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New Synthesis of 2-Heteroarylperfluoropropionic Acids Derivatives by Reaction of Azine *N*-Oxides with Hexafluoropropene

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Dedicated to Professor Paul Tarrant on the occasion of his 93rd birthday in appreciation of his great contribution to fluorine chemistry

Abstract: Hexafluoropropene reacts with aromatic azine *N*-oxides under mild conditions to produce fluorides of 2-heteroarylperfluoropropionic acids. The reaction proceeds as 1,3-dipolar cycloaddition followed by spontaneous scission of the N–O bond in the isoxazolidine ring and elimination of HF. When the reaction is carried out in the presence of alcohols or *N*-alkyl anilines, the in situ formed acyl fluorides give the corresponding esters and amides. They can be also treated separately with nucleophiles to produce the respective acylation products, whereas their hydrolysis leads to unstable carboxylic acids that undergo spontaneous decarboxylation to 1-aryl-1,2,2,2-tetrafluoroethanes. This new reaction provides a simple and general method of synthesizing 2-heteroarylperfluoropropionic acid derivatives that were previously unknown and unavailable.

Keywords: acylation · cycloaddition · fluorine · nitrogen heterocycles · reaction mechanisms

Introduction

Heteroaromatic compounds that incorporate fluorinated substituents in the ring are presently widely applied as novel pharmaceuticals, crop protection agents and liquid crystalline compounds.[1] Their significant and constantly growing practical importance is inspiring the search for new synthetic methods that allow the introduction of such substituents into the aromatic ring, selectively and under mild reaction conditions. In particular, it would be of great interest to develop new reactions that selectively afford products with a partially fluorinated side-chain that bears functional groups suitable for further functionalisation. Such compounds could be used, for example, as precursors in the synthesis of new pharmaceuticals that incorporate a heterocyclic subunit with a side-chain bearing functional groups responsible for the biological activity and fluorine atoms that prevent metabolic oxidative and/or hydrolytic decomposition of the drug.[2]

In particular, there is a growing interest in the new side-chain-fluorinated derivatives of 2-arylpropionic acids—the "profen" family of non-steroidal anti-inflammatory drugs. The presence of a fluorine atom in the α position was expected to prevent racemisation of the compound under physiological conditions and to modify its metabolism and interactions with the receptor.[3] Such a fluorinated analogue would remain active, owing to the similar "physiological" size of fluorine and hydrogen,[4] whereas its configurational stability would enable investigations into the stereochemistry of its binding to the receptor. To date, only few synthetic methods for preparing such compounds have been reported. Rozen and co-workers developed a method based on electrophilic fluorination of ketene acetals with AcOF, leading to 2-fluoroalkanoic acids and esters, including those with aryl groups in the 2 position.[5] Schlosser obtained a 2-fluorinated analogue of ibuprofen by treating the corresponding hydroxyl derivative with diethylaminosulfur trifluoride (DAST).[3] A route via 2-aryl-2-fluoropropanols prepared from 2-arylpropene oxides by BF_3-catalysed ring-opening was described by Haufe et al.[6]

2-Aryl-substituted perfluoropropionic acids have been rarely investigated. Their potentially interesting properties were first pointed out by Ricci and Ruzziconi, who elaborated a general approach to the synthesis of 2-phenanthryl-2-fluoropropionic and 2-phenanthrylperfluoropropionic esters and acids.[7] Apart from their contribution, there are currently no general methods to access 2-arylperfluoropropionic

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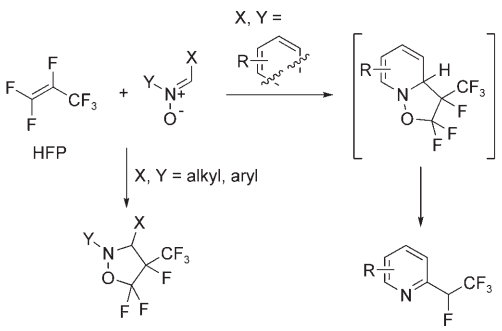
acid derivatives. Only a few examples of such compounds have been reported so far.[8]

In this article, we wish to present a new and general reaction that allows access to a wide range of 2-heteroarylperfluoropropionic and 3,3,3-trifluoropropionic acyl fluorides that are readily converted into esters, amides, etc. with a heteroaryl group at 2-position. However, the respective free carboxylic acids cannot be isolated because they undergo immediate decarboxylation, owing to the presence of a nitrogen atom at the 2 position of the heteroaryl group.

In recent years, our group has been investigating new reactions in which a fluorinated substituent is introduced into the aromatic ring by means of oxidative nucleophilic substitution of hydrogen with fluorinated carbanions. We have already described the oxidative nucleophilic trifluoromethylation of nitroarenes[9] and reactions of azinium (pyridinium, quinolinium etc.) salts with CF_3^-[10] or with perfluoroispropyl carbanions, generated in the reaction mixture from hexafluoropropene ($CF_2{=}CFCF_3$, HFP) and $KF_{(s)}$.[11] The two crucial steps of these reactions were, nucleophilic addition of the carbanions to the electrophilic homo- or heteroaromatic ring and subsequent aromatisation of the negatively charged σ^H complexes or neutral dihydroazines upon addition of an oxidant.

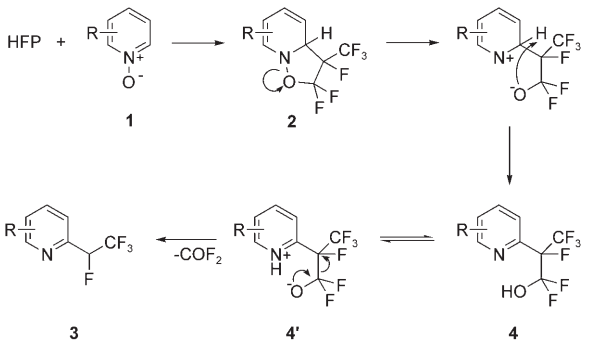
Another mechanistic pathway that starts with the addition of perfluorocarbanion to strongly electrophilic aromatic rings and which might lead to products of similar type could be nucleophilic *cine* substitution in the aromatic azine *N*-oxides. They are well-known as educts for the functionalisation of heteroaromatic rings in reactions with nucleophiles.[12] Unfortunately, our attempts to effect a nucleophilic *cine* substitution in the *O*-acylated or *O*-alkylated *N*-oxides with fluorinated carbanions have been unsuccessful so far. The few positive results we were able to obtain will be published elsewhere. However, in the course of these studies we made interesting observations concerning 1,3-dipolar cycloaddition of azine *N*-oxides with hexafluoropropene, which are the subject of the present paper.

The outcome of the reaction of HFP (and other fluorinated alkenes) with compounds of the general structure **1**, which contain the $X{-}C{=}N^+(Y){-}O^-$ moiety, depends on whether this fragment is or is not part of an aromatic ring (Scheme 1). In the latter case (nitrones), the final products



Scheme 1. Reactions of HFP with nitrones and *N*-oxides of azines.

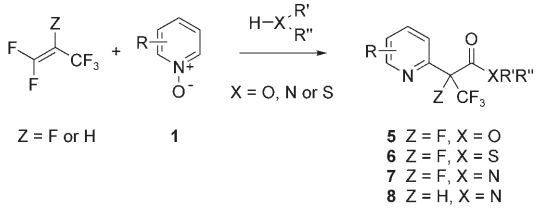
are stable fluorinated isoxazolidine derivatives **2**, as described by Knunyants and co-workers.[13] With azine *N*-oxides, the observed products are azines **3** substituted with a 1,2,2,2-tetrafluoroethyl group in the C2 position of the aromatic ring.[14-16] In this case, re-aromatisation of the ring provides the driving force for N–O bond scission in the transient 4,5,5-trifluoro-4-trifluoromethylisoxazolidines **2**, which generally cannot be isolated. Nevertheless, we have isolated and characterised an isoxazolidine derived from quinoline *N*-oxide **1a**,[16] giving support for the reaction mechanism shown in Scheme 2. This mechanism was proposed by



Scheme 2. The mechanism of the reaction of HFP with azine *N*-oxides proposed in ref. [15].

Banks, Haszeldine et al. and is based on the observation of some side-products.[15] According to this mechanism, further transformations of **2** leading to the products **3** involve loss of difluorophosgene $F_2C{=}O$, which was detected among the volatile products of this reaction, together with carbon dioxide.

In the current paper, we present evidence that the transformation of the isoxazolidines formed in the 1,3-dipolar cycloaddition of fluoroalkenes with aromatic *N*-oxides proceeds according to a different mechanism. These findings allowed us to elaborate a novel, three-component reaction of azine *N*-oxides with HFP in the presence of oxygen, sulphur or nitrogen nucleophiles. It also provides access to a wide range of derivatives of 2-heteroarylperfluoropropionic acids with the general structure **5**–**7** or **8**, containing a partially fluorinated side-chain with an ester or amide functional group (Scheme 3). We have shown that the reaction leading

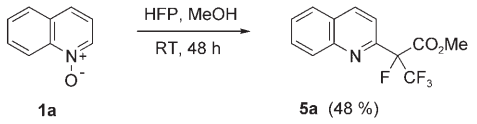


Scheme 3. The novel reaction of azine *N*-oxides **1** with HFP in the presence of protic nucleophiles presented in this paper.

to the products **3** is only a specific case of this general process.

Results and Discussion

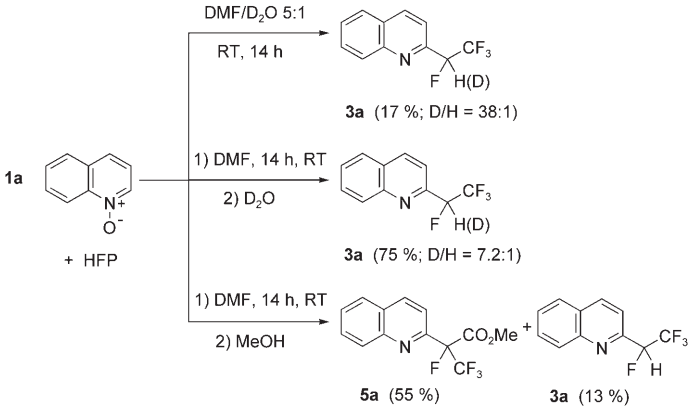
Reactions of quinoline *N*-oxide with HFP and MeOH or D_2O: In the course of our investigations on the reaction of HFP with azines *N*-oxides we were looking for the reaction medium that ensures the highest rate at room temperature and under moderate pressure (glass pressure tube). Under such mild conditions the reaction provides the products **3** very cleanly, but it is rather slow unless a polar solvent is used, such as DMF or MeCN.[16] In particular, it was interesting to perform the reaction in a protic solvent. Unexpectedly, after 48 h of reaction of quinoline *N*-oxide (**1a**) with HFP in MeOH at room temperature we observed exclusive formation of methyl ester **5a** in a moderate yield. No product **3a** containing a $CHFCF_3$ group was formed (Scheme 4).



