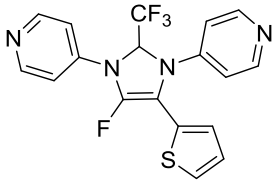


R_f (ethyl acetate/MeOH 10:1) = 0.18. **^{1}H NMR** (600 MHz, DMSO-d_6): δ = 8.56 (d, $J_{H2,H3} = J_{H6,H5}$ = 6.6 Hz, 2 H, H2, H6), 8.38 (d, $J_{H2',H3'} = J_{H6',H5'}$ = 6.5 Hz, 2 H, H2', H6'), 7.84 (d, $J_{H3'',H4''}$ = 7.8 Hz, 1 H, H3''), 7.62 (td, $J_{H5'',H4''} = J_{H5'',H6''}$ = 7.7 Hz, $J_{H5'',H3''}$ = 1.4 Hz, 1 H, H5''), 7.55 (d, $J_{H6'',H5''}$ = 7.8 Hz, 1 H, H6''), 7.50 (t, $J_{H4'',H3''}$ = 7.6, $J_{H4'',H5''}$ = 7.6 Hz, 1 H, H4''), 7.11 – 7.06 (m, 2 H, H3, H5), 6.74 (d, $J_{H3',H2'} = J_{H5',H6'}$ = 6.5 Hz, 2 H, H3', H5'), 5.45 (q, J_{CH,CF_3} = 4.6 Hz, 1 H, $CHCF_3$) ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −82.57 (d, $J_{CF_3,CH}$ = 4.6 Hz, CF_3), −125.75 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 152.95 (C4'), 151.41 (C2, C6), 151.06 (C2', C6'), 149.52 (d, $J_{C,F}$ = 5.9 Hz, C4), 147.72 (d, $J_{C,F}$ = 282.6 Hz, CF), 134.30 (C3''), 133.57 (C5''), 131.27 (d, $J_{C,F}$ = 6.2 Hz, C1''), 129.61 (C4''), 128.40 (C6''), 122.27 (q, $J_{C,F}$ = 283.9 Hz, CF_3), 117.39 (CN), 113.57 (C3', C5'), 112.33 (C3, C5), 111.31 (C2''), 107.63 (d, $J_{C,F}$ = 25.2 Hz, FC*C*N), 82.34 (qd, $J_{C,F}$ = 36.3 Hz, $J_{C,F}$ = 3.8 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{21}H_{14}F_4N_5^+$ $[M+H]^+$ 412.1185, found 412.1177. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 8.82 min, λ = 214 nm. **mp** 94 °C.

N,*N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(thiophen-2-yl)-2,3-dihydro-1*H*-imidazole 2j

The magnesium reagent was prepared from 2-bromothiophene (259 mg, 1.59 mmol) and *i*PrMgCl·LiCl (1.25 M in THF, 1.40 mL, 1.70 mmol) according to **TPII** within 3.5 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (100 mg, 0.45 mmol) was reacted with the *Grignard* reagent in dry THF (5 mL) for 3 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, ethyl acetate/MeOH 25:1) to give the desired imidazole derivative **2j** (95 mg, quant.) as a yellow oil.



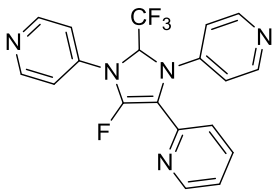
R_f (ethyl acetate/MeOH 10:1) = 0.17. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.51 – 8.47 (m, 2 H, H2, H6), 8.41 – 8.36 (m, 2 H, H2', H6'), 7.67 (dd, $J_{H3'',H4''}$ = 5.1 Hz, $J_{H3'',H5''}$ = 1.2 Hz, 1 H, H3''), 7.24 – 7.20 (m, 2 H, H3, H5), 7.19 (dd, $J_{H5'',H4''}$ = 3.7 Hz, $J_{H5'',H3''}$ = 1.2 Hz, 1 H, H3''), 7.15 (dd, $J_{H4'',H3''}$ = 5.0 Hz, $J_{H4'',H5''}$ = 3.7 Hz, 1 H, H4''), 6.99 – 6.93 (m, 2 H, H3', H5'), 6.65 (q, J_{CH,CF_3} = 4.9 Hz, 1 H, $CHCF_3$) ppm. **^{19}F NMR** (280 MHz, DMSO-d_6): δ = −82.32 (d, $J_{CF_3,CH}$ = 4.8 Hz, CF_3), −132.78 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 152.47 (C4'), 150.82 (C2, C6), 150.31 (C2', C6'), 148.79 (d, $J_{C,F}$ = 6.4 Hz, C4), 145.38 (d, $J_{C,F}$ = 279.5 Hz, CF), 129.18 (d, $J_{C,F}$ = 8.5 Hz, C1''), 128.20 (C4''), 127.49 (C3''), 126.04 (C5''), 122.60 (q, $J_{C,F}$ = 284.2 Hz, CF_3), 114.39 (C3', C5'), 111.83 (C3, C5), 106.21 (d, $J_{C,F}$ = 26.4 Hz, FC*C*N), 79.53 (q, $J_{C,F}$ = 34.4 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{18}H_{13}F_4N_4S^+$ $[M+H]^+$ 393.0797, found 393.0786. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 9.02 min, λ = 214 nm.

_N_,_N'_-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(pyridin-2-yl)-2,3-dihydro-1_H_-imidazole 2k

The magnesium reagent was prepared from 2-bromopyridine (130 µL, 1.36 mmol) and *i*PrMgCl·LiCl (1.25 M in THF, 1.14 mL, 1.40 mmol) according to **TPII** within 3 h at 0 °C.

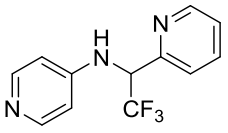
According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (100 mg, 0.45 mmol) was reacted with the *Grignard* reagent in dry THF (5 mL) for 2 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, ethyl acetate/MeOH 50:1 → 10:1) to give the desired imidazole derivative **2k** (37 mg, 42%) as a yellow oil and *N*-(2,2,2-trifluoro-1-(pyridin-2-yl)ethyl)pyridin-4-amine **3k** (44 mg, 39%) as a yellow oil.

_N_,_N'_-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(pyridin-2-yl)-2,3-dihydro-1_H_-imidazole 2k



R$_f$ (ethyl acetate/MeOH 10:1) = 0.18. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.62 (dd, $J_{H3'',H4''}$ = 4.7 Hz, J = 2.7 Hz, 1 H, H3''), 8.52 - 8.48 (m, 2 H, H2, H6), 8.36 – 8.33 (m, 2 H, H2', H6'), 7.86 (td, $J_{H5'',H4''} = J_{H5'',H6''}$ = 7.8 Hz, J = 1.9 Hz, 1 H, H5''), 7.40 (d, $J_{H6'',H5''}$ = 7.9 Hz, 1 H, H6''), 7.33 (ddd, $J_{H4'',H5''}$ = 7.6 Hz, $J_{H4'',H3''}$ = 4.8 Hz, J = 1.1 Hz, 1 H, H4''), 7.28 – 7.22 (m, 2 H, H3, H5), 6.86 – 6-82 (m, 2 H, H3', H5'), 6.72 (q, J_{CH,CF_3} = 4.6 Hz, 1 H, $CHCF_3$) ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −82.05 (d, $J_{CF_3,CH}$ = 4.8 Hz, CF_3), −128.03 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 152.65 (C4'), 150.85 (C2, C6), 150.10 (C2', C6'), 149.95 (C3''), 148.10 (d, $J_{C,F}$ = 6.0 Hz, C4), 147.27 (d, $J_{C,F}$ = 7.8 Hz, C2''), 146.03 (d, $J_{C,F}$ = 272.5 Hz, CF), 137.26 (C5''), 122.74 (C4''), 122.73 (q, $J_{C,F}$ = 285.2 Hz, CF_3), 121.25 (C6''), 113.98 (C3', C5'), 111.89 (C3, C5), 109.56 (d, $J_{C,F}$ = 20.3 Hz, FC*C*N), 78.97 (q, $J_{C,F}$ = 35.1 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{19}H_{14}F_4N_5^+$ $[M+H]^+$ 388.1185, found 388.1175. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 7.77 min, λ = 214 nm.

***N*-(2,2,2-Trifluor-1-(pyridin-2-yl)ethyl)pyridin-4-amine 3k**

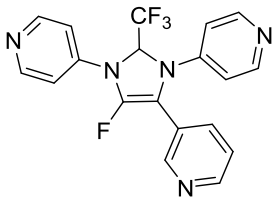


R$_f$ (ethyl acetate/MeOH 10:1) = 0.10. **^{1}H NMR** (600 MHz, DMSO-d_6): δ = 8.65 (ddd, $J_{H3',H4'}$ =4.8 Hz, $J_{H3',H5'}$ = 1.8 Hz, $J_{H3',H6'}$ = 0.9 Hz, 1 H, H3'), 8.09 (d, $J_{H2,H3} = J_{H6,H5}$ = 6.6 Hz, 2 H, H2/H6), 7.90 (td, $J_{H5',H4'} = J_{H5',H6'}$ = 7.7 Hz, $J_{H5',H3'}$ = 1.8 Hz, 1 H, H5'), 7.67 (d, $J_{H6',H5'}$ = 7.9 Hz, 1 H, H6'), 7.47 – 7.43 (m, 2 H, H4', NH), 6.88 (d, $J_{H3,H2} = J_{H5,H6}$ = 6.5 Hz, 2 H, H3, H5), 5.83 (dq, $J_{CH,NH}$ = 9.6 Hz, J_{CH,CF_3} = 7.6 Hz, 1 H, $CHCF_3$) ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −71.76 (d, $J_{CF_3,CH}$ = 7.6 Hz, CF_3) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 152.47 – 152.46 (m, C1'), 152.33 (C4), 149.51 (C2, C6), 149.37 (C3'), 137.38 (C5'), 125.12 (q, $J_{C,F}$ = 283.9 Hz, CF_3), 124.28 (C4'), 123.79 (C6'), 108.33 (C3, C5), 57.18 (q, $J_{C,F}$ = 29.4 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{12}H_{11}F_3N_3^+$ $[M+H]^+$ 254.0905, found 254.0897. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 8.78 min, λ = 214 nm.

_N,N'_-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(pyridin-3-yl)-2,3-dihydro-1_H_-imidazole 2l

The magnesium reagent was prepared from 3-bromopyridine (0.26 mL, 2.70 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 2.50 mL, 3.00 mmol) according to TPII within 2 h at 0 °C.

According to the TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (200 mg, 0.91 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 2 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative 2l (171 mg, 97%) as a yellow solid.

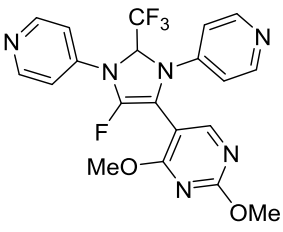


R$_f$ (ethyl acetate/MeOH 10:1) = 0.10. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.70 – 8.66 (m, 1 H, H2''), 8.55 (dd, $J_{H6'',H5''}$ = 4.8 Hz, $J_{H6'',H4''}$ = 1.6 Hz, 1 H, H6''), 8.54 – 8.50 (m, 2 H, H2, H6), 8.40 – 8.33 (m, 2 H, H2', H6'), 7.76 (ddd, $J_{H4'',H5''}$ = 8.0 Hz, $J_{H4'',H2''}$ = 2.5 Hz, $J_{H4'',H6''}$ = 1.7 Hz, 1 H, H4''), 7.47 (ddd, $J_{H5'',H4''}$ = 8.0 Hz, $J_{H5'',H6''}$ = 4.8 Hz, $J_{H5'',H2''}$ = 0.9 Hz , 1 H, H5''), 7.30 – 7.24 (m, 2 H, H3, H5), 6.92 – 6.88 (m, 2 H, H3', H5'), 6.73 (q, J_{CH,CF_3} = 4.9 Hz, 1 H, $CHCF_3$) ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −82.40 (d, $J_{CF_3,CH}$ = 4.9 Hz, CF_3), −131.84 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 152.43 (C4'), 150.41 (C2, C6), 149.71 (C2', C6'), 149.34 (C6''), 148.59 (d, $J_{C,F}$ = 6.1 Hz, C4), 147.62 (d, $J_{C,F}$ = 281.2 Hz, CF), 146.47 (d, $J_{C,F}$ = 5.4 Hz, C2''), 132.91 (C4''), 124.22 (C5''), 123.91 – 123.84 (m, C3''), 122.64 (q, $J_{C,F}$ = 284.4 Hz, CF_3), 114.24 (C3', C5'), 112.06 (C3, C5), 107.18 (d, $J_{C,F}$ = 25.0 Hz, FC*C*N), 79.11 (q, $J_{C,F}$ = 35.3 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{19}H_{14}F_4N_5^+$ $[M+H]^+$ 388.1185, found 388.1180. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 7.31 min, λ = 214 nm. **mp** 95 – 98 °C.

_N,N'_-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(2,4-dimethoxypyrimidin-5-yl)-2,3-dihydro-1_H_-imidazole 2m

The magnesium reagent was prepared from 5-bromo-2,4-dimethoxypyrimidine (449 mg, 2.05 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 1.90 mL, 2.25 mmol) according to TPII within 1 h at 0 °C.

According to the TPI, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (150 mg, 0.68 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 2 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative 2m (120 mg, 79%) as a yellow solid.