Scheme 4. Reaction of quinoline *N*-oxide with HFP in MeOH to give a 2-arylperfluoropropionic acid methyl ester.

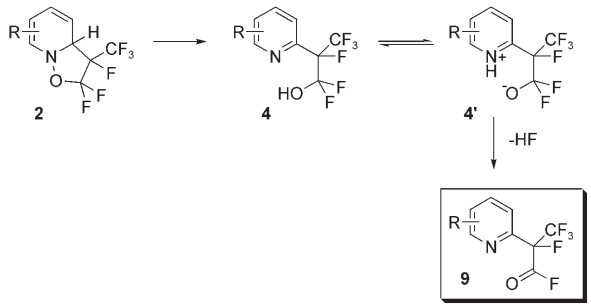
This is an interesting result from the synthetic point of view because a simple change of the reaction medium results in selective formation of a different product. Moreover, it prompted us to investigate the mechanism of the 1,3-dipolar cycloaddition of *N*-oxides with HFP in more detail because none of the intermediates proposed in the previous mechanism (Scheme 2) can account for the formation of an ester of type **5a** instead of product **3a** if an alcohol is present in the reaction mixture.

In our previous studies, the reactions of *N*-oxides with HFP were carried out in an aprotic solvent and gave products **3**, which were isolated by aqueous work-up of the reaction mixture.[16] We decided to perform a few experiments in which D_2O or MeOH were added after the reaction of **1a** with HFP. According to Scheme 2, the carbanion formed after the retro-aldol cleavage of the oxyanion **4′** is protonated by the proton originally present at the C2 position of the aromatic ring. Reaction of *N*-oxide **1a** with HFP in DMF/D_2O 5:1 afforded product **3a**, [16] which was almost completely deuterated in the side-chain. Of course, this may result from H-to-D exchange with the solvent in **3**, **4** or **4′** if they are sufficiently long-lived. However, in another experiment we treated *N*-oxide **1a** with HFP in dry DMF and then added D_2O to the reaction mixture after 14 h at room temperature. In this case, we again obtained deuterated product **3a**. In a separate experiment we confirmed that **3a** does not exchange a proton for a deuteron in the DMF/D_2O mixture. Finally, a similar reaction, but finished by addition of MeOH instead of D_2O, furnished mainly the methyl ester **5a** (Scheme 5).



Scheme 5. Reaction of **1a** with HFP in the presence of a) D_2O and reactions finished by addition of b) D_2O or c) MeOH.

These results strongly indicate that both possible types of products (**3** and **5**) originate from a common intermediate, which is gradually formed in the reaction mixture containing *N*-oxide, HFP and DMF and which does not undergo further transformations until water or MeOH is added. This intermediate is probably an acyl fluoride **9**, which originates from alcohol **4** (or its anion **4′**) by elimination of hydrogen fluoride, instead of C–C bond cleavage to produce COF_2 (Scheme 6). If this bond was cleaved in a process concurrent

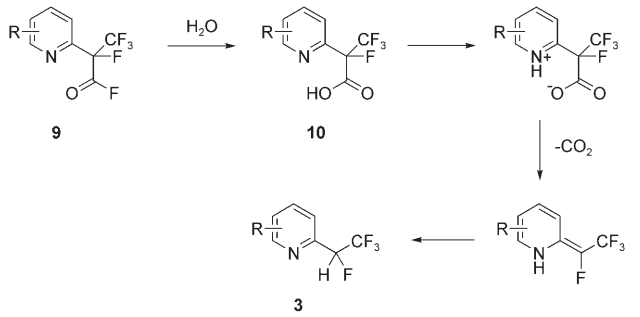


Scheme 6. Formation of acyl fluoride **9** from the isoxazolidine derivative **2**.

to the formation of fluoride **9**, then products **3** would always be present along with the products of type **5**–**8**. This is not the case, as was determined in the experiment from Scheme 4 and many experiments described in the next sections. The formation of non-deuterated **3a** in the reactions in Scheme 5 is attributable to the presence of H_2O in D_2O and MeOH used.

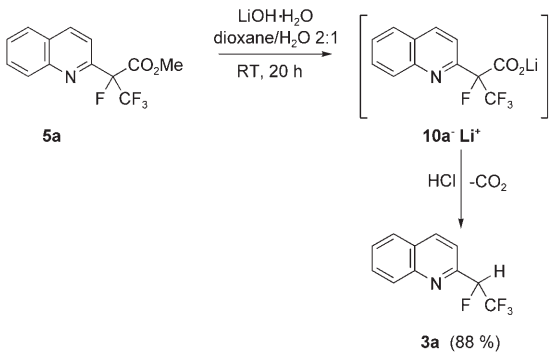
Although the formation of methyl esters **5** from acyl fluoride and MeOH is straightforward, formation of the products containing a $CHFCF_3$ group in the presence of water requires further comment. Apparently, the expected carboxylic acid **10** obtained by hydrolysis of **9** cannot be isolated.

Instead it must undergo a facile decarboxylation according the pathway depicted in Scheme 7 to produce the observed product of type **3**. To verify this hypothesis we performed



Scheme 7. Spontaneous decarboxylation of carboxylic acids **10** derived from acyl fluorides **9**.

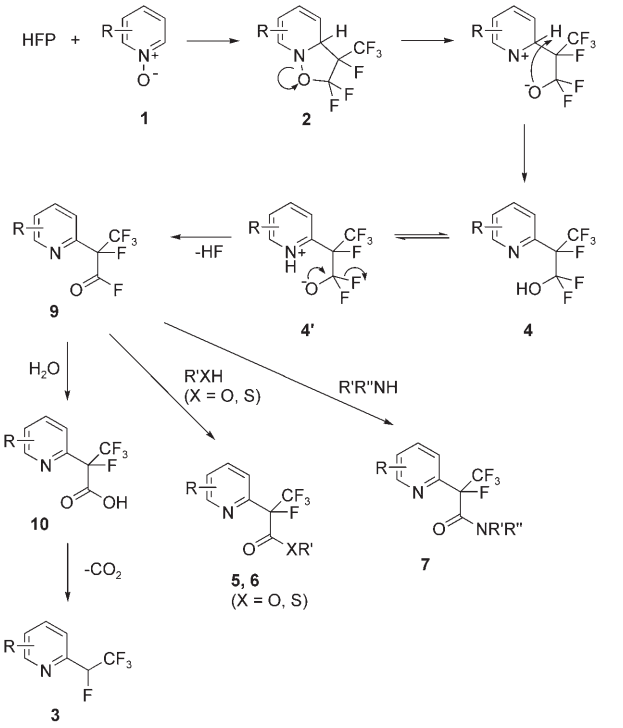
hydrolysis of the ester **5a** under basic conditions. If the reaction mixture was acidified after 20 h, gas evolution was observed and product **3a** was isolated exclusively in a yield of 88% (Scheme 8).



Scheme 8. Hydrolysis of methyl ester **5a** leads to the decarboxylated product **3a** containing a $CHFCF_3$ substituent.

Because a carboxylic acid of type **10** cannot be obtained as a consequence of its facile decarboxylation, we attempted to isolate its salt by using an ion-pair extraction technique. In an experiment similar to the one shown in Scheme 8, instead of acidifying the reaction mixture we diluted it with water, added 2 equivalents of $n\mathrm{Bu_4N^+F^-}\cdot 3\,\mathrm{H_2O}$ and extracted with CH_2Cl_2. We envisioned that lipophilic ion pairs containing an ammonium cation and anion of **10a** would be extracted into the organic phase, provided that the latter ion is sufficiently stable. Drying the CH_2Cl_2 solution over anhydrous Na_2SO_4 and evaporation gave an oily residue. The ^{1}H NMR spectrum of the residue in $CDCl_3$ revealed that it contained an equimolar amount of compound **3a** and some $n\mathrm{Bu_4N^+}$-containing inorganic salt. This result does not directly confirm the isolation of the $(n\mathrm{Bu_4N})^+\mathbf{10a}^-$ salt, but it does suggest that it must have been extracted from water to the CH_2Cl_2 organic phase and then it was probably transformed into **3a** in the chloroform solution, which is slightly acidic.

Discussion of the mechanism: In light of the above experiments a modified, generalised mechanism for the reaction of HFP with aromatic *N*-oxides can be proposed (Scheme 9). The reaction begins with 1,3-dipolar cycloaddi-



Scheme 9. The revised mechanism for the reaction of azine *N*-oxides with HFP, accounting for the formation of the perfluoropropionic acids esters and amides.

tion of *N*-oxide to HFP to give a 4,5,5-trifluoro-4-trifluoromethylisoxazolidine derivative **2**, which could be isolated and characterised in the case of **2a**, as we have previously reported.[16] Re-aromatisation of the heterocyclic ring by means of proton abstraction and N–O bond cleavage leads to oxyanion **4′**. This anion eliminates HF to give acyl fluoride **9**. In the presence of nucleophilic reagents, such as water or alcohols, or in fact any protic nucleophiles of the general type HXR′R″, as described in the following sections, this intermediate is transformed, respectively, into a carboxylic acid **10** or an acylation product **5**–**8** (for example, ester **5a**). In the former case, the acid undergoes spontaneous decarboxylation to give the products **3** with a $CHFCF_3$ group, which have already been observed by Mailey and Ocone or Banks, Haszeldine et al. in reactions between *N*-oxides and HFP finished by aqueous workup.[14,15]

The hypothesis regarding the transformation of **4** into **9** by elimination of HF instead of difluorophosgene differs from the earlier proposal by Banks, Haszeldine et al.[15] However, the main gaseous product in their experiments

was also CO_2, which according to the mechanism from Scheme 9 is formed at the decarboxylation step. COF_2 was also detected, but the experiments were run under harsh conditions (autoclave, high temperature and pressure) that might have caused some other unidentified side-reactions.