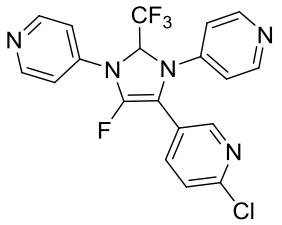
R$_f$ (ethyl acetate/MeOH 10:1) = 0.17. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.50 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 4.4 Hz, 2 H, H2, H6), 8.32 (d, $J_{H2',H3'}$ = $J_{H6',H5'}$ = 4.5 Hz, 2 H, H2', H6'), 8.31 (s, 1 H, H6''), 7.18 (d, $J_{H3,H2}$ = $J_{H5,H6}$ = 4.5 Hz, 2 H, H3, H5), 6.83 (d, $J_{H3',H2'}$ = $J_{H5',H6'}$ = 4.3 Hz, 2 H, H3', H5'), 6.68 (q, J_{CH,CF_3} = 4.8 Hz, 1 H, $CHCF_3$), 4.02 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3) ppm. **^{19}F NMR** (280 MHz, DMSO-d_6: δ = −82.11 (d, $J_{CF_3,CH}$ = 4.9 Hz, CF_3), −130.90 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 167.51 (*C*OCH_3), 165.40 (*C*OCH_3), 157.97 (C6''), 152.30 (C4'), 151.26 (C2, C6), 150.82 (C2', C6'), 149.39

(d, $J_{C,F}$ = 6.0 Hz, C4), 146.48 (d, $J_{C,F}$ = 277.2 Hz, CF), 123.11 (d, $J_{C,F}$ = 277.2 Hz, CF_3), 113.72 (C3', C5'), 112.18 (C3, C5), 103.69 (d, $J_{C,F}$ = 27.3 Hz, FC*C*N), 103.64 (d, $J_{C,F}$ = 6.0 Hz, C1''), 79.13 (q, $J_{C,F}$ = 30.4 Hz, *C*HCF_3), 55.37 (OCH_3), 55.11 (OCH_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{20}H_{17}F_4N_6O_2^+$ $[M+H]^+$ 449.1349, found 449.1338. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 8.28 min, λ = 214 nm. **mp** 154 °C.

N,*N'*-1,3-(Pyridin-4-yl)-2-(trifluoromethyl)-4-fluoro-5-(6-chloropyridin-3-yl)-2,3-dihydro-1*H*-imidazole 2n

The magnesium reagent was prepared from 3-bromo-2-chloropyridine (520 mg, 2.70 mmol) and *i*PrMgCl·LiCl (1.20 M in THF, 2.50 mL, 3.00 mmol) according to TPII within 1 h at 0 °C.

According to the **TPI**, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (200 mg, 0.91 mmol) was reacted with the *Grignard* reagent in dry THF (7 mL) for 4 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, ethyl acetate/MeOH 100:1 → 10:1) to give the desired imidazole derivative **2n** (130 mg, 69%) as a yellow solid.

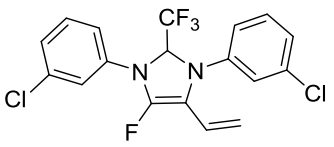


R_f (ethyl acetate/MeOH 10:1) = 0.25. **^{1}H NMR** (400 MHz, DMSO-d_6): δ = 8.53 – 8.50 (m, 2 H, H2, H6), 8.50 – 8.49 (m, 1 H, H2''), 8.42 – 8.36 (m, 2 H, H2', H6'), 7.79 (dd, $J_{H4'',H5''}$ = 8.4 Hz, $J_{H4'',H2''}$ = 2.5 Hz, 1 H, H4''), 7.62 (dd, $J_{H5'',H4''}$ = 8.4 Hz, $J_{H5'',H3''}$ = 0.7 Hz, 1 H, H5''), 7.32 – 7.22 (m, 2 H, H3, H5), 6.95 – 6.88 (m, 2 H, H3', H5'), 6.74 (q, J_{CH,CF_3} = 4.9 Hz, 1 H, $CHCF_3$) ppm. **^{19}F NMR** (380 MHz, DMSO-d_6): δ = −82.39 (d, $J_{CF_3,CH}$ = 4.9 Hz, CF_3), −130.50 (s, CF) ppm. **^{13}C NMR** (100 MHz, DMSO-d_6): δ = 151.87 (C4'), 150.83 (C2, C6), 150.45 (C2', C6'), 149.34 (C6''), 148.24 (d, $J_{C,F}$ = 6.1 Hz, C4), 146.58 (d, $J_{C,F}$ = 5.8 Hz, C3'', C2''), 136.19 (C4''), 122.52 (d, $J_{C,F}$ = 7.2 Hz, C5''), 122.62 (q, $J_{C,F}$ = 284.5 Hz, CF_3), 114.33 (C3', C5'), 112.11 (C3, C5), 106.12 (d, $J_{C,F}$ = 24.6 Hz, FC*C*N), 79.27 (q, $J_{C,F}$ = 34.8 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{19}H_{13}ClF_4N_5^+$ $[M+H]^+$ 422.0790, found 422.0790. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 7.76 min, λ = 214 nm. **mp** 63 – 73 °C

N,*N'*-1,3-(3-Chlorophenyl)-2-(trifluoromethyl)-4-fluoro-5-vinyl-2,3-dihydro-1*H*-imidazole 2o

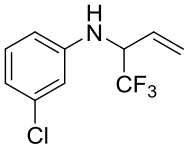
According to the TPI, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline 1a (230 mg, 0.90 mmol) was reacted with vinyl magnesium chloride (1 M in THF, 1.81 mL, 1.81 mmol) in dry THF (12 mL) for 1 h at −15 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane → cyclohexane/DCM 20:1) to give the desired imidazole derivative 2o (30 mg, 17%) as a blue liquid and 3-chloro-*N*-(1,1,1-trifluorobut-3-en-2-yl)aniline 3o (131 mg, 62%) as a colorless liquid.

_N,N'_-1,3-(3-Chlorophenyl)-2-(trifluoromethyl)-4-fluoro-5-vinyl-2,3-dihydro-1_H_-imidazole 2o



^{1}H NMR (400 MHz, DMSO-d_6): δ =7.40 (t, $J_{H5,H4} = J_{H5,H6}$ = 8.1 Hz, 1 H, H5), 7.34 (t, $J_{H5,H4} = J_{H5,H6}$ = 8.1 Hz, 1 H, H5), 7.21 (ddd, $J_{H6,H5}$ = 8.0 Hz, $J_{H6,H5}$ = 2.0 Hz, J = 0.9 Hz, 1 H, H6), 7.18 – 7.10 (m, 3 H, H4, 2 × H2), 7.08 (t, $J_{H2,H4} = J_{H2,H6}$ = 2.1 Hz, 1 H, H4), 7.04 (ddd, $J_{H6,H5}$ = 8.1 Hz, $J_{H6,H5}$ = 2.3 Hz, J = 0.9 Hz, 1 H, H6), 6.63 – 6.46 (m, 1 H, CH_2=C*H*), 6.22 (q, $J_{CH,CF3}$ = 5.2 Hz, 1 H, CH), 5.20 (dt, $J_{CH=CHcis,CH=CH2}$ = 11.2 Hz, J = 1.6 Hz, 1 H, HCH_{cis}=CH), 4.89 (dt, $J_{CH=CHtrans,CH=CH2}$ = 17.4 Hz, J = 1.4 Hz, 1 H, HCH_{trans}=CH) ppm.**^{19}F NMR** (380 MHz, DMSO-d_6): δ = -82.55 (d, $J_{CF3,CH}$ = 5.9 Hz, CF_3), -136.94 (s, CF) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 147.64, 143.85, 133.98, 133.40, 131.22, 130.61, 124.86, 124.52, 124.20, 121.50, 121.43, 121.00, 119.64, 119.22, 117.66, 117.63, 115.52, 115.47, 112.15, 109.86 (d, $J_{C,F}$ = 24.5 Hz) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{18}H_{13}Cl_2F_4N_2^+$ $[M+H]^+$ 403.0386, found 403.0389. **HPLC-MS** (0.05% formic acid, 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 3.19 min, λ = 220 nm.

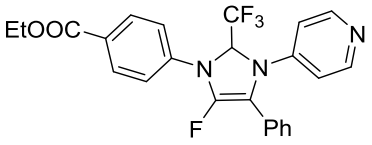
3-Chloro-_N_-(2,2,2-trifluoro-1-vinylethyl)aniline 3o



^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.11 (t, $J_{H5,H4} = J_{H5,H6}$ = 8.1 Hz, 1 H, H5), 6.87 (t, $J_{H2,H4} = J_{H2,H6}$ = 2.1 Hz, 1 H, H2), 6.77 (dd, $J_{H6,H5}$ = 8.0 Hz, $J_{H6,H2}$ = 2.0 Hz, 1 H, H6), 6.64 (ddd, $J_{H4,H5}$ = 7.8 Hz, $J_{H4,H2}$ = 2.0 Hz, $J_{H4,H6}$ = 0.8 Hz, 1 H, H4), 6.48 (d, $J_{NH,CH}$ = 9.7 Hz, 1 H, NH), 5.86 (ddd, $J_{CH=CH2,CH=CHtrans}$ = 16.8 Hz, $J_{CH=CH2,CH=CHcis}$ = 10.4 Hz, $J_{CH=CH2,CH}$ = 6.2 Hz, 1 H, CH_2=C*H*), 5.56 (d, $J_{CH=CHtrans,CH=CH2}$ = 17.1 Hz, 1 H, HCH_{trans}=CH), 5.43 (d, $J_{CH=CHcis,CH=CH2}$ = 10.4 Hz, 1 H, HCH_{cis}=CH), 5.10 – 4.97 (m, 1 H, CH) ppm. **^{19}F NMR** (377 MHz, DMSO-d_6): δ = −73.77 (d, $J_{CF3,CH}$ = 7.7 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d_6): δ = 148.36 (C1), 133.62(C3), 130.36 (C5), 129.80 (CH_2=*C*H), 125.52 (q, $J_{C,F}$ = 283.4 Hz, CF_3), 120.83 (*C*H_2=CH), 116.70 (C4), 112.31 (C2), 111.71 (C6), 55.83 (q, $J_{C,F}$ = 29.4 Hz, *C*CF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{10}H_{10}ClF_3N^+$ $[M+H]^+$ 236.0448, found 236.0452. **HPLC-MS** (0.05% formic acid, 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.53 min, λ = 220 nm.

Ethyl 4-(5-fluoro-4-phenyl-3-(pyridin-4-yl)-2-(trifluoromethyl)-2,3-dihydro-1_H_-imidazol-1-yl)benzoate 2p

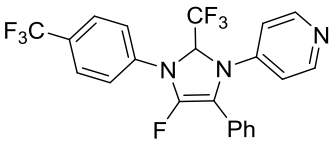
According to the **TPIII**, ethyl 4-((1-ethoxy-2,2,2-trifluoroethyl)amino)benzoate **1e** (60 mg, 0.20 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (52 mg, 0.20 mmol) were reacted with *n*BuLi (1.6 M in hexane, 0.38 mL, 0.60 mmol) in dry THF (6 mL) for 4 h at −30 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 2:1 → ethyl acetate) to give desired imidazole derivative **2p** (57 mg, 62%) as a yellow oil, ethyl 4-((1-ethoxy-2,2,2-trifluoroethyl)amino)benzoate **1e** (25 mg, 37%) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (17 mg, 34%).



R_f (cyclohexane/ethyl acetate 3:1) = 0.50. **^{1}H NMR** (400 MHz, $CDCl_3$): δ =8.33 (d, $J_{H2',H3'} = J_{H6',H5'}$ = 5.5 Hz, 2 H, H2', H6'), 8.06 – 8.00 (m, 2 H, H3, H5), 7.48 (d, $J_{H2'',H3''} = J_{H6'',H5''}$ = 7.3 Hz, 2 H, H2'', H6''), 7.40 (t, $J_{H3'',H4''} = J_{H5'',H4''} = J_{H3'',H2''} = J_{H5'',H6''}$ = 7.6 Hz, 2 H, H3'', H5''), 7.33 (d, J = 7.3 Hz, 1 H, H4''), 7.17 (dd, $J_{H2,H3} = J_{H6,H5}$ = 8.8 Hz, J = 2.4 Hz, 2 H, H2, H6), 6.77 (d, $J_{H3',H2'} = J_{H5',H6'}$ = 6.0 Hz, 2 H, H3', H5'), 5.34 (dq, J_{CH,CF_3} = 4.8 Hz, 1 H, CH), 4.35 (q, J_{CH_2,CH_3} = 7.1 Hz, 2 H, CH_2), 1.36 (t, J_{CH_3,CH_2} = 7.1 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (380 MHz, $CDCl_3$): δ = −82.76 (d, $J_{CF_3,CH}$ = 4.9 Hz, CF_3), −131.73 (s, CF) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 165.79 (*C*OOEt), 154.01 (C4'), 150.69 (C2', C6'), 147.42 (d, $J_{C,F}$ = 277.8 Hz, CF), 147.19 (d, $J_{C,F}$ = 6.0 Hz, C1), 131.57 (C3, C5), 129.18 (C3'', C5''), 128.35 (C4''), 128.09 (d, $J_{C,F}$ = 6.8 Hz, C1''), 126.93, 126.13 (d, $J_{C,F}$ = 4.8 Hz, C2'', C6''), 122.45 (q, $J_{C,F}$ = 283.6 Hz, CF_3), 118.24 (C2, C6), 113.84 (C3', C5'), 109.91 (d, $J_{C,F}$ = 23.9 Hz, FC*C*N), 83.65 (qd, $J_{C,F}$ = 35.7 Hz, $J_{C,F}$ = 4.6 Hz, *C*HCF$_3$), 61.18 (CH_2), 14.44 (CH_3) ppm. **HRMS** (EI): *m/z* calcd. for $C_{24}H_{20}F_4N_3O_2^+$ $[M+H]^+$ 458.1486, found 458.14895.