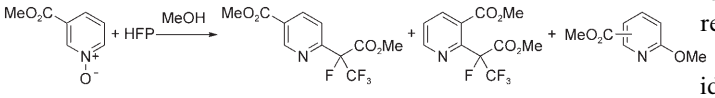
The mechanism shown in Scheme 9 has potentially useful synthetic implications—one may expect that apart from products **3** the reaction of aromatic *N*-oxides and perfluoroalkenes may afford a variety of esters of the general type $Ar{-}CFR_f{-}CO_2R'$ ($R_f = CF_3$ in the case of HFP). Moreover, the fact that the nucleophile can be added after the reaction of the *N*-oxide with HFP to give **9** is completed implies that it is possible to use nucleophiles which normally react directly with HFP, for example, amines. In fact, the range of accessible products would be limited only by the range of nucleophiles that can be acylated by an acyl fluoride. In the following sections we describe preparative reactions with protic nucleophiles of the type HXR′R″, where X=O, N or S.

Optimisation of the reaction of methyl nicotinate *N*-oxide with HFP and MeOH: As alcohols do not react with HFP in the absence of strong bases, their reaction with **1** and HFP to give heteroarylperfluoropropionic esters $Ar{-}CFR_f{-}CO_2R'$ can be performed by mixing all the reagents together at the beginning of the reaction. Because the reaction of comparatively reactive quinoline *N*-oxide (**1a**) in the preliminary experiment in Scheme 4 gave **5a** only in a moderate yield, we attempted to find better conditions. The reactions of moderately active methyl nicotinate *N*-oxide (**1b**) with HFP and MeOH under various conditions are shown in Table 1.

The reaction under conditions similar to those from Scheme 4 (Table 1, entry 1) gave a mixture of isomeric products **5b** and **5b′** in a moderate total yield of 36% together with isomeric 2- and 6-methoxynicotinic acid methyl esters. These side-products were probably formed by means of a *cine* nucleophilic substitution in the *N*-oxide with MeOH acting as a nucleophile and probably HFP or other electrophilic species transforming the *N*-oxide oxygen atom into a good leaving group. Increasing the temperature to 80°C raised the yield to 61% (entry 2). Considering that during the reaction 2 equiv of HF are produced, we attempted to neutralise the mixture by adding various bases (entries 3–5). Unfortunately, the yields were actually lower. In the case of K_2CO_3, the only reaction was oligomerisation of HFP. Finally, we attempted to use additional solvents with MeOH used only as an additive to the reaction mixture. The reactions with mixtures of MeOH and MeCN or DMF gave the expected esters **5b** and **5b′** as the sole products in a high combined yield of 87% (entry 9, DMF/MeOH 6.2:1, i.e., 10 equiv of MeOH relative to **1b**). These conditions were then used to investigate reactions of other *N*-oxides, as described in the next section.

It should be noted that no products of type **3** were detected in any of experiments shown in Table 1.

Table 1. Optimisation of the conditions of the reaction between HFP, **1b** and MeOH.



1b **5b** **5b'**

	Conditions	Yields of products (%)			
		5b	**5b′**	**5b+5b′**	2-OMe
1	MeOH, RT, 24 h	24	12	36	≈20
2	MeOH, 80°C, 24 h	24	37	61	17
3	MeOH, 1.2 equiv K_2CO_3, RT, 24 h	0	0	0[a]	0
4	MeOH, 2.4 equiv $NaHCO_3$, RT, 24 h	8	11	19	≈5
5	MeOH, 2.4 equiv Py, RT, 24 h	traces	traces	–	traces
6	PhMe/MeOH 6.2:1, 80°C, 5 h	all products detected; low conversion			
7	MeCN/MeOH 6.2:1, 80°C, 5 h	29[b]	42[b]	71	traces
8	DMF/MeOH 3:1, 80°C, 5 h	35	44	79	0
9	DMF/MeOH 6.2:1, 80°C, 5 h	34	53	87	0

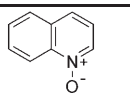
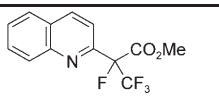
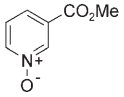
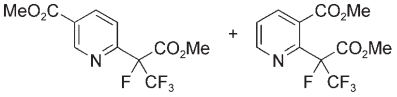
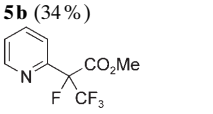
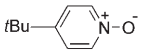
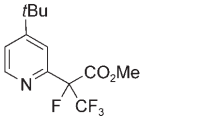
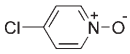
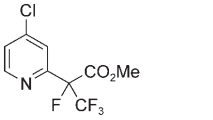
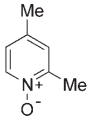
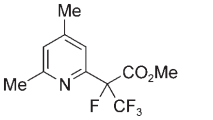
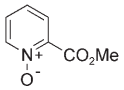
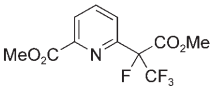
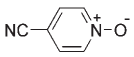
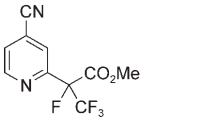
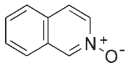
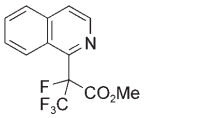
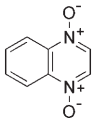
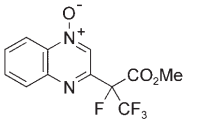
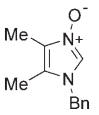
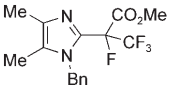
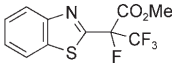
[a] Oligomerisation of HFP occurred. [b] Based on the ^{1}H NMR spectrum of the mixture of **5b** and **5b′** purified by column chromatography.

Synthesis of esters of 2-heteroarylperfluoropropionic acids from *N*-oxides, HFP and alcohols: The optimized conditions (Table 1, entry 9) were used to perform a series of reactions of various *N*-oxides of six- and five-membered heterocycles. The results are summarised in Table 2. Pyridine *N*-oxides containing substituents of different electronic and steric character (H, alkyl, Cl, CN, CO_2Me), as well as *N*-oxides of imidazole or thiazole, all afforded the respective 2-heteroarylperfluoropropionic acid methyl esters in good or very good yields. These compounds were the exclusive products or were formed along with only traces of the products of type **3**, with the exception of the reaction with quinoxaline dioxide **1j** that produced large amounts of **3j**. Its formation results from the presence of water in the substrate, which is a highly hygroscopic compound. In some cases, the reaction performed at room temperature (entries 6, 11, 12) or over a longer period of time (entry 7) gave comparable or better results compared to the standard conditions.

To check the scalability of the process, the reaction of pyridine *N*-oxide (**1c**; Table 2, entry 3) was performed with 19 mmol of substrate. The product, which is volatile in this case, was isolated in a good yield after aqueous work-up and distillation under reduced pressure.

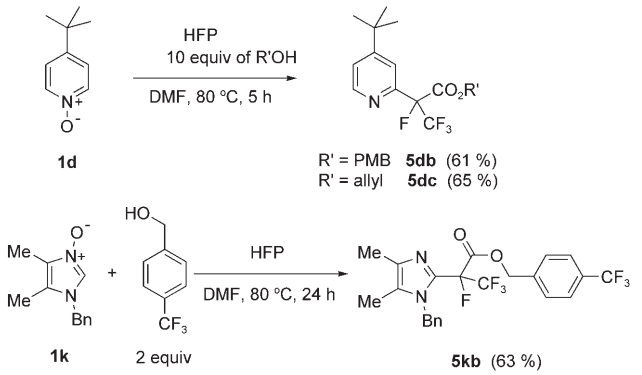
Instead of MeOH, other alcohols can be also used to produce the respective esters, as demonstrated by the examples of the reactions of 4-*tert*-butylpyridine *N*-oxide (**1d**) and 3-benzyl-4,5-dimethylimidazole *N*-oxide (**1k**) shown in Scheme 10. We also attempted a reaction of **1d** with HFP and 2,2,2-trifluoroethanol. Formation of the expected product was confirmed by the ^{1}H NMR spectrum of the crude reaction mixture, but we were unable to obtain an analytical sample because it was too prone to decompose by hydrolysis and decarboxylation to give **3d**.

Table 2. Synthesis of methyl 2-heteroarylperfluoropropionates from *N*-oxides, HFP and methanol.

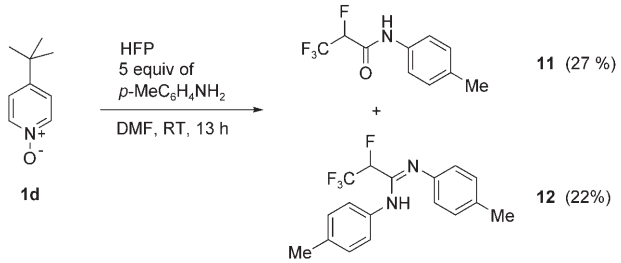
	Substrate		Products and yields	
1		**1a**		**5a** (75%)
2		**1b**		**5b** (34%) + **5b′** (53%)
3		**1c**		**5c** (76%)
4		**1d**		**5d** (70%)
5		**1e**		**5e** (85%)
6		**1f**		**5f** (34%)[a]
7		**1g**		**5g** (30%)[b]
8		**1h**		**5h** (43%)
9		**1i**		**5i** (28%)
10		**1j**		**5j** (38%) (+37% of **3j**)
11		**1k**[17]		**5k** (34%)[c]
12		**1l**		**5l** (80%)[d]

[a] 44% after 24 h at RT. [b] 29% after 24 h at 80°C. [c] 30% after 16 h at RT. [d] After 24 h at RT.

Synthesis of amides of 2-heteroarylperfluoropropionic acids: As expected, preliminary attempts to obtain amides of 2-heteroarylperfluoropropionic acids analogously to the synthesis of esters, that is by mixing together HFP, azine *N*-oxide and aliphatic or primary aromatic amines, did not provide any of the expected amides because a direct reaction between the amine and HFP prevailed. For example, reaction of HFP, **1d** and *p*-toluidine afforded products **11** and **12** exclusively (Scheme 11).[18]

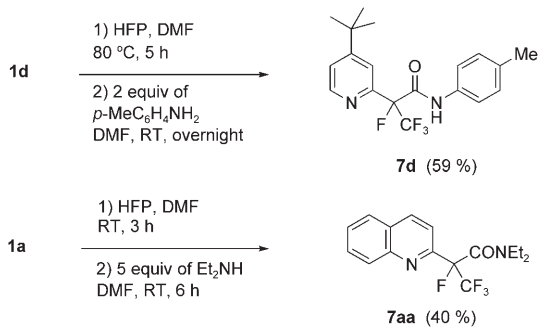


Scheme 10. Examples of preparation of esters from *N*-oxides, HFP and alcohols.



Scheme 11. Reaction of HFP with primary amine is faster than the reaction with an *N*-oxide.