4-(4-Fluoro-5-phenyl-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazol-1-yl)pyridine 2q

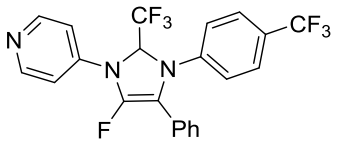
According to the TPIII, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline **1q** (57 mg, 0.20 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (50 mg, 0.20 mmol) were reacted with *n*BuLi (2.5 M in hexane, 0.18 mL, 0.44 mmol) in dry THF (6 mL) for 4 h at −30 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 5:1 → ethyl acetate) to give desired imidazole derivative **2q** (59 mg, 65%) as a yellow oil, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline **1q** (14 mg, 25%) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (17 mg, 34%).



R_f (cyclohexane/ethyl acetate 5:1) = 0.27. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.34 (dd, $J_{H2,H3} = J_{H6,H5}$ = 4.9 Hz, J = 1.4 Hz, 2 H, H2, H6), 7.62 (d, $J_{H3',H2'} = J_{H5',H6'}$ = 8.5 Hz, 2 H, H3', H5'), 7.50 – 7.46 (m, 2 H, H2'', H6''), 7.41 (t, $J_{H3'',H4'',H5''} = J_{H5'',H4'',H3''}$ = 7.4 Hz, 2 H, H3'', H5''), 7.36 – 7.30 (m, 1 H, H4''), 7.24 (dd, $J_{H2',H3'} = J_{H6',H5'}$ = 8.6 Hz, J = 2.0 Hz, 2 H, H2', H6'), 6.78 (dd, $J_{H3,H2} = J_{H5,H6}$ = 4.7 Hz, J = 1.6 Hz, 2 H, H3, H5), 5.29 (dq, J_{CH,CF_3} = 4.8 Hz, 1 H, CH) ppm. **^{19}F NMR** (380 MHz, $CDCl_3$): δ = −62.36 (CF_3), -82.91 (d, $J_{CF_3,CH}$ = 4.8 Hz, CF_3), −134.36 (s, CF) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 153.99 (d, $J_{C,F}$ = 1.4 Hz, C4), 150.80 (C2, C6), 147.28 (d, $J_{C,F}$ = 277.7 Hz, CF), 146.39 (d, $J_{C,F}$ = 6.2 Hz, C1'), 129.22 (d, $J_{C,F}$ = 0.8 Hz, C3'', C5''), 128.44 (d, $J_{C,F}$ = 1.8 Hz, C4''), 128.04 (d, $J_{C,F}$ = 6.8 Hz, C1''), 127.29 (q, $J_{C,F}$ = 3.8 Hz, C4'), 127.04 (C3', C5'), 126.17 (d, $J_{C,F}$ = 4.8 Hz, C2'', C6''), 123.94 (d, $J_{C,F}$ = 271.8 Hz, CF_3), 122.43 (q, $J_{C,F}$ = 283.2 Hz, CF_3), 119.20 – 118.90 (m, C2', C6'), 113.86 (C3, C5), 110.02 (d, $J_{C,F}$ = 23.7 Hz, FC*C*N), 83.80 (qd, $J_{C,F}$ = 35.8 Hz, $J_{C,F}$ = 4.8 Hz, *C*HCF$_3$) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{22}H_{15}F_4N_3^+$ $[M+H]^+$ 454.1149, found 454.1146. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 16.43 min, λ = 214 nm.

4-(5-Fluoro-4-phenyl-2-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1*H*-imidazol-1-yl)pyridine 2r

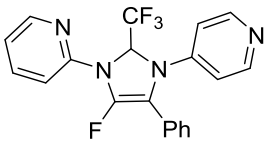
According to the TPIII, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b** (59 mg, 0.26 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)-4-(trifluoromethyl)aniline **3r** (127 mg, 0.4 mmol) were reacted with *n*BuLi (2.5 M in hexane, 0.31 mL, 0.78 mmol) in dry THF (6 mL) for 4 h at −30 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 5:1 → ethyl acetate) to give desired imidazole derivative **2r** (31 mg, 26%) as a yellow oil, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b** (43 mg, 61%) and *N*-(2,2,2-trifluoro-1-phenylethyl)-4-(trifluoromethyl)aniline **3r** (30 mg, 63%).



R$_f$ (ethyl acetate) = 0.44. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.50 (d, $J_{H2,H3} = J_{H6,H5}$ = 5.6 Hz, 2 H, H2, H6), 7.47 (m, 4 H, H3', H5', H2", H6"), 7.43 – 7.35 (m, 2 H, H3", H5"), 7.35 – 7.28 (m, 1 H, H4"), 7.06 (d, $J_{H2',H3'} = J_{H6',H5'}$ = 8.5 Hz, 2 H, H2', H6'), 7.00 (dt, $J_{H3,H2} = J_{H5,H6}$ = 4.5 Hz, J = 2.1 Hz, 2 H, H3, H5), 5.30 (dq, $J_{CH,CF3}$ = 4.8 Hz, 1 H, CH) ppm. **^{19}F NMR** (380 MHz, $CDCl_3$): δ = −62.25 (CF_3), −82.76 (d, $J_{CF3,CH}$ = 4.9 Hz, CF_3), -134.24 (s, CF) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 151.24 (C2, C6), 150.15 (C1'), 149.93 (C4), 146.28 (d, $J_{C,F}$ = 280.5 Hz, CF), 129.15 (C3", C5"), 128.77 (C4"), 128.46 (d, $J_{C,F}$ = 2.0 Hz, C1"), 127.91 (d, $J_{C,F}$ = 6.9 Hz, C3', C5'), 126.92 (q, $J_{C,F}$ = 3.8 Hz, CCF_3), 126.36 (d, $J_{C,F}$ = 5.0 Hz, C2", C6"), 120.56 (C2', C6'), 111.67 (C3, C5), 111.14 (d, $J_{C,F}$ = 21.6 Hz, FC*C*N), 83.15 (qd, $J_{C,F}$ = 35.9 Hz, $J_{C,F}$ = 4.3 Hz, *C*HCF_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{22}H_{15}F_4N_3^+$ $[M+H]^+$ 454.1149, found 454.1148. **HPLC** (0.1% TFA, 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 15.84 min, λ = 214 nm.

2-(5-Fluoro-4-phenyl-3-(pyridin-4-yl)-2-(trifluoromethyl)-2,3-dihydro-1*H*-imidazol-1-yl)pyridine 2s

According to the TPIII, *N*-(1-ethoxy-2,2,2-trifluoroethyl)aminopyridine **1b** (50 mg, 0.23 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (87 mg, 0.35 mmol) were reacted with *n*BuLi (1.6 M in hexane, 0.43 mL, 0.69 mmol) in dry THF (8 mL) for 4 h at −30 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 1:1 → ethyl acetate) to give desired imidazole derivative **2s** (75 mg, 85%) as a colorless oil.

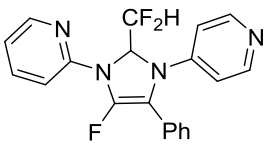


R$_f$ (ethyl acetate) = 0.50. **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.40 – 8.30 (m, 2 H, $H2_{pyrid\text{-}4\text{-}yl}$, $H6_{pyrid\text{-}4\text{-}yl}$), 8.25 (ddd, $J_{H6,H5}$ = 4.9 Hz, $J_{H6,H4}$ = 1.9 Hz, J = 0.9 Hz, 1 H, $H6_{pyrid\text{-}2\text{-}yl}$), 7.70 – 7.63 (m, 1 H, $H4_{pyrid\text{-}2\text{-}yl}$), 7.49 – 7.44 (m, 2 H, H2", H6"), 7.43 – 7.36 (m, 2 H, H3", H5"), 7.36 – 7.29 (m, 1 H, H4"), 7.19 (ddt, $J_{H3,H4}$ = 8.4 Hz, $J_{H3,H5}$ = 3.2 Hz, J = 0.9 Hz, 1H, $H3_{pyrid\text{-}2\text{-}yl}$), 6.98 (ddd, $J_{H5,H4}$ = 7.3 Hz, $J_{H5,H6}$ = 4.9 Hz, J = 0.8 Hz, 1 H, $H5_{pyrid\text{-}2\text{-}yl}$), 6.86 – 6.76 (m, 2 H, $H3_{pyrid\text{-}4\text{-}yl}$, $H5_{pyrid\text{-}4\text{-}yl}$), 6.61 (dq, $J_{CH,CF3}$ = 5.0 Hz, 1 H, CH) ppm. **^{19}F NMR** (380 MHz, $CDCl_3$): δ = −82.69 (d, $J_{CF3,CH}$ = 5.1 Hz, CF_3), −131.29 (t, J = 3.9 Hz, CF) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 154.25 (d, $J_{C,F}$ = 7.0 Hz, $H2_{pyrid\text{-}2\text{-}yl}$), 154.14 ($H4_{pyrid\text{-}4\text{-}yl}$), 150.25 ($C2_{pyrid\text{-}4\text{-}yl}$, $C6_{pyrid\text{-}4\text{-}yl}$), 148.22 ($C6_{pyrid\text{-}2\text{-}yl}$), 147.65 (d, $J_{C,F}$ = 279.1 Hz, CF), 138.75 ($C4_{pyrid\text{-}2\text{-}yl}$), 129.13 (C3", C5"), 128.43 (d, $J_{C,F}$ = 6.8 Hz, C1"), 128.16 (C4"), 126.10 (C2", C6"), 122.85 (q, $J_{C,F}$ = 284.0 Hz, CF_3), 119.06 ($C5_{pyrid\text{-}2\text{-}yl}$), 113.68, ($C3_{pyrid\text{-}4\text{-}yl}$, $C5_{pyrid\text{-}4\text{-}yl}$),

110.81 (d, J = 9.2 Hz, C3$_{\text{pyrid-2-yl}}$), 109.33 (d, $J_{C,F}$ = 25.4 Hz, FC*C*N), 78.03 (q, $J_{C,F}$ = 35.9 Hz, *C*HCF$_3$). **HRMS** (ESI+): *m/z* calcd. for $C_{20}H_{15}F_4N_4^+$ $[M+H]^+$ 387.1227, found 387.1225.

2-(2-(Difluoromethyl)-5-fluoro-4-phenyl-3-(pyridin-4-yl)-2,3-dihydro-1*H*-imidazol-1-yl)pyridine 2t

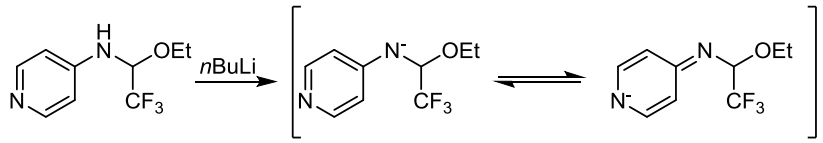
According to the TPIII, *N*-(1-ethoxy-2,2-difluoroethyl)pyridin-2-amine **1t** (36 mg, 0.18 mmol) and *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (68 mg, 0.27 mmol) were reacted with *n*BuLi (2.5 M in hexane, 0.24 mL, 0.60 mmol) in dry THF (6 mL) for 4 h at −30 °C. The crude product was purified by flash chromatography (SiO_2, cyclohexane/ethyl acetate 1:1 → ethyl acetate) to give desired imidazole derivative **2t** (50 mg, 75%) as a colorless oil.



R$_f$ (ethyl acetate) = 0.45. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.31 (d, $J_{H3,H2} = J_{H5,H6}$ = 5.4 Hz, 2 H, H2$_{\text{pyrid-4-yl}}$, H6$_{\text{pyrid-4-yl}}$), 8.24 (ddd, $J_{H6,H5}$ = 5.0 Hz, $J_{H6,H4}$ = 1.9 Hz, J = 0.9 Hz, 1 H, H6$_{\text{pyrid-2-yl}}$), 7.64 (ddd, $J_{H4,H3}$ = 8.4, $J_{H4,H5}$ = 7.3 Hz, J = 1.9 Hz, 1 H, H4$_{\text{pyrid-2-yl}}$), 7.47 (d, $J_{H2'',H3''} = J_{H6'',H5''}$ = 7.2 Hz, 2 H, H2'', H6''), 7.38 (dd, $J_{H3'',H2''} = J_{H5'',H6''}$ = 8.5 Hz, $J_{H3'',H4''} = J_{H5'',H4''}$ = 6.9 Hz, 2 H, H3'', H5''), 7.33 – 7.27 (m, 1 H, H4''), 7.13 (ddt, $J_{H3,H4}$ = 8.4 Hz, $J_{H3,H5}$ = 3.4 Hz, J = 1.0 Hz, 1 H, H3$_{\text{pyrid-2-yl}}$), 6.94 (ddd, $J_{H5,H4}$ = 7.3 Hz, $J_{H5,H6}$ = 4.9 Hz, J = 0.9 Hz, 1 H, H5$_{\text{pyrid-2-yl}}$), 6.84 – 6.73 (m, 2 H, H3$_{\text{pyrid-4-yl}}$, H5$_{\text{pyrid-4-yl}}$), 6.18 (m, 1 H, CH), 6.10 (td, J_{CHF_2,CHF_2} = 55.3 Hz, $J_{CHF_2,CH}$ = 3.3 Hz, 1 H, CF_2H) ppm. **^{19}F NMR** (380 MHz, $CDCl_3$): δ = −129.27 (ddd, J_{CHF_2,CHF_2} = 287.6, J_{CHF_2,CHF_2} = 55.0, $J_{CHF_2,CH}$ = 3.0 Hz), −132.99 (t, J = 4.1 Hz, CF), −137.21 (ddd, J_{CHF_2,CHF_2} = 287.6, J_{CHF_2,CHF_2} = 55.6, $J_{CHF_2,CH}$ = 13.9 Hz) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 154.55 (H4$_{\text{pyrid-4-yl}}$), 154.13 (d, $J_{C,F}$ = 6.7 Hz, H2$_{\text{pyrid-2-yl}}$), 150.34 (C2$_{\text{pyrid-4-yl}}$, C6$_{\text{pyrid-4-yl}}$), 148.37 (C6$_{\text{pyrid-2-yl}}$), 147.44 (d, $J_{C,F}$ = 279.4 Hz, CF), 138.59 (C4$_{\text{pyrid-2-yl}}$), 129.06 (C3'', C5''), 128.82 (d, $J_{C,F}$ = 7.0 Hz, C1''), 127.80 (C4''), 125.93 (d, $J_{C,F}$ = 4.9 Hz, C2'', C6''), 118.38 (C5$_{\text{pyrid-2-yl}}$), 115.04 – 109.77 (m, CF_2H), 113.80 (C3$_{\text{pyrid-4-yl}}$, C5$_{\text{pyrid-4-yl}}$), 110.31 (d, $J_{C,F}$ = 9.3 Hz, C3$_{\text{pyrid-2-yl}}$), 108.74 (d, $J_{C,F}$ = 24.2 Hz, FC*C*N), 81.11 – 79.62 (m, *C*HCF_2H) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{20}H_{15}F_3N_4^+$ $[M+H]^+$ 369.1322, found 369.1322.