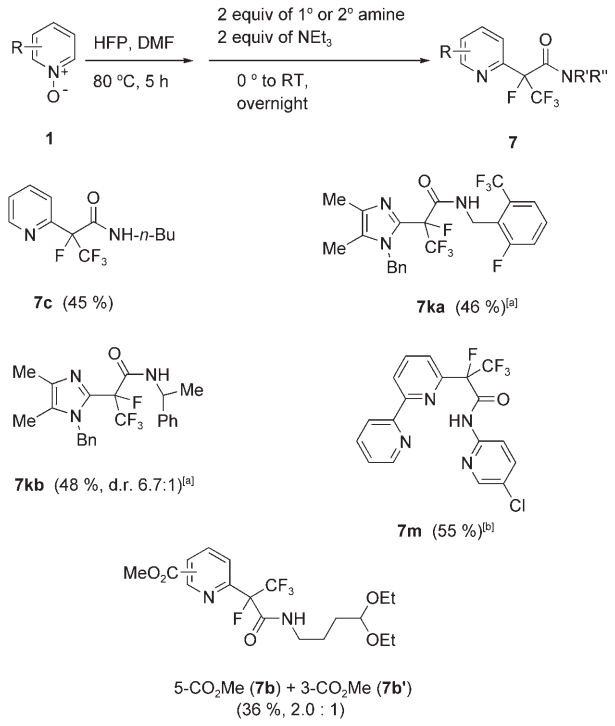
From the discussion of the previous sections it follows that this problem could be solved by separating the two steps of the reaction with respect to time, namely, formation of acyl fluorides followed by their subsequent reaction with a nucleophile. An example of such a process is the esterification reaction in Scheme 5. The following experiment was thus performed (Scheme 12): 4-*tert*-butylpyridine *N*-oxide and HFP were reacted in DMF at 80°C for 5 h in a pressure tube, then the reaction mixture was cooled to room temperature, excess HFP was evaporated under reduced pressure,



Scheme 12. The two step, one-pot procedure for the preparation of amides **7**.

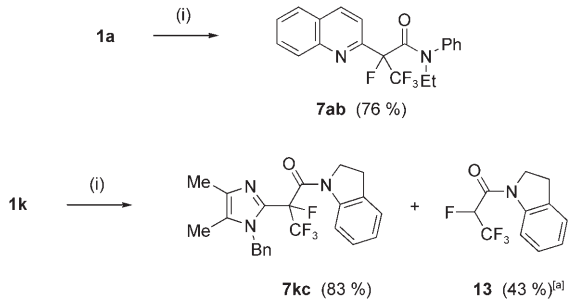
and *p*-toluidine (2 equivalents) in DMF was added dropwise. After 14 h at room temperature and aqueous work-up, toluamide **7d** was isolated in a good yield. Similarly to the synthesis of esters, no product containing a $CHFCF_3$ substituent was detected. A similar reaction of quinoline *N*-oxide and diethylamine produced tertiary amide **7aa**.

In the course of further experiments we found that better yields of amides can be obtained if triethylamine is added at 0°C along with the amine which is acylated. Its role is probably to neutralise HF evolved during the formation of the acyl fluoride intermediate. We used this protocol to obtain more elaborate amides **7b**, **7b′**, **7c**, **7ka**, **7kb** and **7m** (from 2,2′-bipyridyl *N*-oxide (**1m**)) in fairly good yields (Scheme 13).



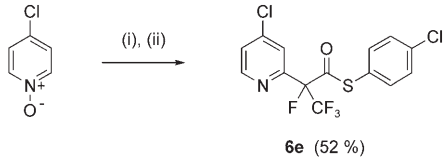
Scheme 13. The two-step, one-pot procedure for the preparation of amides **7** in the presence of NEt_3. [a] The first step for 24 h at RT. [b] The first step for 24 h.

Activity of some alkylarylamines towards HFP is low enough to allow a simplified synthesis of the respective 2-heteroaryl-perfluoropropionic amides in a way analogous to the synthesis of esters. For example, quinoline *N*-oxide reacts with HFP and *N*-ethylaniline at room temperature to provide amide **7ab** as the sole product. The reaction of **1k** and indoline gave amide **7kc** together with some side-product **13** from the reaction of indoline with HFP (Scheme 14).



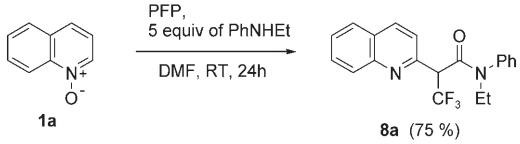
Scheme 14. Direct preparation of tertiary amides of 2-heteroarylperfluoropropionic acids with secondary amines of low nucleophilicity. i) HFP, DMF, 2 equiv of amine, RT, 24 h; [a] yield based on the starting indoline.

Synthesis of thioesters from thiols: The preparation of thioesters is exemplified by the reaction performed according to the two-step, one-pot protocol in which the acyl fluoride **9e** is first formed from 4-chloropyridine *N*-oxide and HFP, followed by its reaction with 4-chlorothiophenol to give **6e** in a moderate yield (Scheme 15).



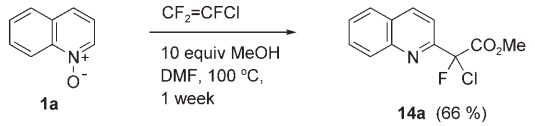
Scheme 15. The two-step, one-pot procedure for the preparation of thioester **6e**. i) HFP, DMF, 80°C, 5 h; ii) 2 equiv of *p*-ClC_6H_4SH, DMF, RT, 14 h.

Reactions of other fluorinated alkenes: In the preliminary experiments we found that 2H-pentafluoropropene (PFP) reacts with aromatic *N*-oxides and protic nucleophiles in a manner similar to HFP. Reaction of **1a** with *N*-ethylaniline in the presence of PFP in DMF at room temperature afforded the expected tertiary amide **8a** in a good yield. Compound **8a** was obtained in nearly the same yield as the analogous product **7ab** from HFP, which suggests that both alkenes exhibit similar activity in the 1,3-dipolar cycloaddition reaction with aromatic *N*-oxides (Scheme 16).



Scheme 16. Preparation of trifluoropropionic amide **8**.

Chlorotrifluoroethylene, CF_2=CFCl, exhibits a much lower activity than HFP towards aromatic *N*-oxides. Its reaction with MeOH and **1a**, which is one of the most active *N*-oxides we studied in the reactions with HFP, provided the ester **14a** in a reasonable yield only under forcing conditions (Scheme 17).



Scheme 17. Reaction of quinoline *N*-oxide (**1a**) with chlorotrifluoroethylene and MeOH.

Further investigation of the scope of the reactions of PFP and other fluoroalkenes is under way in our laboratory.

Conclusion

Hexafluoropropene reacts with azine *N*-oxides along a 1,3-dipolar cycloaddition pathway to produce unstable isoxazolidines that undergo rapid aromatisation by N–O bond scission, followed by elimination of HF to give 2-heteroaryl-2,3,3,3-tetrafluoropropionic acid fluorides as the final products. These intermediates, which are stable in anhydrous aprotic media, can react with a variety of protic nucleophiles. Quenching the reaction mixture with water causes hydrolysis of the fluoride followed by decarboxylation. The overall result is thus an introduction of a 1,2,2,2-tetrafluoroethyl group into the heteroaromatic ring. When the reaction of HFP with *N*-oxides is carried out in the presence of weak nucleophiles, such as alcohols and alkyl aryl amines, the corresponding esters and amides of 2-arylperfluoropropionic acids are obtained in good yields. Alternatively, acylation of a variety of amines and thiols can be performed by means of a two-step, one-pot procedure.[19]

The above-described reaction has a general character: by changing the *N*-oxide, fluoroalkene and nucleophile it is possible to independently modify the three parts of the desired molecule, the heterocyclic moiety, the fluorinated fragment and the functionality present in the acyl group. This process could be thus applied to the construction of combinatorial libraries of partially fluorinated compounds in the search for new pharmacologically interesting lead structures.

Experimental Section

General information: The reactions of fluoroalkenes were performed under an argon atmosphere (technical grade argon) in a flame-dried glass pressure tube (≈3.5 mL volume) equipped with a Teflon valve and a magnetic stirring element. The solvents used in these reactions were commercially available puriss p.a. grade solvents (DMF, MeCN, MeOH) or were distilled before use (toluene). Solvents for extraction or chromatography were freshly distilled before use. Other reagents were either used as obtained from the manufacturer or purified according to literature procedures.[20] Flash chromatography was performed by using silica gel 60 (0.040–0.063 mm). Thin-layer chromatography was performed by using pre-coated silica gel plates and visualised under a UV lamp. NMR spectra were recorded in $CDCl_3$ at the spectrometer frequencies indicated in the description of each compound. Chemical shifts are given in ppm relative to TMS for ^1H and ^{13}C NMR spectra and $CFCl_3$ for ^{19}F NMR spectra. IR spectra were recorded by using a FT-IR spectrometer. Mass spectra were obtained by using electron impact (EI) or electrospray (ESI) ionisation.

The azine *N*-oxides were prepared either by the traditional method (heating with 30% H_2O_2-AcOH)[12a] or from the reaction with a urea-hydrogen peroxide complex (UHP) and trifluoroacetic anhydride.[21]

General procedure for reactions of azines *N*-oxides with fluoroalkenes and alcohols. Synthesis of 2-heteroarylperfluoropropionic methyl esters: The fluoroalkene (≈0.5 mL, 4 mmol) was condensed in a glass pressure tube at −78 °C under an argon atmosphere. DMF (2.4 mL; or other solvent, see text), *N*-oxide (0.95 mmol) and MeOH (0.385 mL, 9.50 mmol) were introduced, and the pressure tube was closed with a Teflon valve. The contents of the tube were stirred vigorously at 80 °C for 5 h. The tube was opened, the reaction mixture was poured into water (10 mL), and the products were extracted with CH_2Cl_2 (3×5 mL). Combined organic layers were washed with water (5×10 mL), dried over anhydrous Na_2SO_4 and concentrated. The products were purified by column chromatography (silica gel; 10:1 or 5:1 mixtures of hexanes/AcOEt or hexanes/Et_2O).