6.3 Mechanistic experiments and NMR-studies

Deprotonation of *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine 1b with *n*BuLi

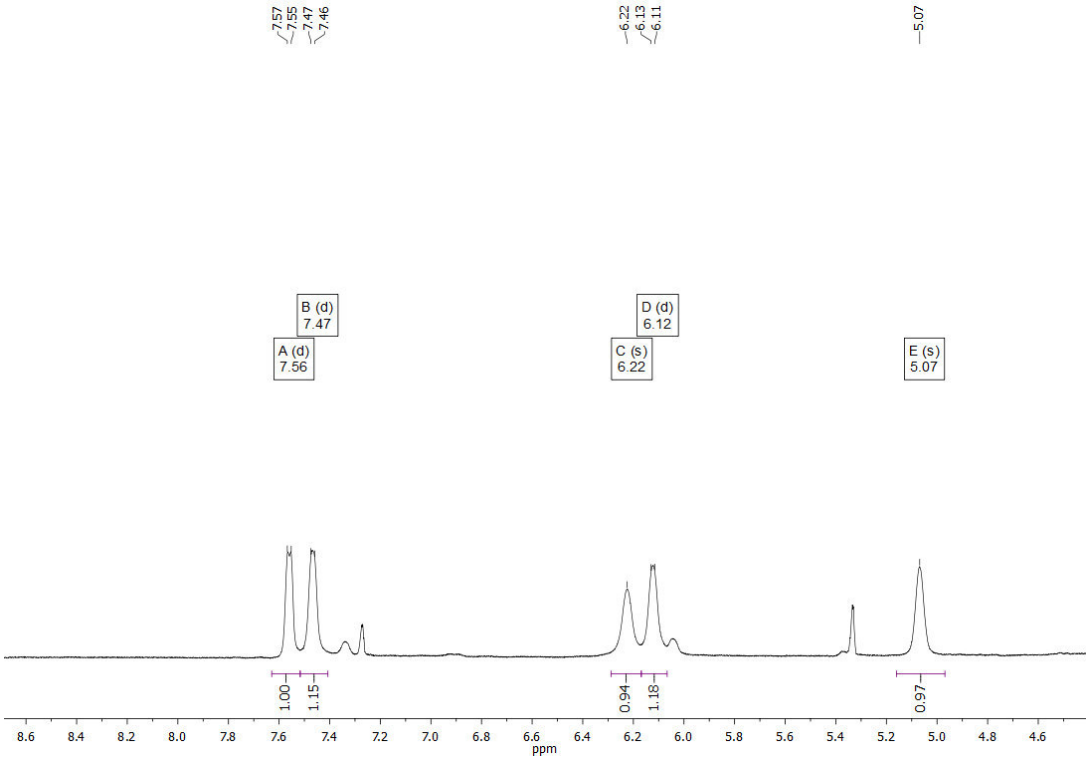


1b **5b**

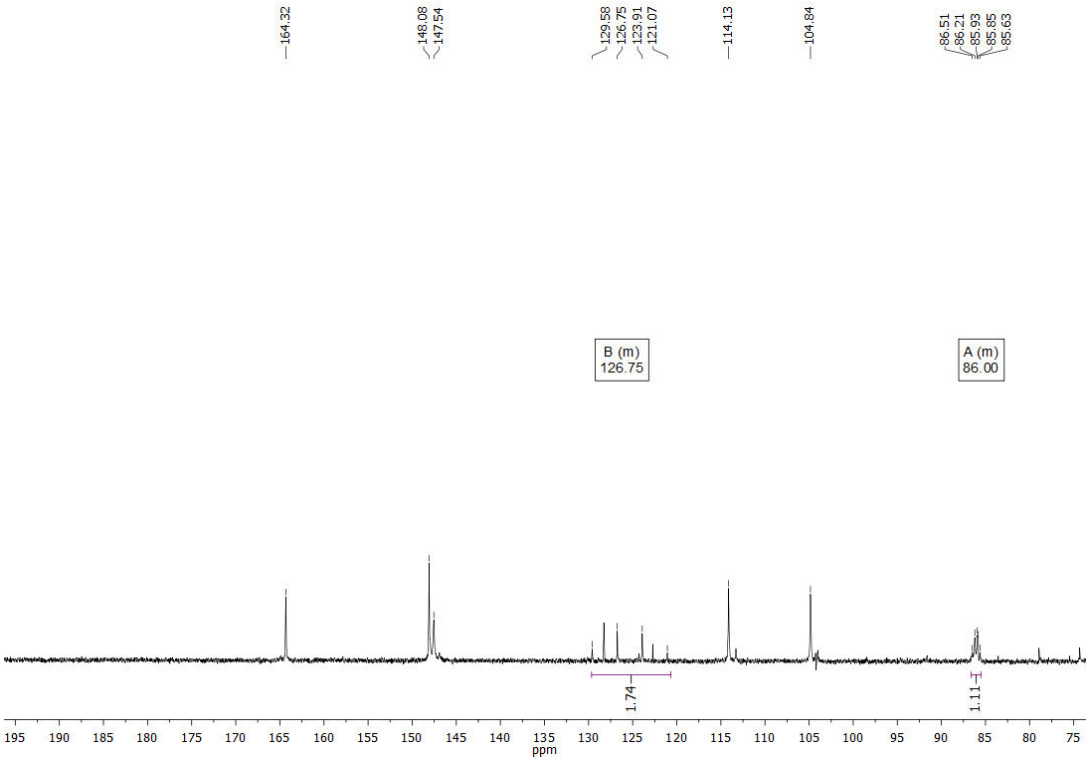
In a dry and argon flushed NMR tube containing a thin, fused capillary tube with CD_3OD, *N*,*O*-acetal **1b** (25 mg, 0.11 mmol) was solved in freshly distilled THF (0.7 mL) and cooled to −78 °C. *n*BuLi (2.5 M in hexane, 0.05 mL, 0.11 mmol) was added at once. The NMR tube was well shaken to ensure a homogeneous distribution of the base.

^{1}H, and **^{13}C NMR** were measured at −30 °C.

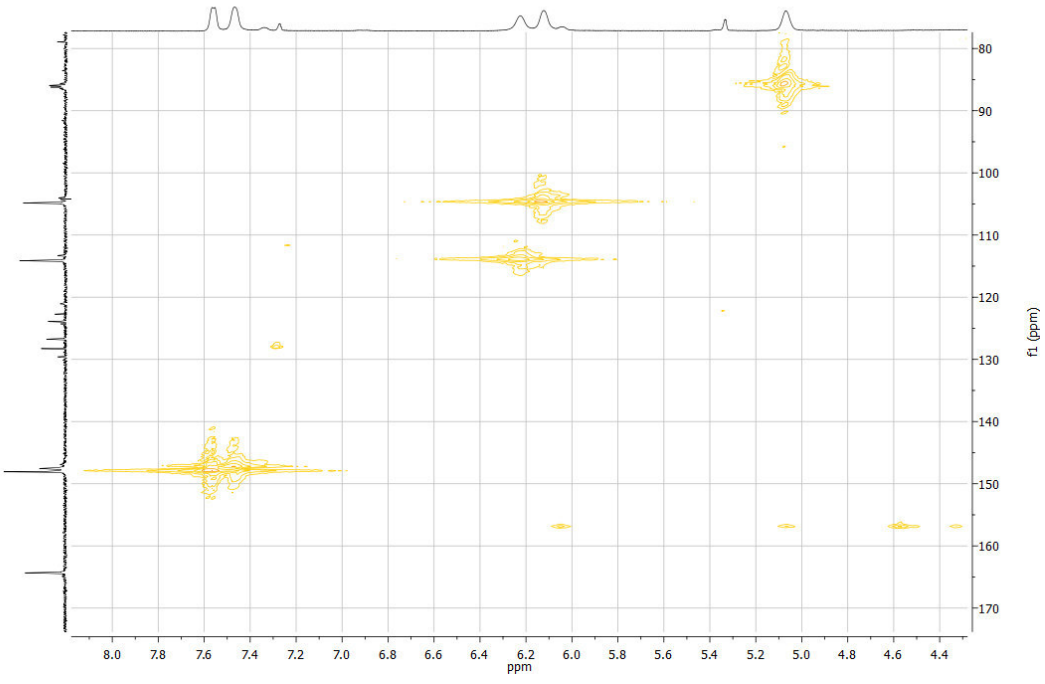
^{1}H NMR:



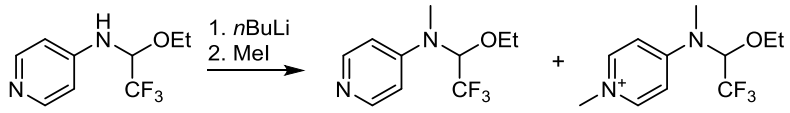
^{13}C NMR:


164.32
148.08
147.54
129.58
126.75
123.91
121.07
114.13
104.84
86.51
86.21
85.93
85.85
85.63
B (m)
126.75
A (m)
86.00
1.74
1.11
ppm

HSQC:


f1 (ppm)
ppm

Deprotonation of *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine 1b with *n*BuLi

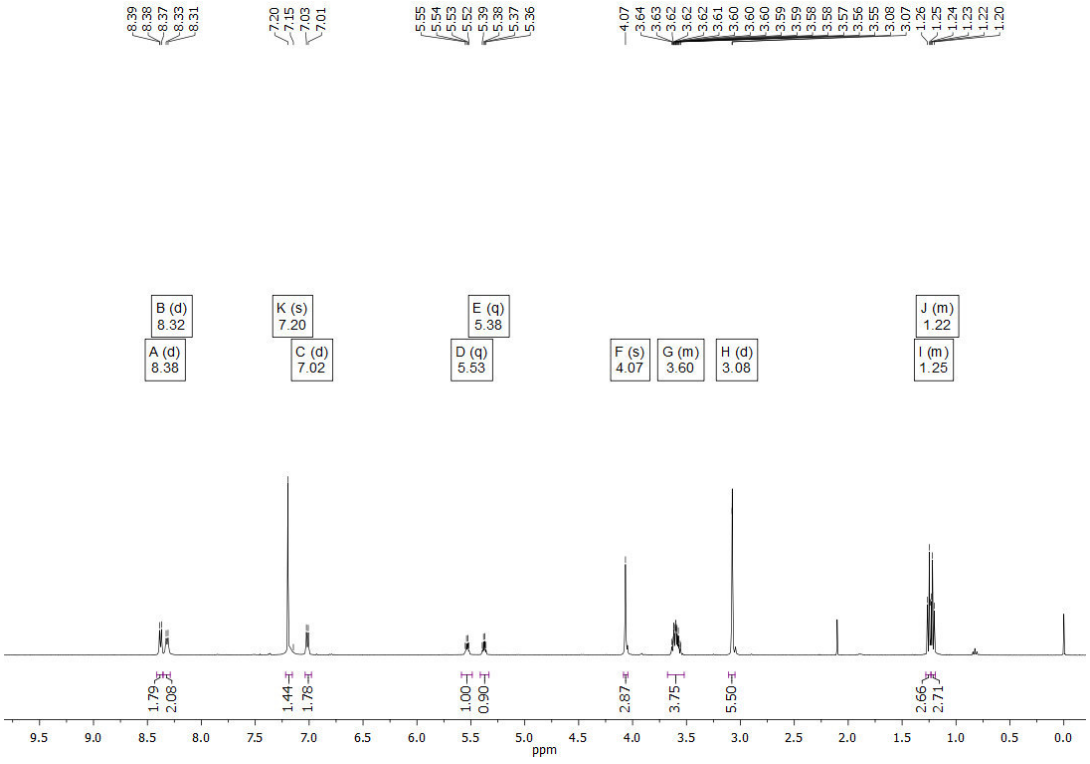


1b

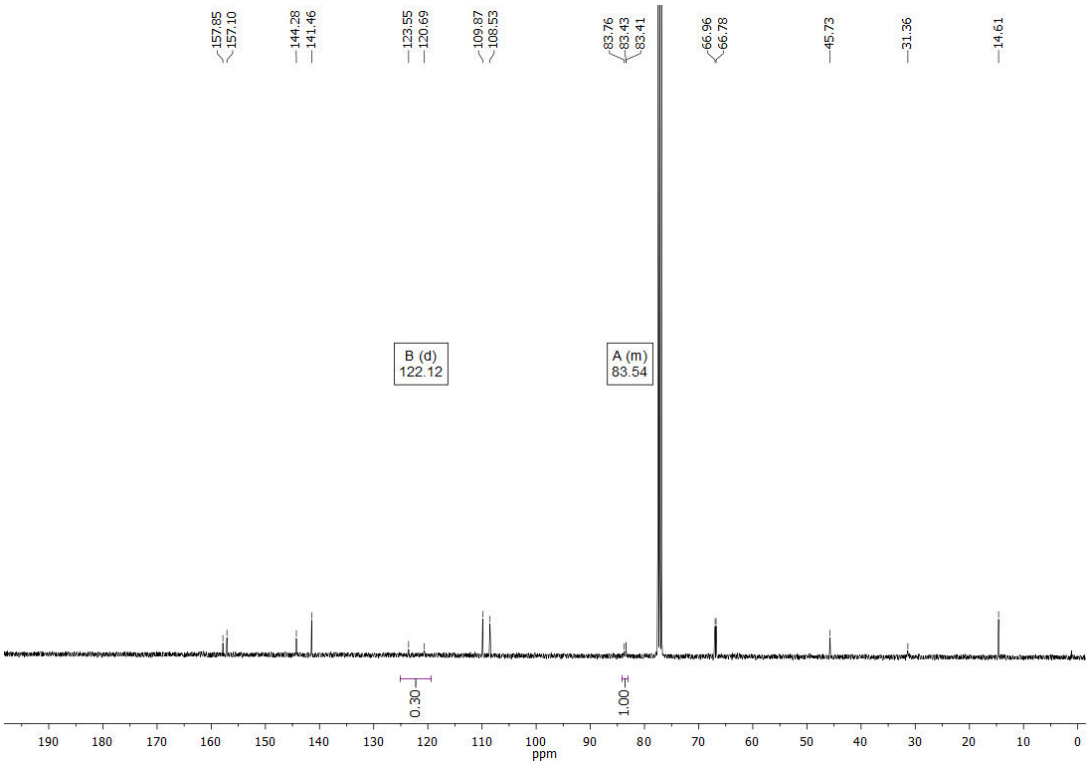
In a dry and argon flushed *Schlenk*-flask the *N*,*O*-acetal **1b** (50 mg, 0.23 mmol) was solved in freshly distilled THF (3 mL) and cooled to −78 °C. *n*BuLi (2.5 M in hexane, 0.11 mL, 0.27 mmol) was added dropwise to the reaction mixture, which was stirred for 30 min at −78 °C. Subsequently iodomethane (35 mg, 0.25 mmol) was added to the solution. After 2 h the reaction mixture was quenched with methanol (2 mL) and the solvent was removed *in vacuo*.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (d, J = 7.3 Hz, 2 H, H2, H6), 8.32 (d, J = 7.2 Hz, 2 H, H2', H6'), 7.20 (m, 2 H, H3', H5'), 7.02 (d, J = 6.8 Hz, 2 H, H3, H5), 5.53 (q, J = 4.7 Hz, 1 H, CH), 5.38 (q, J = 4.7 Hz, 1 H, CH'), 4.07 (s, 3 H, CH_3'), 3.68 – 3.52 (m, 4 H, 2 × CH_2), 3.08 (d, J = 1.3 Hz, 6 H, 2 × CH_3), 1.28 – 1.23 (m, 3 H, CH_3), 1.23 – 1.19 (m, 3 H, CH_3) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 157.85 (C1), 157.10 (C1'), 144.28 (C2', C6'), 141.46 (C2, C6), 122.12 (q, $J_{C,F}$ = 287.5 Hz, CF_3), 109.87 (C3', C5'), 108.53 (C3, C5), 84.14 – 83.02 (m, *C*HCF$_3$), 66.96 (CH_2), 66.78 (CH_2), 45.73 (CH_3), 31.36 (CH_3), 14.61(CH_2*C*H$_3$) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{10}H_{14}F_3N_2O^+$ $[M+H]^+$ 235.1053, found 253.10508. **HRMS** (ESI+): *m/z* calcd. for $C_{11}H_{16}F_3N_2O^+$ $[M+H]^+$ 249.1209, found 249.1209.

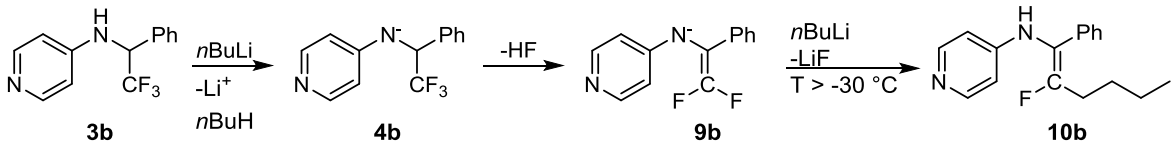
^{1}H NMR:



^{13}C NMR:


157.85
157.10
144.28
141.46
123.55
120.69
109.87
108.53
83.76
83.43
83.41
66.96
66.78
45.73
31.36
14.61
B (d)
122.12
A (m)
83.54
0.30
1.00
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

Reaction of *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine 3b with two equivalents of *n*BuLi

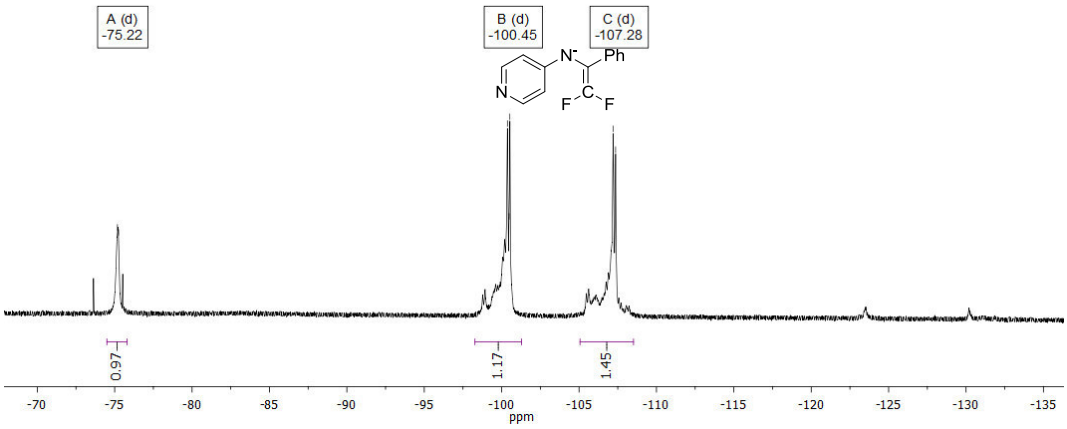


In a dry and argon flushed NMR tube, containing a thin, fused capillary tube with CD_3OD, the CF_3-amine **3b** (25 mg, 0.10 mmol) was solved in freshly distilled THF (0.7 mL) and cooled to −78 °C. Two equivalents of *n*BuLi (2.5 M in hexane, 0.08 mL, 0.20 mmol) were added at once. The NMR tube was well shaken to ensure a homogeneous distribution of the base.

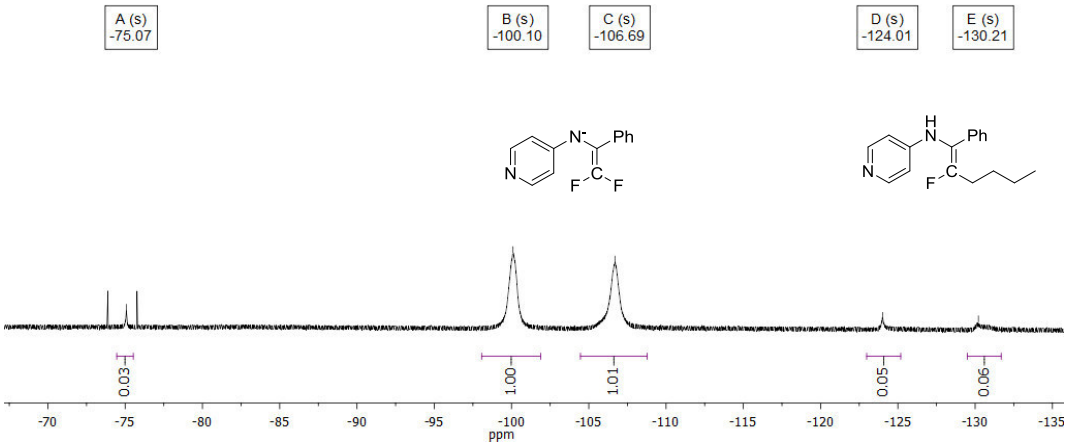
^{19}F NMR were measured at the stated temperatures below.

After the measurement was completed, the mixture was quenched with water and extracted with Et_2O (3 x 20 mL). The solvent was dried with $MgSO_4$, filtered and evaporated to give a mixture of (*E*)- and (*Z*)-*N*-(2-fluoro-1-phenylhex-1-en-1-yl)pyridin-4-amine **10b** as a yellow oil.

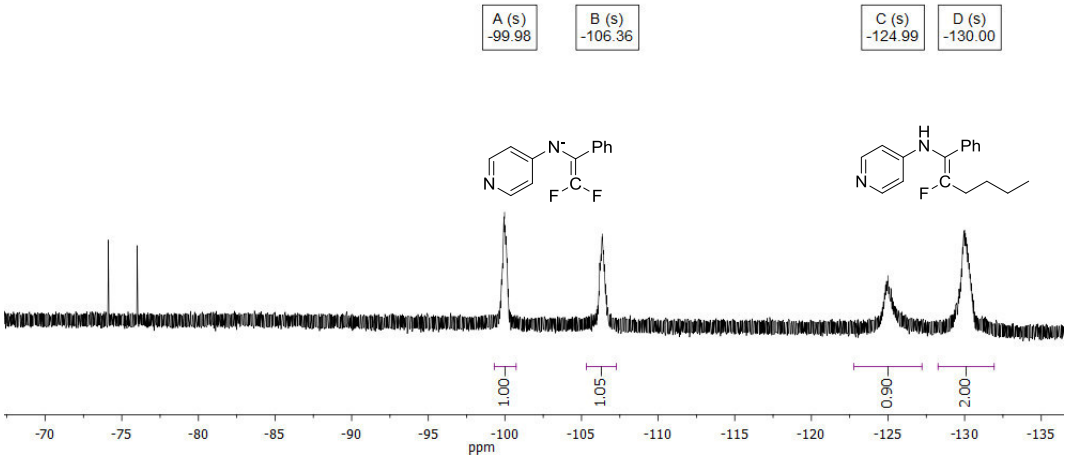
–60 °C



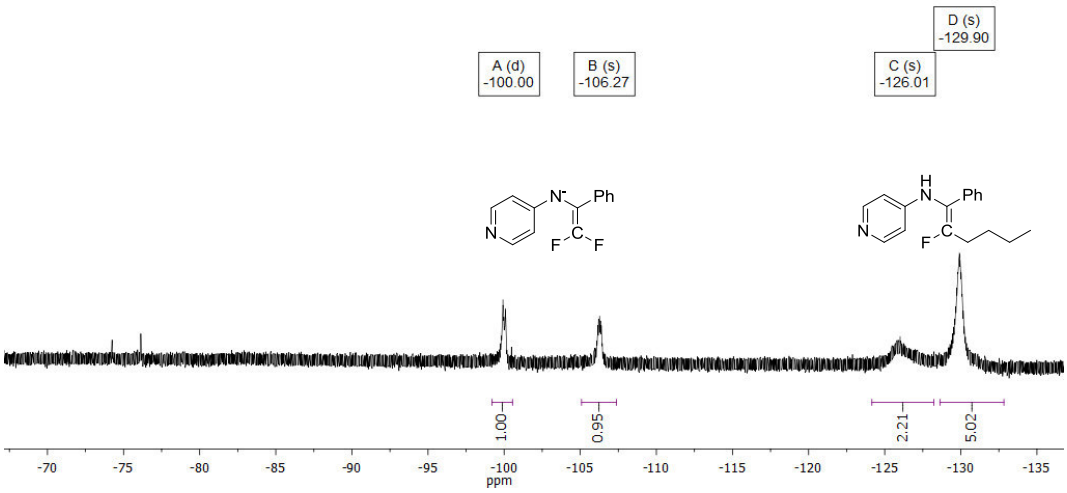
–40 °C



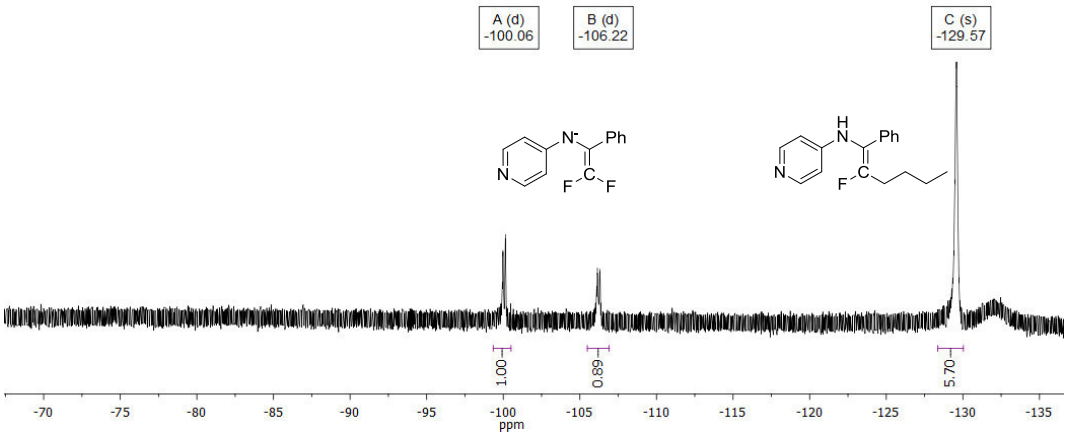
–20 °C


A (s)
-99.98
B (s)
-106.36
C (s)
-124.99
D (s)
-130.00
1.00
1.05
0.90
2.00
-70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135
ppm