Methyl 2-(2′-quinolinyl)perfluoropropionate (5a): Pale yellow oil; ^1H NMR (400 MHz): $\delta=3.99$ (d, $^5J(H,F)=0.4$ Hz, 3H; OCH_3), 7.63 (ddd, $^3J(H,H)=8.1$ Hz, 6.9 Hz, $^4J(H,H)=1.1$ Hz, 1H; H_{ar}), 7.74–7.80 (m, 2H; H_{ar}), 7.87 (dd, $^3J(H,H)=8.2$ Hz, $^4J(H,H)=1.1$ Hz, 1H; H_{ar}), 8.13 (dd, $^3J(H,H)=8.5$ Hz, $^4J(H,H)=0.7$ Hz, 1H; H_{ar}), 8.31 ppm (d, $^3J(H,H)=8.7$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta=53.6$, 93.6 (dq, $^1J(C,F)=200.0$ Hz, $^2J(C,F)=31.0$ Hz), 118.0 (dd, $^3J(C,F)=5.2$ Hz, $^4J(C,F)=1.7$ Hz), 121.1 (qd, $^1J(C,F)=285.4$ Hz, $^2J(C,F)=30.2$ Hz), 127.6, 128.2, 128.2, 130.1, 130.3, 137.7, 147.0 (d, $^4J(C,F)=1.7$ Hz), 149.9 (d, $^2J(C,F)=25.9$ Hz), 163.5 ppm (d, $^2J(C,F)=23.3$ Hz); ^{19}F NMR (376.4 MHz): $\delta=-168.53$ (q, $^3J(F,F)=8.3$ Hz, 1F, C*F*CF$_3$), −75.78 ppm (d, $^3J(F,F)=8.3$ Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}=3066$, 2960, 1770, 1596, 1505, 1439, 1301, 1276, 1209, 1181, 1114, 1041, 829, 801, 759 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 287 (100) $[M]^+$, 272 (22), 256 (7), 243 (12), 228 (62), 178 (54), 174 (29), 158 (32), 128 (41); EI-HRMS: *m*/*z*: calcd for $C_{13}H_9NO_2F_4$: 287.0569 $[M]^+$; found: 287.0574; elemental analysis calcd (%) for $C_{13}H_9NO_2F_4$ (287.2): C 54.37, H 3.16, N 4.88, F 26.46; found: C 53.92, H 2.97, N 5.01, F 26.43.

Methyl 2-(5′-methoxycarbonylpyridin-2′-yl)perfluoropropionate (5b): Colourless crystalline solid, m.p. 94–95 °C (hexanes/Et_2O); ^1H NMR (400 MHz): $\delta=3.95$ (d, $^5J(H,F)=0.3$ Hz, 3H; OCH_3), 3.99 (s, 3H; OCH_3), 7.81 (d, $^3J(H,H)=8.2$ Hz, 1H; H_{ar}), 8.46 (dd, $^3J(H,H)=8.3$ Hz, $^4J(H,H)=2.1$ Hz, 1H; H_{ar}), 9.22 ppm (dm, $^4J(H,H)=2.1$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta=52.8$, 53.9, 92.8 (dq, $^1J(C,F)=200.9$ Hz, $^2J(C,F)=31.0$ Hz), 120.8 (qd, $^1J(C,F)=285.4$ Hz, $^2J(C,F)=29.3$ Hz), 121.4 (d, $^3J(C,F)=6.9$ Hz), 127.4, 138.5, 150.4 (d, $^4J(C,F)=1.7$ Hz), 153.6 (d, $^2J(C,F)=25.9$ Hz), 162.9 (d, $^2J(C,F)=22.4$ Hz), 164.7 ppm; ^{19}F NMR (376.4 MHz): $\delta=-170.15$ (q, $^3J(F,F)=7.8$ Hz, 1F, C*F*CF$_3$), −76.25 ppm (d, $^3J(F,F)=7.8$ Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}=2961$, 1772, 1735, 1599, 1439, 1295, 1212, 1192, 1123, 1042, 1026, 740 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 295 (52) $[M]^+$, 280 (51), 264 (41), 251 (79), 236 (72), 186 (81), 59 (100); EI-HRMS: *m*/*z*: calcd for $C_{11}H_9NO_4F_4$: 295.0468 $[M]^+$; found: 295.0466; elemental analysis calcd (%) for $C_{11}H_9NO_4F_4$ (295.2): C 44.76, H 3.07, N 4.75, F 25.74; found: C 44.68, H 3.10, N 4.71, F 25.71.

Methyl 2-(3′-methoxycarbonylpyridin-2′-yl)perfluoropropionate (5b′): Pale yellow oil; ^1H NMR (400 MHz): $\delta=3.90$ (s, 3H; OCH_3), 3.90 (s, 3H; OCH_3), 7.50 (ddd, $^3J(H,H)=7.8$ Hz, 4.8 Hz, $J=0.8$ Hz, 1H; H_{ar}), 8.15 (dd, $^3J(H,H)=7.8$ Hz, $^4J(H,H)=1.5$ Hz, 1H; H_{ar}), 8.78 ppm (dd, $^3J(H,H)=4.9$ Hz, $^4J(H,H)=1.3$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta=52.9$, 53.9, 92.9 (dq, $^1J(C,F)=202.6$ Hz, $^2J(C,F)=30.2$ Hz), 121.0 (qd, $^1J(C,F)=287.1$ Hz, $^2J(C,F)=27.6$ Hz), 124.4, 127.0, 138.5, 149.6 (d, $^2J(C,F)=25.0$ Hz), 150.3, 163.6 (d, $^2J(C,F)=24.1$ Hz), 166.0 ppm; ^{19}F NMR (376.4 MHz): $\delta=-162.88$ (q, $^3J(F,F)=8.1$ Hz, 1F, C*F*CF$_3$), −73.52 ppm (d, $^3J(F,F)=8.1$ Hz, 3F, CFC*F*$_3$); IR (KBr): $\tilde{\nu}=3017$, 2963, 1758, 1726, 1588, 1442, 1300, 1268, 1215, 1169, 1144, 1115, 1091, 1062, 1035, 971, 778, 755, 681, 636 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 295 (10) $[M]^+$, 280 (18), 264 (26), 250 (39), 236 (100), 206 (45), 177 (16), 150 (38), 139 (31); EI-HRMS: *m*/*z*: calcd for $C_{11}H_9NO_4F_4$: 295.0468 $[M]^+$; found: 295.0455; elemental analysis calcd (%) for $C_{11}H_9NO_4F_4$ (295.2): C 44.76, H 3.07, N 4.75, F 25.74, found: C 44.66, H 3.02, N 4.77, F 25.73.

Methyl 2-(4′-*tert*-butylpyridin-2′-yl)perfluoropropionate (5d): Colourless oil; ^1H NMR (400 MHz): $\delta=1.35$ (s, 9H; *t*Bu), 3.95 (s, 3H; OCH_3), 7.39 (dd, $^3J(H,H)=5.3$ Hz, $^4J(H,H)=1.8$ Hz, 1H; H_{ar}), 7.68 (s, 1H; H_{ar}),

8.54 ppm (d, ^3J(H,H) = 5.3 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 30.4, 35.1, 53.7, 93.2 (dq, ^1J(C,F) = 200.0 Hz, ^2J(C,F) = 31.0 Hz), 118.5 (d, ^3J-(C,F) = 5.2 Hz), 121.2 (qd, ^1J(C,F) = 285.4 Hz, ^2J(C,F) = 29.3 Hz), 122.3, 149.3 (d, ^4J(C,F) = 1.7 Hz), 150.0 (d, ^2J(C,F) = 25.0 Hz), 161.9, 163.6 ppm (d, ^2J(C,F) = 23.3 Hz); ^{19}F NMR (376.4 MHz): δ = −169.38 (q, ^3J(F,F) = 7.8 Hz, 1F, C*F*CF$_3$), −76.47 ppm (d, ^3J(F,F) = 7.8 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 2968, 2875, 1771, 1602, 1439, 1309, 1275, 1209, 1181, 1098, 1046, 1002, 852, 807 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 293 (45) $[M]^+$, 278 (100), 234 (70), 218 (40); EI-HRMS: *m*/*z*: calcd for $C_{13}H_{15}NO_2F_4$: 293.1039 $[M]^+$; found: 293.1031; elemental analysis calcd (%) for $C_{13}H_{15}NO_2F_4$ (293.3): C 53.24, H 5.16, N 4.78, F 25.91; found: C 53.00, H 5.20, N 4.81, F 25.76.

Methyl 2-(4′-chloropyridin-2′-yl)perfluoropropionate (5e): White solid, m.p. 45–46 °C; ^{1}H NMR (400 MHz): δ = 3.94 (s, 3H; OCH_3), 7.44 (dd, ^3J-(H,H) = 5.3 Hz, ^4J(H,H) = 1.8 Hz, 1H; H_{ar}), 7.72 (s, 1H; H_{ar}), 8.55 ppm (d, ^3J(H,H) = 5.3 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 53.9, 92.4 (dq, ^1J(C,F) = 201.7 Hz, ^2J(C,F) = 31.9 Hz), 120.7 (qd, ^1J(C,F) = 285.4 Hz, ^2J-(C,F) = 29.3 Hz), 122.3 (d, ^3J(C,F) = 6.9 Hz), 125.7, 145.7, 150.3 (d, ^4J-(C,F) = 1.7 Hz), 151.5 (d, ^2J(C,F) = 25.9 Hz), 162.8 ppm (d, ^2J(C,F) = 23.3 Hz); ^{19}F NMR (376.4 MHz): δ = −170.15 (q, ^3J(F,F) = 7.6 Hz, 1F, C*F*CF$_3$), −76.37 ppm (d, ^3J(F,F) = 7.6 Hz, 3F, CFC*F*$_3$); IR (KBr): $\tilde{\nu}$ = 2970, 2925, 1760, 1578, 1306, 1281, 1210, 1195, 1127, 1042, 852, 705 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 271 (26) $[M]^+$, 256 (27), 240 (7), 227 (22), 212 (27), 193 (10), 177 (15), 162 (50), 112 (26), 59 (100); EI-HRMS: *m*/*z*: calcd for $C_9H_6NO_2{}^{35}ClF_4$: 271.0023 $[M]^+$; found: 271.0015; elemental analysis calcd (%) for $C_9H_6NO_2ClF_4$ (271.6): C 39.80, H 2.23, N 5.16, Cl 13.05, F 27.98; found: C 39.65, H 1.98, N 5.24, Cl 12.91, F 28.00.

Methyl 2-(4′,6′-dimethylpyridin-2′-yl)perfluoropropionate (5f): Yellow crystalline solid, m.p. 35–36 °C (hexanes/Et_2O); ^{1}H NMR (400 MHz): δ = 2.37 (s, 3H; CH_3), 2.49 (s, 3H; CH_3), 3.93 (d, ^5J(H,F) = 0.4 Hz, 3H; OCH_3), 7.06 (d, ^4J(H,H) = 0.6 Hz, 1H; H_{ar}), 7.30 ppm (s, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 21.1, 24.1, 53.5, 93.3 (dq, ^1J(C,F) = 200.0 Hz, ^2J(C,F) = 31.9 Hz), 119.5 (d, ^3J(C,F) = 4.3 Hz), 121.1 (qd, ^1J(C,F) = 284.5 Hz, ^2J(C,F) = 29.3 Hz), 125.7, 148.6, 149.3 (d, ^2J(C,F) = 24.1 Hz), 158.4, 163.8 ppm (d, ^2J(C,F) = 24.1 Hz); ^{19}F NMR (376.4 MHz): δ = −167.88 (q, ^3J(F,F) = 8.1 Hz, 1F, C*F*CF$_3$), −76.18 ppm (d, ^3J(F,F) = 8.1 Hz, 3F, CFC*F*$_3$); IR (KBr): $\tilde{\nu}$ = 2964, 1763, 1613, 1445, 1302, 1211, 1183, 1159, 1108, 1067, 1032, 862, 792, 687 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 265 (100) $[M]^+$, 250 (28), 246 (5), 234 (13), 221 (20), 206 (85), 187 (22), 171 (14), 156 (55); EI-HRMS: *m*/*z*: calcd for $C_{11}H_{11}NO_2F_4$: 265.0726 $[M]^+$; found: 265.0731; elemental analysis calcd (%) for $C_{11}H_{11}NO_2F_4$ (265.2): C 49.82, H 4.18, N 5.28, F 28.65; found: C 49.50, H 4.12, N 5.30, F 28.70.

Methyl 2-(6′-methoxycarbonylpyridin-2′-yl)perfluoropropionate (5g): Pale yellow oil; ^{1}H NMR (400 MHz): δ = 3.98 (s, 3H; OCH_3), 3.99 (s, 3H; OCH_3), 7.89 (dd, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 0.6 Hz, 1H; H_{ar}), 8.02 (t, ^3J(H,H) = 8.0 Hz, 1H; H_{ar}), 8.22 ppm (dm, ^3J(H,H) = 7.8 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 52.9, 53.8, 92.9 (dq, ^1J(C,F) = 200.9 Hz, ^2J-(C,F) = 31.9 Hz), 120.9 (qd, ^1J(C,F) = 285.4 Hz, ^2J(C,F) = 29.3 Hz), 124.9 (d, ^3J(C,F) = 5.2 Hz), 126.4, 138.5, 147.9, 150.3 (d, ^2J(C,F) = 25.0 Hz), 163.2 (d, ^2J(C,F) = 23.3 Hz), 164.7 ppm; ^{19}F NMR (376.4 MHz): δ = −167.93 (q, ^3J(F,F) = 7.9 Hz, 1F, C*F*CF$_3$), −76.03 ppm (d, ^3J(F,F) = 7.8 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 2965, 1761, 1732, 1458, 1445, 1317, 1295, 1237, 1218, 1186, 1160, 1138, 1082, 1042, 996, 806, 768, 757, 747, 722, 697, 644 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 295 (<1) $[M]^+$, 265 (12), 237 (100), 206 (7), 186 (10), 177 (27); EI-HRMS: *m*/*z*: calcd for $C_{11}H_9NO_4F_4$: 295.0468 $[M]^+$; found: 295.0458; elemental analysis calcd (%) for $C_{11}H_9NO_4F_4$ (295.2): C 44.76, H 3.07, N 4.75, F 25.74; found: C 44.78, H 2.94, N 4.79, F 25.66.

Methyl 2-(4′-cyanopyridin-2′-yl)perfluoropropionate (5h): Pale yellow oil; ^{1}H NMR (400 MHz): δ = 3.95 (d, ^5J(H,F) = 0.6 Hz, 3H; OCH_3), 7.69 (ddd, ^3J(H,H) = 5.0 Hz, ^4J(H,H) = 1.5 Hz, J = 0.4 Hz, 1H; H_{ar}), 7.95 (m, 1H; H_{ar}), 8.86 ppm (ddd, ^3J(H,H) = 5.0 Hz, J = 0.9 Hz, 0.7 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 54.1, 92.3 (dq, ^1J(C,F) = 202.6 Hz, ^2J(C,F) = 31.9 Hz), 115.4, 120.6 (qd, ^1J(C,F) = 285.4 Hz, ^2J(C,F) = 28.4 Hz), 122.3, 123.5 (d, ^3J(C,F) = 8.6 Hz), 126.9, 150.5 (d, ^4J(C,F) = 1.7 Hz), 151.7 (d, ^2J-(C,F) = 25.9 Hz), 162.4 ppm (d, ^2J(C,F) = 23.3 Hz); ^{19}F NMR (376.4 MHz): δ = −170.50 (q, ^3J(F,F) = 8.3 Hz, 1F, C*F*CF$_3$), −76.30 ppm (d, ^3J(F,F) = 8.3 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 3080, 2964, 2243, 1771, 1600, 1440, 1312, 1276, 1212, 1162, 1132, 1046, 1008, 796 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 262 (13) $[M]^+$, 247 (11), 231 (4), 218 (34), 203 (24), 153 (37), 59 (100); EI-HRMS: m/z: calcd for $C_{10}H_6N_2O_2F_4$: 262.0365 $[M]^+$; found: 262.0370; elemental analysis calcd (%) for $C_{10}H_6N_2O_2F_4$ (262.2): C 45.82, H 2.31, N 10.69, F 28.99; found: C 45.89, H 2.38, N 10.65, F 29.07.

Methyl 2-(1′-isoquinolinyl)perfluoropropionate (5i): Yellow oil; ^{1}H NMR (400 MHz): δ = 3.91 (d, ^5J(H,F) = 0.4 Hz, 3H; OCH_3), 7.66 (ddd, ^3J-(H,H) = 8.6 Hz, 6.8 Hz, ^4J(H,H) = 1.5 Hz, 1H; H_{ar}), 7.73 (dd, ^3J(H,H) = 8.1 Hz, ^4J(H,H) = 1.1 Hz, 1H; H_{ar}), 7.76 (d, ^3J(H,H) = 6.0 Hz, 1H; H_{ar}), 7.89 (d, ^3J(H,H) = 8.2 Hz, 1H; H_{ar}), 8.42 (dm, ^3J(H,H) = 8.6 Hz, 1H; H_{ar}), 8.54 ppm (d, ^3J(H,H) = 5.5 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 53.8, 96.1 (dq, ^1J(C,F) = 199.6 Hz, ^2J(C,F) = 31.0 Hz), 121.5 (qd, ^1J(C,F) = 286.2 Hz, ^2J(C,F) = 29.3 Hz), 123.4, 125.0 (d, ^3J(C,F) = 13.8 Hz), 126.5 (d, ^4J(C,F) = 2.6 Hz), 127.7, 128.5 (d, ^4J(C,F) = 2.6 Hz), 130.5, 137.3 (d, J-(C,F) = 1.7 Hz), 140.7 (d, J(C,F) = 1.7 Hz), 148.5 (d, ^2J(C,F) = 24.1 Hz), 164.1 ppm (d, ^2J(C,F) = 24.1 Hz); ^{19}F NMR (376.4 MHz): δ = −164.39 (qd, ^3J(F,F) = 8.5 Hz, ^5J(F,H) = 3.1 Hz, 1F, C*F*CF$_3$), −74.08 ppm (d, ^3J(F,F) = 8.6 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 3061, 2960, 1771, 1587, 1439, 1341, 1297, 1270, 1259, 1215, 1204, 1170, 1123, 1081, 1034, 941, 833, 752 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 287 (100) $[M]^+$, 272 (41), 256 (5), 243 (7), 228 (68), 208 (18), 178 (28), 174 (26), 158 (16), 128 (38); EI-HRMS: *m*/*z*: calcd for $C_{13}H_9NO_2F_4$: 287.0569 $[M]^+$; found: 287.0574; elemental analysis calcd (%) for $C_{13}H_9NO_2F_4$ (287.2): C 54.37, H 3.16, N 4.88, F 26.46; found: C 53.79, H 3.26, N 4.80, F 26.40.

Methyl ester (5j): Pale yellow oil; ^{1}H NMR (400 MHz): δ = 4.01 (s, 3H; OCH_3), 7.81–7.93 (m, 2H; H_{ar}), 8.17 (dm, ^3J(H,H) = 8.3 Hz, 1H; H_{ar}), 8.57 (dm, ^3J(H,H) = 8.5 Hz, 1H; H_{ar}), 8.69 ppm (s, 1H; CH=N); ^{13}C NMR (100.6 MHz): δ = 54.1, 91.9 (dq, ^1J(C,F) = 204.3 Hz, ^2J(C,F) = 32.8 Hz), 118.8, 120.5 (qd, ^1J(C,F) = 286.2 Hz, ^2J(C,F) = 29.3 Hz), 127.5 (d, ^3J(C,F) = 7.8 Hz), 130.6, 131.7, 132.6, 137.4, 144.2, 147.2 (d, ^2J(C,F) = 25.9 Hz), 162.0 ppm (d, ^2J(C,F) = 23.3 Hz); ^{19}F NMR (376.4 MHz): δ = −171.58 (q, ^3J(F,F) = 7.8 Hz, 1F, C*F*CF$_3$), −75.83 ppm (d, ^3J(F,F) = 7.8 Hz, 3F, CFC*F*$_3$); IR (CH_2Cl_2): $\tilde{\nu}$ = 3095, 2962, 1773, 1580, 1499, 1375, 1302, 1272, 1212, 1124, 1044, 906, 800, 773 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 304 (100) $[M]^+$, 288 (8), 245 (25), 229 (23), 179 (33), 59 (86); elemental analysis calcd (%) for $C_{12}H_8N_2O_3F_4$(304.2): C 47.38, H 2.65, N 9.21, F 24.98; found: C 47.37, H 2.94, N 9.09, F 25.04.