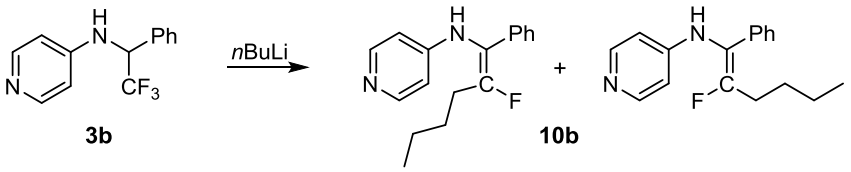
–10 °C


A (d)
-100.00
B (s)
-106.27
C (s)
-126.01
D (s)
-129.90
1.00
0.95
2.21
5.02
-70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135
ppm

20 °C


A (d)
-100.06
B (d)
-106.22
C (s)
-129.57
1.00
0.89
5.70
-70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135
ppm

Reaction of *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine 3b with two equivalents of *n*BuLi

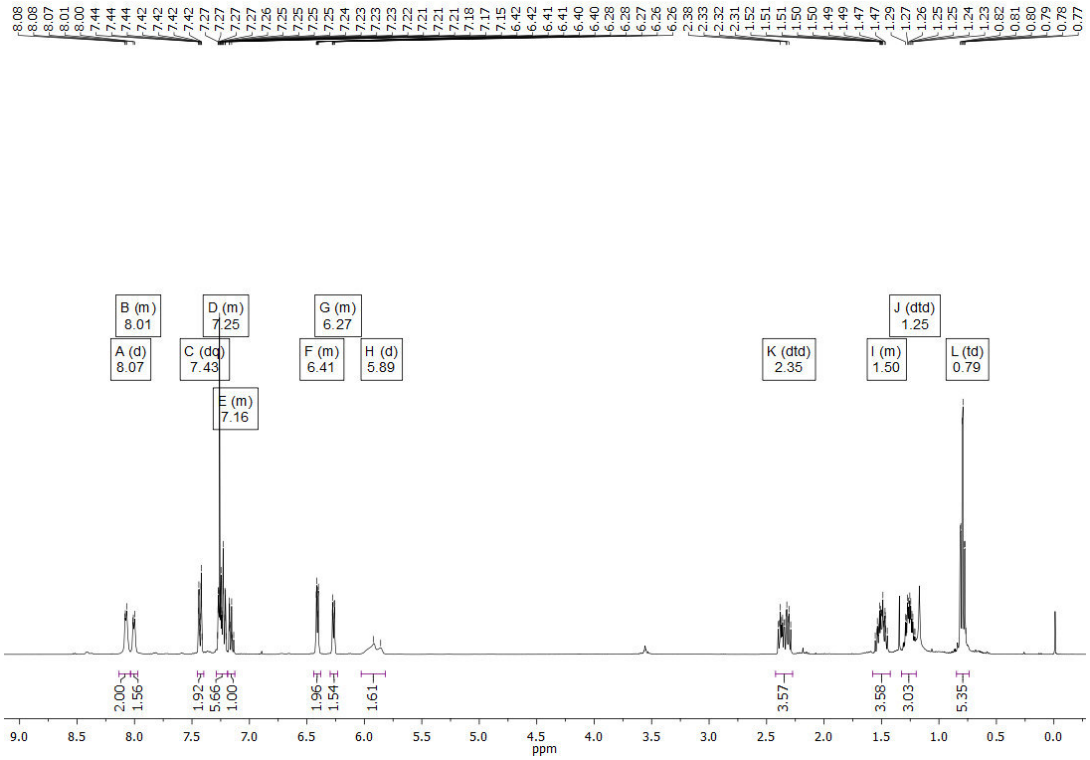


3b **10b**

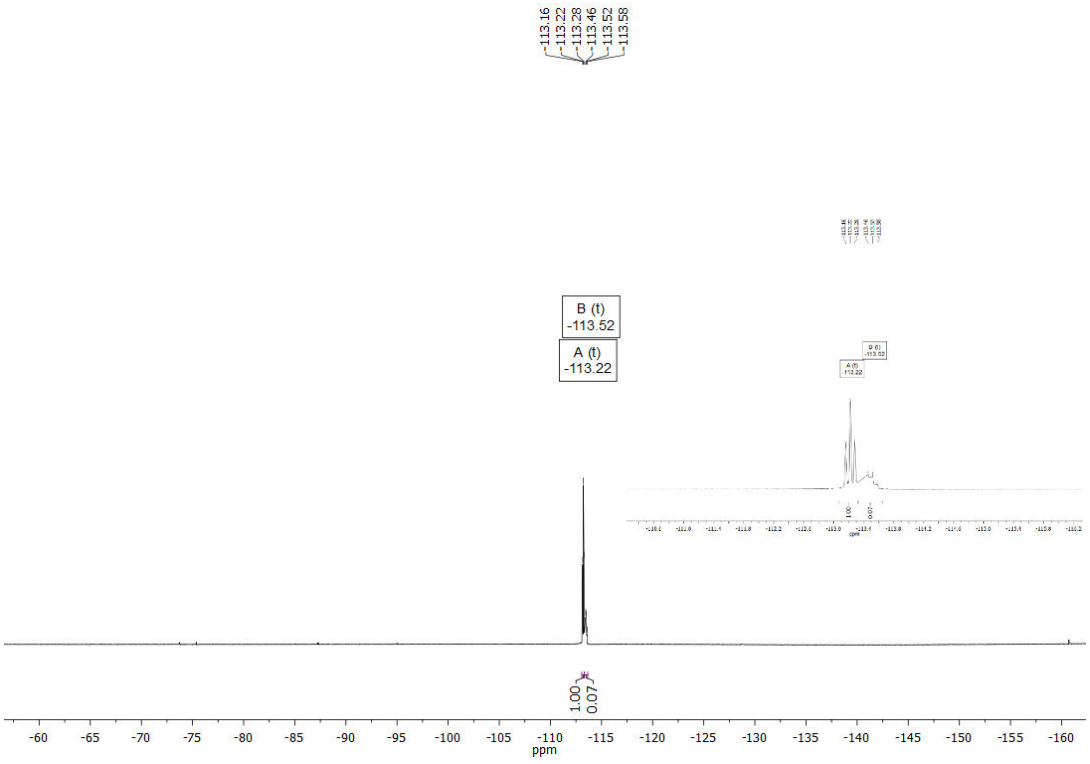
N-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (30 mg, 0.12 mmol) was solved in freshly distilled THF (2 mL) in a dry and argon flushed flask, equipped with a magnetic stirrer and a septum and cooled to –40 °C. *n*BuLi (2.5 M in hexane, 0.11 mL, 0.26 mmol) was added dropwise with a syringe and the solution was warmed up to –20 C and stirred for 1.5 h at –20 °C. After the reaction was completed, sat. NH_4Cl solution (5 mL) was added and the mixture was extracted three times with Et_2O (3 x 20 mL). The solvent was dried with $MgSO_4$, filtered and evaporated to give a mixture of (*E*)- and (*Z*)-*N*-(2-fluoro-1-phenylhex-1-en-1-yl)pyridin-4-amine **10b** as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, $J_{H2,H3} = J_{H6,H5}$ = 4.8 Hz, 2 H, $H2_{Pyridyl}$, $H6_{Pyridyl}$), 8.03 – 7.97 (m, 2 H, $H2_{Pyridyl}$, $H6_{Pyridyl}$), 7.43 (d, $J_{H2',H3'} = J_{H6',H5'}$ = 7.4 Hz, 4 H, $H2_{Phenyl}$, $H6_{Phenyl}$), 7.29 – 7.19 (m, 4 H, $H3_{Phenyl}$, $H5_{Phenyl}$), 7.19 – 7.13 (m, 2 H, $H4_{Phenyl}$), 6.44 – 6.38 (m, 2 H, $H3_{Pyridyl}$, $H5_{Pyridyl}$), 6.30 – 6.23 (m, 2 H, $H3_{Pyridyl}$, $H5_{Pyridyl}$), 5.89 (m, 2 H, NH), 2.35 (dtd, $J_{CH_2,CF}$ = 23.9 Hz, J_{CH_2,CH_2} = 7.7 Hz, J = 5.2 Hz, 4 H, CH_2), 1.58 – 1.42 (m, 4 H, CH_2), 1.25 (dtd, J_{CH_2,CH_2} = 14.6 Hz, J_{CH_2,CH_3} = 7.4 Hz, J = 3.4 Hz, 4 H, CH_2), 0.79 (td, J_{CH_3,CH_2} = 7.3 Hz, J = 2.5 Hz, 6 H, CH_3) ppm. **^{19}F NMR** (380 MHz, $CDCl_3$): δ = –113.22 (t, J_{CF,CH_2} = 22.1 Hz, CF), –113.52 (t, J_{CF,CH_2} = 23.7 Hz, CF) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 161.40 (d, $J_{C,F}$ = 264.3 Hz, CF), 153.90 (d, $J_{C,F}$ = 253.7 Hz, CF), 152.79 ($C4_{Pyridyl}$), 150.91 ($C4_{Pyridyl}$), 150.12 ($C2_{Pyridyl}$, $C6_{Pyridyl}$), 149.74 ($C2_{Pyridyl}$, $C6_{Pyridyl}$), 134.21 (d, $J_{C,F}$ = 4.3 Hz, $C1_{Phenyl}$), 133.98 (d, $J_{C,F}$ = 5.0 Hz, $C1_{Pheny}$), 128.81 (C_{Phenyl}), 128.78 (C_{Phenyl}), 128.53 (C_{Phenyl}), 128.46 (C_{Phenyl}), 127.92 (C_{Phenyl}), 127.90 (C_{Phenyl}), 127.75 (C_{Phenyl}), 127.68 (C_{Phenyl}), 119.53 (d, $J_{C,F}$ = 15.4 Hz, CNH), 117.61 (d, $J_{C,F}$ = 29.5 Hz, CNH), 109.99 ($C3_{Pyridyl}$, $C5_{Pyridyl}$), 108.67 ($C3_{Pyridyl}$, $C5_{Pyridyl}$), 29.14 (CH_2), 29.12 (d, $J_{C,F}$ = 25.3 Hz, CH_2), 28.66 (d, $J_{C,F}$ = 25.3 Hz, CH_2), 28.21 (CH_2), 22.37 (CH_2), 22.33 (CH_2), 13.89 (CH_3), 13.85 (CH_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{17}H_{20}FN_2^+$ $[M+H]^+$ 271.1605, found 271.1605.

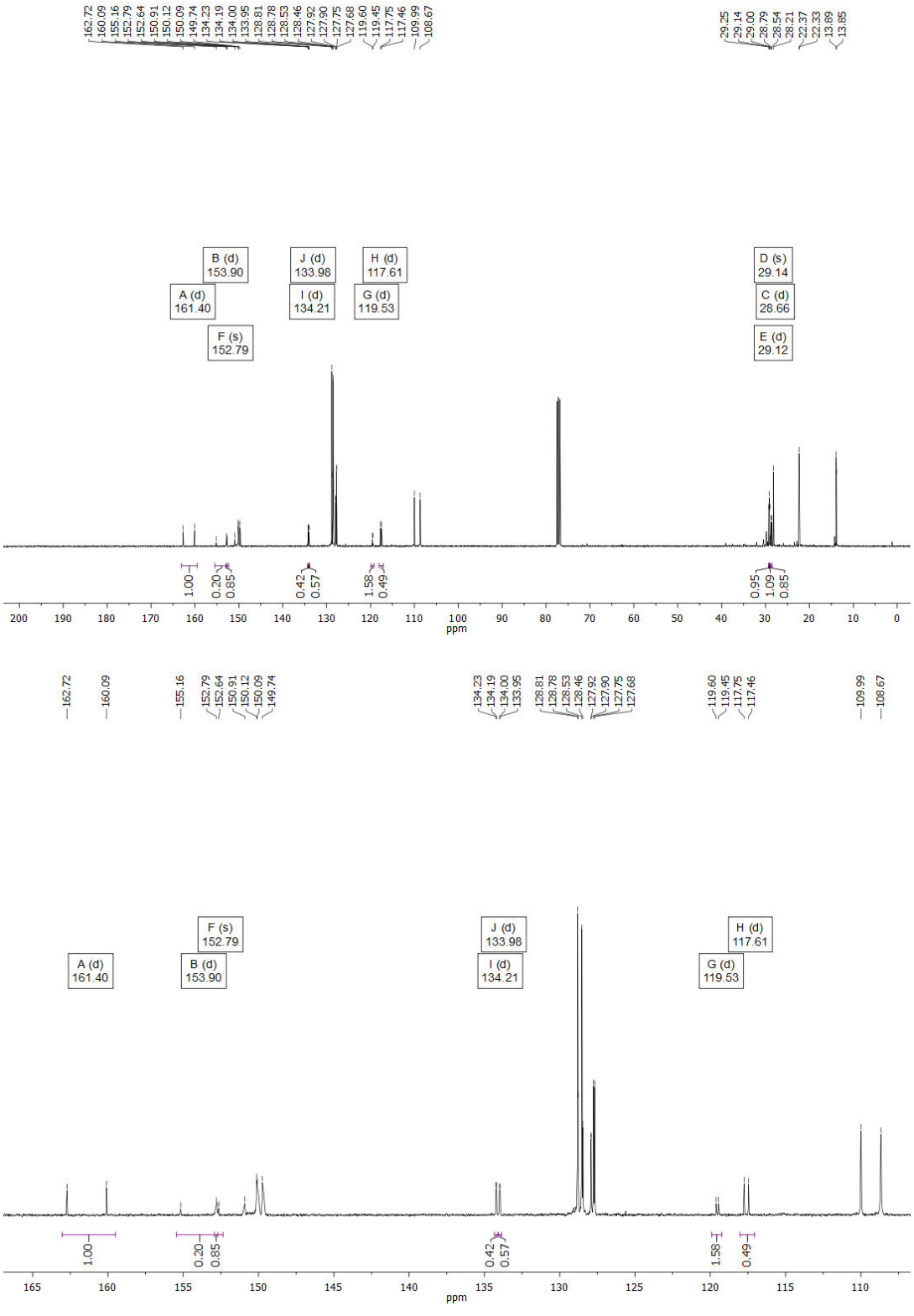
^{1}H NMR:



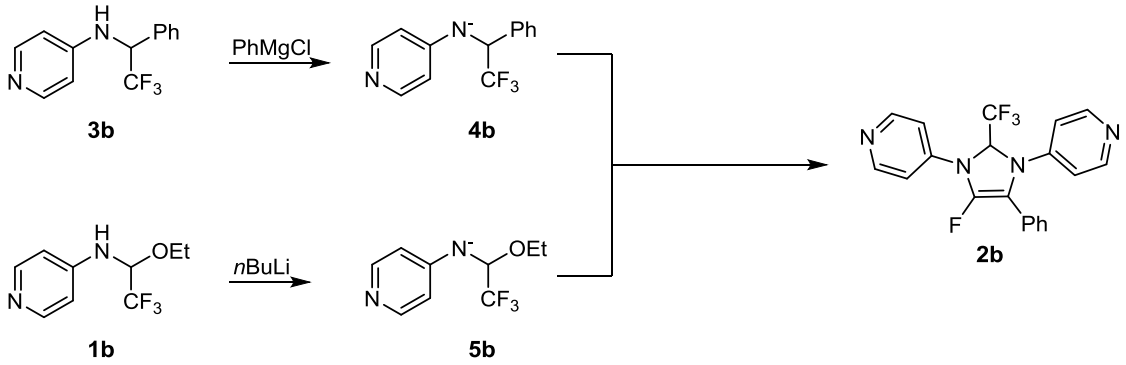
^{19}F NMR:



^{13}C NMR:


162.72
160.09
155.16
152.79
152.64
150.91
150.12
150.09
149.74
134.23
134.19
134.00
133.95
128.81
128.78
128.53
128.46
127.92
127.90
127.75
127.68
119.60
119.45
117.75
117.46
109.99
108.67
29.25
29.14
29.00
28.79
28.54
28.21
22.37
22.33
13.89
13.85
B (d) 153.90
J (d) 133.98
H (d) 117.61
A (d) 161.40
I (d) 134.21
G (d) 119.53
F (s) 152.79
D (s) 29.14
C (d) 28.66
E (d) 29.12
1.00
0.20
0.85
0.42
0.57
1.58
0.49
0.95
1.09
0.85
ppm
A (d) 161.40
F (s) 152.79
B (d) 153.90
J (d) 133.98
I (d) 134.21
H (d) 117.61
G (d) 119.53
1.00
0.20
0.85
0.42
0.57
1.58
0.49
ppm

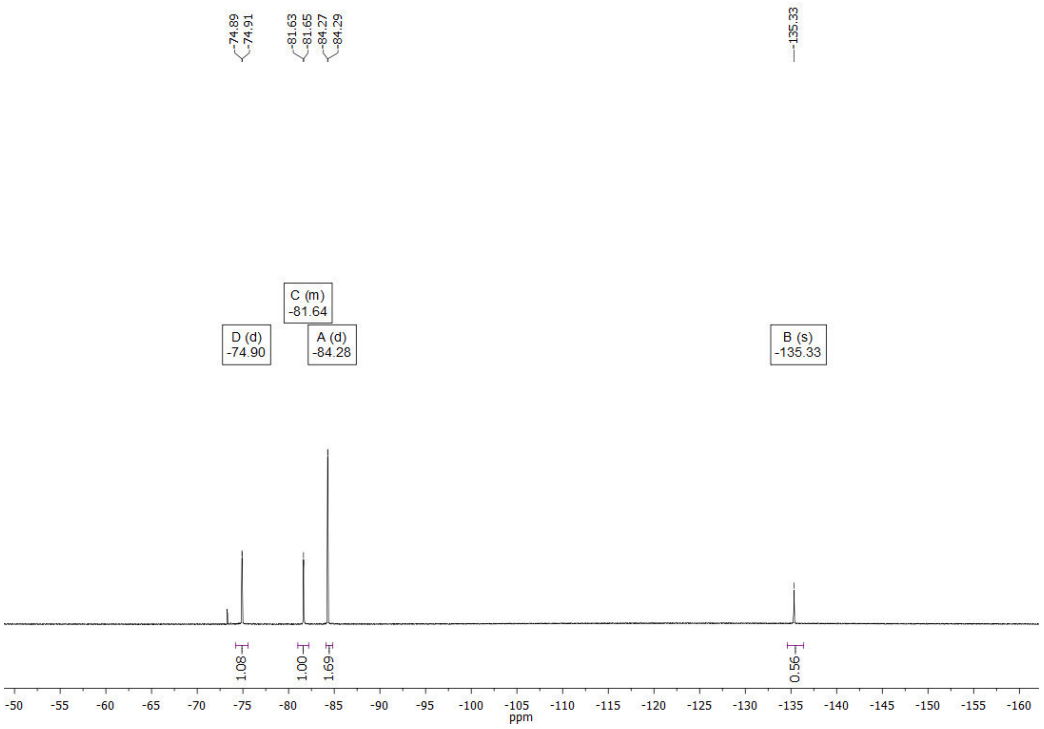
Reaction of *N*-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine 3b and *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine 1b



N-(2,2,2-trifluoro-1-phenylethyl)pyridin-4-amine **3b** (57 mg, 0.23 mmol) was solved in freshly distilled THF (3 mL) in a dry and argon flushed flask, equipped with a magnetic stirrer and a septum and cooled to −20 °C. After dropwise addition of PhMgCl (2.8 M in hexane, 0.10 mL, 0.23 mmol), the solution was stirred for 30 min. In a second *Schlenk*-flask *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-4-amine **1b** was solved in freshly distilled THF (3 mL) and cooled to −60 °C. *n*BuLi (1.6 M in hexane, 0.14 mL, 0.23 mmol) was added dropwise with a syringe and the solution was stirred at −60 °C for 30 min. Subsequently, the solution containing the deprotonated amine **4b** was added to the second flask. After stirring the reaction mixture for 3 h, sat. NH_4Cl solution (5 mL) was added and the mixture was extracted with Et_2O (3 x 20 mL). The solvent was dried with $MgSO_4$, filtered and evaporated to give a mixture of imidazole derivative **2b** and both starting materials **3b** and **1b** in a 1.7:1:1 ratio.

The crude product mixture was analyzed *via* **^{19}F NMR** in $CDCl_3$.

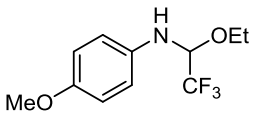
^{19}F NMR:


-74.89
-74.91
-81.63
-81.65
-84.27
-84.29
-135.33
C (m)
-81.64
D (d)
-74.90
A (d)
-84.28
B (s)
-135.33
1.08
1.00
1.69
0.56
-50 -55 -60 -65 -70 -75 -80 -85 -90 -95 -100 -105 -110 -115 -120 -125 -130 -135 -140 -145 -150 -155 -160
ppm

7. Experimental Procedures and Analytical Data: *ψ[CH(CF$_3$)NH]-Gly Dipeptide Building Blocks for Peptide Synthesis*

4-Methoxy-*N*-(2,2,2-trifluoro-1-ethoxyethyl)aniline 35

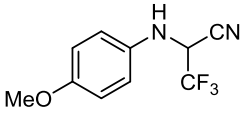
In a round bottom flask, *p*-Anisidine (1.50 g, 12.2 mmol) was dissolved in EtOH (20 mL) and TFAE (1.90 mL, 14.6 mmol) and *p*TSA·H$_2$O (116 mg, 0.61 mmol) were added to the solution. The resulting reaction mixture was refluxed at 80 °C until no further conversion was observed (4 h). After removal of the solvent, flash column chromatography (SiO_2, gradient: cyclohexane → cyclohexane/CH_2Cl_2 1:4) furnished hemiaminal ether **35** as a colorless oil (2.31 g, 76%).



^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 6.91 – 6.81 (m, 2 H, 2 × H$_{ar}$), 6.80 – 6.72 (m, 2 H, 2 × H$_{ar}$), 6.18 (d, $J_{NH,CH}$ = 10.5 Hz, 1 H, NH), 5.39 (dq, $J_{CH,NH}$ = 10.7 Hz, $J_{CH,CF3}$ = 5.4 Hz, 1H, CH), 3.76 – 3.49 (m, 2 H, CH_2), 3.66 (s, 3 H, CH_3), 1.09 (t, $J_{CH3,CH2}$ = 7.0 Hz, 3 H, CH_3) ppm. **^{19}F NMR** (376 MHz, DMSO-d$_6$): δ = -78.39 (d, $J_{CF3,CH}$ = 5.5 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, DMSO-d$_6$): δ = 152.32 (C_q), 139.56 (C_q), 123.45 (q, $J_{C,F}$ = 283.9 Hz, CF_3), 115.20 (CH_{ar}), 114.42 (CH_{ar}), 81.63 (q, $J_{C,F}$ = 32.3 Hz, *C*CF_3), 63.26 (CH_2), 55.14 (CH_3), 14.98 (CH_3) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{11}H_{15}F_3NO_2^+$ $[M+H]^+$ 250.1049, found 250.1048. **HPLC-MS** (0.1% formic acid. 0 min: 4% B → 2.8 min: 100% B, flow: 2.4 mL/min): t_R = 2.32 min, λ = 220 nm.

3,3,3-Trifluoro-2-4-methoxyphenylaminopropanenitrile 36

A dry *Schlenk* flask was flushed with argon, equipped with a magnetic stirrer and a septum and charged with *N*-aryl hemiaminal ether **35** (5.00 g, 19.0 mmol) in dry MeCN (100 mL). The solution was cooled to 0 °C, boron trifluoride diethyl etherate (0.47 mL, 3.80 mmol) and then trimethylsilyl cyanide (3.57 mL, 28.5 mmol) were added dropwise, and the solution was stirred at 0 °C until complete consumption of the starting material (ca. 7 h). Then, the solution was quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. Purification by flash chromatography (cyclohexane/ethyl acetate, 30:1 → 10:1) furnished the desired nitrile **36** (4.20 g, 96%) as a yellow oil.

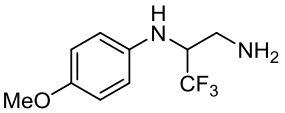


^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 – 6.85 (m, 2 H, H2, H6), 6.83 – 6.77 (m, 2 H, H3, H5), 4.69 (dq, $J_{CH,NH}$ = 11.2 Hz, $J_{CH,CF3}$ = 6.0 Hz, 1 H, CH), 3.82 (d, $J_{NH,CH}$ = 11.3 Hz, 1 H, NH) 3.78 (s, 3 H, OCH_3) ppm. **^{19}F NMR** (375 MHz, $CDCl_3$): δ = -74.17 (d, $J_{CF3,CH}$ = 6.1 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 155.68 (C4), 136.41 (C1), 121.75 (q, $J_{C,F}$ = 282.0 Hz, CF_3) 118.94 (C3, C5), 115.29 (C2, C6), 113.14 (CN), 55.59 (OCH_3), 52.07 (q, $J_{C,F}$ = 35.2 Hz, CH) ppm. **HRMS** (ESI-): *m/z* calcd. for $C_{10}H_8F_3N_2O^-$

$[M-H]^-$ 229.0594, found 229.0593. **HPLC-MS** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 16.85 min, λ = 220 nm.

3,3,3-Trifluoro-*N*^{2}-4-methoxyphenylpropan-1,2-diamine 37

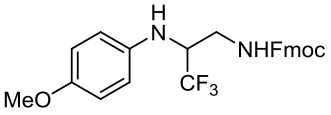
A suspension of lithiumaluminium hydride (LAH) (2.80 g, 72.9 mmol) in dry diethyl ether (250 mL) was cooled to 0 °C, followed by the dropwise addition of a solution of nitrile **36** (4.20 g, 18.2 mmol) in dry diethyl ether (50 mL). The reaction mixture was allowed to warm up to r.t. and was stirred for 18 h. After cooling the mixture to 0 °C, the excess of LAH was carefully reacted with H_2O (2 mL), a solution of aqueous KOH (15%, 2 mL) and finally H_2O (4 mL). The suspension was filtered over a thin pad of Hyflo®, which was washed with diethyl ether several times, before the solvent was removed *in vacuo*. Purification by flash chromatography (cyclohexane/ethyl acetate, 10:1) furnished the desired amine **37** (3.09 g, 73%) as a yellow oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 – 6.77 (m, 2 H, H2, H6), 6.72 – 6.67 (m, 2 H, H3, H5), 4.08 (d, $J_{NH,CH}$ = 9.3 Hz, 1 H, NH), 3.83 – 3.70 (m, 1 H, CH), 3.75 (s, 3 H, OCH_3), 3.05 (d, $J_{CH2,CH}$ = 5.2 Hz, 2 H, CH_2) ppm. **^{19}F NMR** (375 MHz, $CDCl_3$): δ = -74.04 (d, $J_{CF3,CH}$ = 6.0 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 153.20 (C4), 140.70 (C1), 126.27 (q, $J_{C,F}$ = 284.5 Hz, CF_3), 115.63 (C3, C5), 115.03 (C2, C6), 58.53 (q, $J_{C,F}$ = 27.6 Hz, CH), 55.70 (OCH_3), 40.60 (CH_2) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{10}H_{14}F_3N_2O^+$ $[M+H]^+$ 235.1053, found 235.1059. **HPLC-MS** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 10.25 min, λ = 220 nm.