2-(1′,2′,2′,2′-Tetrafluoroethyl)quinoxaline 4-oxide (3j): Yellow solid, m.p. 84–85 °C; ^{1}H NMR (400 MHz): δ = 5.90 (dq, ^2J(H,F) = 44.1 Hz, ^3J(H,F) = 5.9 Hz, 1H; CHF), 7.83 (dd, ^3J(H,H) = 8.5 Hz, 7.0 Hz, 1H; H_{ar}), 7.90 (dd, ^3J(H,H) = 8.4 Hz, 7.0 Hz, 1H; H_{ar}), 8.15 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.0 Hz, 1H; H_{ar}), 8.58 ppm (dd, ^3J(H,H) = 8.7 Hz, ^4J(H,H) = 1.4 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 88.3 (dq, ^1J(C,F) = 190.5 Hz, ^2J(C,F) = 35.4 Hz), 118.9, 121.4 (qd, ^1J(C,F) = 282.8 Hz, ^2J(C,F) = 27.6 Hz), 127.6 (d, ^3J(C,F) = 6.0 Hz), 130.3, 131.3, 132.5, 137.4, 144.6 (d, ^4J(C,F) = 1.7 Hz), 147.7 ppm (d, ^2J(C,F) = 24.1 Hz); ^{19}F NMR (376.4 MHz): δ = −201.91 (dq, ^2J(F,H) = 45.4 Hz, ^3J(F,F) = 12.4 Hz, 1F, CHF), −77.89 ppm (dd, ^3J(F,F) = 12.0 Hz, ^3J(F,H) = 6.0 Hz, 3F, CF_3); IR (KBr): $\tilde{\nu}$ = 3061, 1589, 1504, 1380, 1266, 1187, 1141, 1083, 798, 766, 699 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 246 (100) $[M]^+$, 227 (5), 177 (3); EI-HRMS: *m*/*z*: calcd for $C_{10}H_6N_2OF_4$: 246.0416 $[M]^+$; found: 246.0408; elemental analysis calcd (%) for $C_{10}H_6N_2OF_4$ (246.2): C 48.79, H 2.46, N 11.38, F 30.87; found: C 48.90, H 2.48, N 11.38, F 30.93.

Methyl ester (5k): Pale yellow oil; ^{1}H NMR (400 MHz): δ = 1.98 (d, ^6J-(H,F) = 1.4 Hz, 3H; CH_3), 2.21 (s, 3H; CH_3), 3.58 (s, 3H; OCH_3), 5.11 (d, ^2J(H,H) = 17.3 Hz, 1H; NCH_2), 5.30 (d, ^2J(H,H) = 17.3 Hz, 1H; NCH_2), 6.88 (d, ^3J(H,H) = 7.0 Hz, 2H; H_{ar}), 7.23–7.34 ppm (m, 3H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 9.0, 13.1, 48.0 (d, ^4J(C,F) = 6.0 Hz), 54.1, 90.3 (dq, ^1J(C,F) = 198.3 Hz, ^2J(C,F) = 32.8 Hz), 121.0 (qd, ^1J(C,F) = 286.2 Hz, ^2J(C,F) = 29.3 Hz), 125.7, 127.6, 127.8, 129.0, 133.9 (d, ^2J(C,F) = 24.1 Hz), 135.1, 135.9, 162.9 ppm (d, ^2J(C,F) = 27.6 Hz); ^{19}F NMR (376.4 MHz): δ = −168.53 (q, ^3J(F,F) = 10.6 Hz, 1F, C*F*CF$_3$), −75.78 ppm (d, ^3J(F,F) = 10.6 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 3037, 2960, 2926, 2865, 1771, 1498, 1435, 1357, 1301, 1263, 1238, 1212, 1181, 1130, 1093, 1057, 1030, 939, 819, 741, 696, 667 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 344 (13) $[M]^+$, 285 (3), 91 (100); EI-HRMS: *m*/*z*: calcd for $C_{16}H_{16}N_2O_2F_4$: 344.1148 $[M]^+$; found: 344.1154; elemental analysis calcd (%) for $C_{16}H_{16}N_2O_2F_4$ (344.3): C 55.82, H 4.68, N 8.14, F 22.07; found: C 55.31, H 4.55, N 8.06, F 21.94.

Methyl 2-(benzothiazol-2′-yl)perfluoropropionate (51): Pale yellow oil; ^{1}H NMR (400 MHz): δ = 4.01 (s, 3H; OCH_3), 7.49 (dd, ^3J(H,H) = 7.9 Hz, 7.2 Hz, 1H; H_{ar}), 7.55 (dd, ^3J(H,H) = 8.3 Hz, 7.3 Hz, 1H; H_{ar}), 7.95 (dm, ^3J(H,H) = 8.1 Hz, 1H; H_{ar}), 8.16 ppm (dm, ^3J(H,H) = 8.2 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 54.4, 91.4 (dq, ^1J(C,F) = 201.7 Hz, ^2J(C,F) = 33.6 Hz), 120.3 (qd, ^1J(C,F) = 286.2 Hz, ^2J(C,F) = 29.3 Hz), 121.7, 124.5, 126.8, 126.9, 135.1, 152.4, 157.8 (d, ^2J(C,F) = 28.4 Hz), 161.7 ppm (d, ^2J-(C,F) = 24.1 Hz); ^{19}F NMR (376.4 MHz): δ = −161.49 (q, ^3J(F,F) = 8.4 Hz, 1F, C*F*CF_3), −76.21 ppm (d, ^3J(F,F) = 8.9 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 2970, 1772, 1512, 1435, 1308, 1260, 1203, 1184, 1138, 1010, 942, 910, 796, 759, 725, 670 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 293 (100) $[M]^+$, 249 (19), 234 (65), 215 (11), 184 (93), 148 (44); EI-HRMS: *m*/*z*: calcd for $C_{11}H_7NO_2SF_4$: 293.0134 $[M]^+$; found: 293.0139; elemental analysis calcd (%) for $C_{11}H_7NO_2SF_4$ (293.2): C 45.06, H 2.41, N 4.78, S 10.94, F 25.91; found: C 45.03, H 2.42, N 4.67, S 11.22, F 25.52.

Large-scale preparation of methyl 2-(2′-pyridyl)perfluoropropionate (5c): HFP (≈8.2 g, 55 mmol) was condensed into a thick-walled, round-bottomed flask (100 mL volume) at −78 °C under an argon atmosphere. DMF (48 mL), methanol (7.7 mL) and freshly vacuum-dried pyridine *N*-oxide (**1c**; 1.80 g, 18.9 mmol) were added and the flask was sealed. The reaction mixture was vigorously stirred at 80–85 °C for 5 h. After cooling to RT, the reaction mixture was poured into water (≈200 mL), and the product was extracted with CH_2Cl_2 (3×100 mL). The organic phase was washed with water (5×100 mL), dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by distillation (55 °C at ≈0.1 mmHg) to obtain 3.40 g (76%) of **5c** as a colourless liquid. ^{1}H NMR (400 MHz): δ = 3.95 (s, 3H; OCH_3), 7.42 (ddm, ^3J(H,H) = 7.7 Hz, 5.0 Hz, 1H; H_{ar}), 7.71 (d, ^3J(H,H) = 8.1 Hz, Hz, 1H; H_{ar}), 7.86 (td, ^3J(H,H) = 7.9 Hz, ^4J(H,H) = 1.8 Hz, 1H; H_{ar}), 8.66 ppm (dm, ^3J(H,H) = 4.8 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 53.7, 93.0 (dq, ^1J(C,F) = 200.0 Hz, ^{2}J(C,F) = 31.0 Hz), 121.0 (qd, ^1J(C,F) = 284.5 Hz, ^2J(C,F) = 29.3 Hz), 121.6 (d, ^3J(C,F) = 7.8 Hz), 125.2, 137.4, 149.4, 150.1 (d, ^2J-(C,F) = 25.0 Hz), 163.4 ppm (d, ^2J(C,F) = 23.3 Hz); ^{19}F NMR (376.4 MHz): δ = −169.33 (q, ^3J(F,F) = 7.8 Hz, 1F, C*F*CF_3), −76.44 ppm (d, ^3J(F,F) = 7.8 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 3065, 2962, 1770, 1589, 1439, 1317, 1303, 1276, 1209, 1183, 1126, 1041, 784, 753, 726 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 237 (63) $[M]^+$, 222 (63), 206 (12), 193 (34), 178 (62), 159 (21), 143 (35), 128 (100), 78 (57), 59 (96); EI-HRMS: *m*/*z*: calcd for $C_9H_7NO_2F_4$: 237.0413 $[M]^+$; found 237.0416; elemental analysis calcd (%) for $C_9H_7NO_2F_4$ (237.2): C 45.58, H 2.97, N 5.91, F 32.04; found: C 44.89, H 2.91, N 5.96, F 31.51.

Methyl 2-chloro-2-fluoro-2-(2′-quinolinyl)acetate (14a): Pale yellow oil; ^{1}H NMR (400 MHz): δ = 3.96 (s, 3H; OCH_3), 7.61 (ddd, ^3J(H,H) = 8.1 Hz, 6.9 Hz, ^4J(H,H) = 1.1 Hz, 1H; H_{ar}), 7.75 (ddd, ^3J(H,H) = 8.4 Hz, 7.0 Hz, ^4J(H,H) = 1.5 Hz, 1H; H_{ar}), 7.85 (dd, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.2 Hz, 1H; H_{ar}), 7.89 (d, ^3J(H,H) = 8.6 Hz, 1H; H_{ar}), 8.11 (dd, ^3J(H,H) = 8.5 Hz, ^4J(H,H) = 0.8 Hz, 1H; H_{ar}), 8.30 ppm (d, ^3J(H,H) = 8.6 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 54.1, 104.4 (d, ^1J(C,F) = 252.6 Hz), 117.4 (d, ^4J(C,F) = 2.6 Hz), 127.5, 128.1, 129.9, 130.3, 137.9, 146.5, 154.9 (d, ^2J-(C,F) = 25.9 Hz), 165.1 ppm (d, ^2J(C,F) = 29.3 Hz); ^{19}F NMR (376.4 MHz): δ = −109.18 ppm (s); IR (film): $\tilde{\nu}$ = 3064, 2957, 1770, 1595, 1504, 1437, 1280, 1097, 1021, 824, 783, 706 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 253 (32) $[M]^+$, 194 (100), 158 (39), 128 (34); EI-HRMS: *m*/*z*: calcd for $C_{12}H_9NO_2{}^{35}ClF$: 253.0306 $[M]^+$; found: 253.0311; elemental analysis calcd (%) for $C_{12}H_9NO_2ClF$ (253.7): C 56.82, H 3.58, N 5.52, Cl 13.98, F 7.49; found: C 56.67, H 3.53, N 5.51, Cl 13.69, F 7.59.

The preparation of esters from other alcohols was performed according to the procedure described for methyl esters and by using 10 equiv of the appropriate alcohol.