(9*H*-Fluoren-9-yl)methyl (3,3,3-trifluoro-2-((4-methoxyphenyl)amino)propyl)carbamate 38

Fmoc-*O*-Succinimid (450 mg, 5.34 mmol) was added in small portions to a solution of amine **37** (1.25 g, 5.34 mmol) and $NaHCO_3$ (1.8 g, 5.34 mmol) in acetone/H_2O (1:1, 200 mL) and the reaction mixture was stirred for 18 h at r.t. The mixture was acified with concentrated hydrochloric acid to pH = 2, before the aceton was removed *in vacuo*. The remaining aqueous solution was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic phases were washed with aqueous hydrochloric acid (1M, 100 mL) and saturated NaCl solution (100 mL). After drying the solvent with $MgSO_4$, it was evaporated *in vacuo*. The crude product was recrystallized from CH_2Cl_2 to give **38** (1.64 g, 67%) was a white solid.

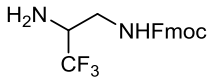


^{1}H NMR (800 MHz, DMSO-d_6): δ = 7.87 (d, $J_{H4,H3}$ = $J_{H5,H6}$ = 7.5 Hz, 2 H, H4-, H5-Fmoc), 7.62(d, $J_{H1,H2}$ = $J_{H8,H7}$ = 7.6 Hz, 2 H, H1-, H8-Fmoc), 7.50 (t, $J_{H3,H2}$ = $J_{H3,H4}$ = $J_{H6,H5}$ = $J_{H6,H7}$ = 7.5 Hz, 2 H, H3-, H6-Fmoc), 7.28 (t, $J_{H2,H1}$ = $J_{H2,H3}$ = $J_{H7,H6}$ = $J_{H7,H8}$ = 6.9 Hz, 2 H, H2-, H7-Fmoc) 6.76 (d, $J_{H2,H3}$ = $J_{H6,H5}$ = 8.4 Hz, 2 H, H2, H6), 6.66 (d, $J_{H3,H2}$ = $J_{H5,H6}$ = 8.4 Hz, 2 H, H3, H5), 5.06 – 5.03 (m, 1 H, N*H*-Fmoc), 4.30 (d, J = 7.0 Hz, 2 H, CH_2-Fmoc), 4.14 (t, $J_{C9,CH2\text{-}Fmoc}$ = 7.0 Hz, 1 H, C9-Fmoc), 4.17 – 4.10 (m, 1 H, CH), 3.77 – 3.73 (m, 1 H, N*H*-PMP), 3.62 (s, 3 H, OCH_3), 3.47 – 3.38 (m, 1 H, CH_2), 3.29 – 3.22 (m, 1 H, CH_2) ppm. **^{19}F NMR** (375 MHz, DMSO-d_6): δ = -73.10 (d, $J_{CF3,CH}$ = 7.5 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, DMSO-d_6) δ = 156.96

(C=O-Urethan), 153.40 (C4), 143.55 (C1a-, C8a-Fmoc), 141.28 (C4a-, C5a-Fmoc), 140.15 (C1), 127.73 (C3-, C6-Fmoc), 127.04 (C2-, C7-Fmoc), 124.91 (C1-, C8-Fmoc), 119.99 (C4-, C5-Fmoc), 115.51 (C3, C5), 114.88 (C2, C6), 67.13 (CH_2-Fmoc), 58.10 (q, $J_{C,F}$ = 27.1 Hz, CH) 55.64 (OCH_3), 47.11 (C9-Fmoc), 40.25 (CH_2) ppm. **HRMS** (ESI+): *m/z* calcd. for $C_{25}H_{23}F_3N_2O_3^+$ $[M+H]^+$ 456.1655, found 457.1734. **mp** 173 °C. **HPLC-MS** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 20.96 min, λ = 220 nm.

(9*H*-Fluoren-9-yl)methyl (2-amino-3,3,3-trifluoropropyl)carbamate 31

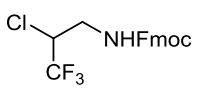
The fully protected diamine **38** (140 mg, 0.307 mmol) was solved in MeCN (25 mL) and cooled to 0 °C. A solution of ammonium cer(IV) nitrate (CAN) (842 mg, 1.54 mmol) in H_2O (3 mL) was added dropwise, the reaction was allowed to warm up to r.t. and stirred for 2 h. After addition of aqueous $NaHCO_3$ solution (20 mL), the mixture was extracted with ethyl acetate (4 × 25 mL) and the combined organic phases were dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (cyclohexane/ethyl acetate, 10:1) furnished the desired amine **31** (71 mg, 66%) as a yellow solid.



^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (dt, $J_{H4,H3} = J_{H5,H6}$ = 7.5 Hz, $J_{H4,H2} = J_{H5-,H7-Fmoc}$ = 1.0 Hz, 2 H, H4-, H5-Fmoc), 7.59 (dt, $J_{H1,H2} = J_{H8,H7}$ = 7.5 Hz, $J_{H1,H3} = J_{H8,H6}$ = 1.0 Hz, 2 H, H1-, H8-Fmoc), 7.40 (td, $J_{H3,H4} = J_{H6,H5}$ = 7.5 Hz, $J_{H3,H1} = J_{H6,H8}$ = 1.0 Hz, $J_{H3,H2} = J_{H6,H7}$ = 0.6 Hz, 2 H, H3-, H6-Fmoc), 7.32 (td, $J_{H2,H1} = J_{H7,H8}$ = 7.5 Hz, $J_{H2,H4} = J_{H7,H5}$= 1.0 Hz, 2 H, H2-, H7-Fmoc), 5.14 (s, 1 H, NH), 4.45 (d, *J* = 6.9 Hz, 2 H, CH_2-Fmoc), 4.22 (t, $J_{H9,CH2}$ = 6.9 Hz, 1 H, H9-Fmoc), 3.74 – 3.62 (m, 1H, CH_2), 3.37 – 3.27 (m, 1 H, CH), 3.19 – 3.08 (m, 1 H, CH_2) ppm. **^{19}F NMR** (375 MHz, $CDCl_3$): δ = -74.73 (d, $J_{CF3,CH}$ = 6.8 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 156.50 (C=O-Urethan), 143.76 (C1a-, C8a-Fmoc), 141.32 (C4a-, C5a-Fmoc), 127.71 (C3-, C6-Fmoc), 127.03 (C2-, C7-Fmoc), 124.95 (C1-, C8-Fmoc), 119.99 (C4-, C5-Fmoc), 66.86 (CH_2-Fmoc), 53.67 (q, $J_{C,F}$ = 28.9 Hz, CH), 47.07 (C9-Fmoc), 40.74 (CH_2).). **HRMS** (ESI+): *m/z* calcd. for $C_{18}H_{17}F_3N_2O_2^+$ $[M+H]^+$ 350.1237 found 351.1325. mp 101 °C. **HPLC-MS** (0.1% TFA. 0 min: 4% B → 15 min: 100% B, flow: 1 mL/min): t_R = 13.17 min, λ = 220 nm.

(9*H*-fluoren-9-yl)methyl(2-chloro-3,3,3-trifluoropropyl)carbamate 40

Amine **31** (50 mg, 0.14 mmol) was suspended in 6 M HCl (5 mL) and cooled to 0 °C. A solution of sodium nitrite (15 mg, 0.21 mmol) in H_2O (1 mL) was added dropwise, the reaction was allowed to warm up to r.t. and stirred for 18 h. After addition of aqueous $NaHCO_3$ solution (100 mL), the mixture was extracted with ethyl acetate (4 × 100 mL) and the combined organic phases were dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (cyclohexane/ethyl acetate, 30:1) furnished the desired choride **40** (30 mg, 58%) as a colorless oil.

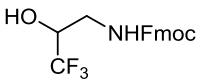


^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.77 (dt, $J_{H4,H3} = J_{H5,H6}$ = 7.6 Hz, $J_{H4,H2} = J_{H5,H7}$ = 1.0 Hz, 2 H, H4-, H5-Fmoc), 7.58 (d, $J_{H1,H2} = J_{H8,H7}$ = 7.6 Hz, 2 H, H1-, H8-Fmoc), 7.41 (tt, $J_{H3,H4} = J_{H6,H5}$ = 7.5 Hz, $J_{H3,H1} = J_{H6,H8}$ = 0.9 Hz, 2 H, H3-, H6-Fmoc), 7.33 (t,

$J_{H2,H1} = J_{H7,H8}$ = 7.5 Hz, 2 H, H2-, H7-Fmoc), 5.16 (s, 1 H, NH), 4.47 (d, J = 6.9 Hz, 2 H, CH_2-Fmoc), 4.35 – 4.27 (m, 1 H, CH), 4.23 (t, $J_{H9,CH2}$ = 6.7 Hz, 1 H, H9-Fmoc), 3.98 – 3.86 (m, 1 H, CH_2), 3.52 – 3.35 (m, 1 H, CH_2) ppm. **^{19}F NMR** (375 MHz, $CDCl_3$): δ = -73.27 (d, $J_{CF3,CH}$ = 6.7 Hz, CF_3) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$): δ = 156.17 (C=O-Urethan), 143.71 (C1a-, C8a-Fmoc), 141.50 (C4a-, C5a-Fmoc), 127.96 (C3-, C6-Fmoc), 127.23 (C2-, C7-Fmoc), 125.07 (C1-, C8-Fmoc), 123.50 (q, $J_{C,F}$ = 279.7 Hz, CF_3), 120.21 (C4-, C5-Fmoc), 67.28 (CH_2-Fmoc), 56.36 (q, $J_{C,F}$ = 31.9 Hz, CH), 47.31 (C9-Fmoc), 42.16 (CH_2) ppm. **HRMS** (ESI-): *m/z* calcd. for $C_{19}H_{16}ClF_3NO_4^-$ $[M\text{-}HCOO]^-$ 414.0735 found 414.0732.

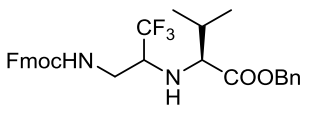
9*H*-fluoren-9-yl)methyl (3,3,3-trifluoro-2-hydroxypropyl)carbamate 41

Amine **31** (200 mg, 0.57 mmol) was solved in acetic acid/H_2O (4:1, 40 mL) and cooled to 0 °C. A solution of sodium nitrite (51 mg, 0.74 mmol) in H_2O (2 mL) was added dropwise, the reaction was allowed to warm up to r.t. and stirred for 18 h. After addition of aqueous $NaHCO_3$ solution (100 mL), the mixture was extracted with ethyl acetate (4 × 100 mL) and the combined organic phases were dried with $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash chromatography (cyclohexane/ethyl acetate, 20:1) furnished the desired compound **41** (105 mg, 52%) as a colorless oil.



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (dt, $J_{H4,H3} = J_{H5,H6}$ = 7.6 Hz, $J_{H4,H2} = J_{H5,H7}$ = 0.9 Hz, 2 H, H4-, H5-Fmoc), 7.56 (d, $J_{H1,H2} = J_{H8,H7}$ = 7.5 Hz, 2 H, H1-, H8-Fmoc), 7.44 – 7.33 (m 2 H, H3-, H6-Fmoc), 7.33 – 7.20 (m, 2 H, H2-, H7-Fmoc), 5.74 (t, $J_{NH,CH2}$ = 6.0 Hz, 1 H, NH), 5.45 (d, $J_{OH,CH2}$ = 5.9 Hz, 1 H. OH), 4.38 (d, J = 6.9 Hz, 2 H, CH_2-Fmoc), 4.18 (t, $J_{H9,CH2}$ = 6.9 Hz, 1 H, H9-Fmoc), 4.01 (m, 1 H, CH), 3.65 – 3.54 (m, 1 H, CH_2), 3.31 – 3.17 (m, 1 H, CH_2) ppm. **^{19}F NMR** (375 MHz, $CDCl_3$): δ = -78.28 (d, $J_{CF3,CH}$ = 7.1 Hz, CF_3) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 156.99 (C=O-Urethan), 143.85 (C1a-, C8a-Fmoc), 141.32 (C4a-, C5a-Fmoc), 127.75 (C3-, C6-Fmoc), 127.11 (C2-, C7-Fmoc), 125.09 (C1-, C8-Fmoc), 120.00 (C4-, C5-Fmoc), 69.28 (q, $J_{C,F}$ = 31.9 Hz, CH), 66.85 (CH_2-Fmoc), 47.22 (C9-Fmoc), 41.15 (CH_2) ppm. **HRMS** (ESI-): *m/z* calcd. for $C_{19}H_{17}F_3NO_5^-$ $[M\text{-}HCOO]^-$ 396.1064 found 396.1069.

Benzyl (3-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino)-1,1,1-trifluoropropan-2-yl)-L-valinate 39 (ψ[CH(CF$_3$)NH]-Gly-Val)



Compound **41** (51 mg, 0.15 mmol) was solved in dry CH_2Cl_2 (10 mL) and cooled to -78 °C. 2,6-Lutidine (37 µL, 0.32 mmol) and Tf_2O (27 µL, 0.16 mmol) was added to the reaction mixture which was subsequently allowed to warm up to 0 °C and stirred for 6 h. Benzyl L-valinate (36 mg, 0.17 mmol) solved in dry CH_2Cl_2 (1 mL) was then added dropwise to the solution. After stirring the reaction mixture for 16 h, the solvent was removed *in vacuo*.

HRMS (ESI+): *m/z* calcd. for $C_{30}H_{32}F_3N_2O_3^+$ $[M+H]^+$ 541.2309 found 541.2314.

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