***p*-Methoxybenzyl 2-(4′-*tert*-butylpyridin-2′-yl)perfluoropropionate (5db)**: Pale yellow oil; ^{1}H NMR (400 MHz): δ = 1.31 (s, 9H; *t*Bu), 3.79 (s, 3H; OCH_3), 5.32 (AB, ^2J(H,H) = 11.9 Hz, 2H; CH_2), 6.86 (dm, ^3J(H,H) = 8.8 Hz, 2H; C_6H_4), 7.29 (dm, ^3J(H,H) = 8.8 Hz, 2H; C_6H_4), 7.36 (dd, ^3J-(H,H) = 5.1 Hz, ^4J(H,H) = 1.8 Hz, 1H; H_{ar}), 7.62 (s, 1H; H_{ar}), 8.50 ppm (d, ^3J(H,H) = 5.1 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 30.4, 35.0, 55.2, 68.3, 93.1 (dq, ^1J(C,F) = 200.0 Hz, ^2J(C,F) = 31.0 Hz), 113.9, 118.6 (d, ^3J(C,F) = 6.0 Hz), 121.1 (qd, ^1J(C,F) = 285.4 Hz, ^2J(C,F) = 29.3 Hz), 122.3, 126.5, 130.2, 149.2, 149.9 (d, ^2J(C,F) = 25.0 Hz), 159.8, 161.8, 163.1 ppm (d, ^2J(C,F) = 23.3 Hz); ^{19}F NMR (376.4 MHz): δ = −168.88 (q, ^3J(F,F) = 8.0 Hz, 1F, C*F*CF_3), −76.21 ppm (d, ^3J(F,F) = 7.4 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 2968, 1765, 1602, 1517, 1305, 1250, 1208, 1178, 1098, 1035, 1002, 851, 826 cm^{-1}; MS (EI 70 eV) *m*/*z* (%): 399 (2) $[M]^+$, 235 (100), 220 (10), 200 (6), 121 (28); HRMS: *m*/*z*: calcd for $C_{20}H_{21}NO_3F_4$: 399.1458 $[M]^+$; found: 399.1451; elemental analysis calcd (%) for $C_{20}H_{21}NO_3F_4$ (399.4): C 60.15, H 5.30, N 3.51, F 19.03; found: C 60.34, H 5.50, N 3.36, F 19.10.

Allyl 2-(4′-*tert*-butylpyridin-2′-yl)perfluoropropionate (5dc): Colourless oil; ^{1}H NMR (400 MHz): δ = 1.34 (s, 9H; *t*Bu), 4.85 (m, 2H; OCH_2), 5.28 (dd, ^3J(H,H) = 10.4 Hz, ^2J(H,H) = 1.2 Hz, 1H; CH=C(H,H)), 5.37 (dd, ^3J-(H,H) = 17.1 Hz, ^2J(H,H) = 1.2 Hz, 1H; CH=C(H,H)), 5.93 (ddt, ^3J-(H,H) = 17.3 Hz, 10.6 Hz, 5.7 Hz, 1H; C*H*=CH_2), 7.39 (dd, ^3J(H,H) = 5.2 Hz, ^4J(H,H) = 1.8 Hz, 1H; H_{ar}), 7.68 (s, 1H; H_{ar}), 8.54 ppm (d, ^3J-(H,H) = 5.2 Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): δ = 30.4, 35.1, 67.3, 93.1 (dq, ^1J(C,F) = 200.0 Hz, ^2J(C,F) = 31.0 Hz), 118.5 (d, ^3J(C,F) = 5.2 Hz), 119.4, 120.9 (qd, ^1J(C,F) = 284.5 Hz, ^2J(C,F) = 29.3 Hz), 122.3, 149.2 (d, ^4J-(C,F) = 1.7 Hz), 149.9 (d, ^2J(C,F) = 25.0 Hz), 161.8, 163.1 ppm (d, ^2J-(C,F) = 22.4 Hz); ^{19}F NMR (376.4 MHz): δ = −169.11 (q, ^3J(F,F) = 7.3 Hz, 1F, C*F*CF_3), −76.35 ppm (d, ^3J(F,F) = 7.3 Hz, 3F, CFC*F*$_3$); IR (film): $\tilde{\nu}$ = 2970, 2875, 1770, 1603, 1481, 1407, 1367, 1308, 1273, 1208, 1183, 1141, 1099, 1039, 1002, 938, 852 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 319 (6) $[M]^+$, 304 (18), 275 (46), 260 (18), 236 (62), 234 (72), 220 (41), 206 (20), 41 (100); EI-HRMS: *m*/*z*: calcd for $C_{15}H_{17}NO_2F_4$: 319.1195 $[M]^+$; found: 319.1184; elemental analysis calcd (%) for $C_{15}H_{17}NO_2F_4$ (319.3): C 56.43, H 5.37, N 4.39, F 23.80; found: C 56.36, H 5.27, N 4.47, F 23.95.

Ester 5kb: Colourless oil; ^{1}H NMR (400 MHz): δ = 1.95 (s, 3H; CH_3), 2.18 (s, 3H; CH_3), 4.99 (d, ^2J(H,H) = 12.9 Hz, 1H; CH_2), 5.09 (d, ^2J-(H,H) = 17.3 Hz, 1H; CH_2), 5.17 (d, ^2J(H,H) = 12.9 Hz, 1H; CH_2), 5.26 (d, ^2J(H,H) = 17.3 Hz, 1H; CH_2), 6.87 (m, 2H; Ph), 7.22–7.30 (m, 3H; Ph), 7.40 (d, ^3J(H,H) = 8.0 Hz, 2H; C_6H_4), 7.59 ppm (d, ^3J(H,H) = 8.1 Hz, 2H; C_6H_4); ^{13}C NMR (100.6 MHz): δ = 8.6, 12.6, 47.8 (d, ^4J(C,F) = 6.0 Hz), 67.5, 90.4 (dq, ^1J(C,F) = 199.2 Hz, ^2J(C,F) = 32.8 Hz), 120.7 (qd, ^1J(C,F) = 285.4 Hz, ^2J(C,F) = 29.3 Hz), 123.9 (q, ^1J(C,F) = 272.5 Hz), 125.4, 125.4, 127.5, 127.5, 127.9, 128.7, 130.6 (q, ^2J(C,F) = 31.9 Hz), 133.3 (d, ^2J-(C,F) = 24.1 Hz), 134.9, 135.7, 138.1, 161.8 ppm (d, ^2J(C,F) = 25.9 Hz); ^{19}F NMR (376.4 MHz): δ = −163.50 (q, ^3J(F,F) = 9.9 Hz, 1F, C*F*CF_3), −74.49 (d, ^3J(F,F) = 9.9 Hz, 3F, CFC*F*$_3$), −63.22 ppm (s, 3F, CF_3); IR (CH_2Cl_2): $\tilde{\nu}$ = 2926, 1772, 1436, 1327, 1299, 1261, 1169, 1129, 1067, 1018 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 488 (17) $[M]^+$, 469 (2), 285 (8), 91 (100); EI-HRMS: *m*/*z*: calcd for $C_{23}H_{19}N_2O_2F_7$: 488.1335 $[M]^+$; found: 488.1350; elemental analysis calcd (%) for $C_{23}H_{19}N_2O_2F_7$ (488.4): C 56.56, H 3.92, N 5.74, F 27.23; found: C 56.76, H 3.88, N 5.55, F 27.13.

Amide 7d: HFP (≈0.5 mL, 4 mmol) was condensed at −78 °C into a glass pressure tube. DMF (2.0 mL) and 4-*tert*-butylpyridine *N*-oxide (**1d**; 144 mg, 0.95 mmol) were added, and the tube was sealed with a Teflon valve. The reaction mixture was vigorously stirred at 80 °C for 5 h. After cooling to RT, the pressure tube was opened, and the unreacted hexafluoropropene and products of its oligomerisation were removed under reduced pressure (water pump). *p*-Toluidine (204 mg, 1.9 mmol) solution in DMF (1.0 mL) was added, and the reaction mixture was stirred overnight at RT (≈14 h). It was then poured into water (10 mL), and the product was extracted with CH_2Cl_2 (3×5 mL). The organic phase was washed with water (5×20 mL), dried (Na_2SO_4) and evaporated. The crude product was purified by column chromatography (SiO_2, hexanes/AcOEt 5:1). After evaporation, the title compound was obtained as a light-yellow crystalline solid. Yield: 207 mg (59%); m.p. 130–131 °C (cyclohexane/Et_2O); ^{1}H NMR (400 MHz): δ = 1.35 (s, 9H; *t*Bu), 2.32 (s, 3H; CH_3), 7.15 (d, ^3J(H,H) = 8.0 Hz, 2H; C_6H_4), 7.44 (dd, ^3J(H,H) = 5.2 Hz, ^4J-(H,H) = 1.8 Hz, 1H; H_{ar}), 7.49 (d, ^3J(H,H) = 8.6 Hz, 2H; C_6H_4), 7.82 (m, 1H; H_{ar}), 8.60 (^3J(H,H) = 5.2 Hz, 1H; H_{ar}), 10.22 ppm (s, 1H; NH); ^{13}C NMR (100.6 MHz): δ = 20.9, 30.4, 35.3, 91.2 (m), 118.7 (d, ^3J(C,F) = 9.5 Hz), 120.1, 121.1 (qd, ^1J(C,F) = 286.2 Hz, ^2J(C,F) = 29.3 Hz), 122.1, 129.6, 134.3, 134.8, 148.5 (d, ^4J(C,F) = 2.6 Hz), 150.0 (d, ^2J(C,F) = 25.0 Hz), 158.8 (d, ^2J(C,F) = 23.3 Hz), 162.8 ppm (d, ^4J(C,F) = 1.7 Hz); ^{19}F NMR (376.4 MHz): δ = −177.13 (q, ^3J(F,F) = 8.8 Hz, 1F, C*F*CF_3), −76.96 ppm (d, ^3J(F,F) = 8.8 Hz, 3F, CFC*F*$_3$); IR (KBr): $\tilde{\nu}$ = 3331, 2972, 1690, 1611, 1548, 1512, 1209, 1176, 1091, 824 cm^{-1}; MS (70 eV, EI): *m*/*z*

(%): 368 (4) $[M]^+$, 353 (1), 235 (100), 215 (13), 200 (22); EI-HRMS: m/z: calcd for $C_{19}H_{20}N_2OF_4$: 368.1512 $[M]^+$; found: 368.1519; elemental analysis calcd (%) for $C_{19}H_{20}N_2OF_4$ (368.4): C 61.95, H 5.47, N 7.60, F 20.63; found: C 61.97, H 5.39, N 7.59, F 20.60.

2,3,3,3-Tetrafluoropropionic toluamide (11): Pale yellow crystals, m.p. 90–91 °C (hexanes/Et_2O); ^{1}H NMR (400 MHz): $\delta = 2.33$ (s, 3H; CH_3), 5.18 (dq, $^2J(H,F) = 46.3$ Hz, $^3J(H,F) = 6.3$ Hz, 1H; CHF), 7.16 (d, $^3J(H,H) = 8.5$ Hz, 2H; H_{ar}), 7.43 (d, $^3J(H,H) = 8.5$ Hz, 2H; H_{ar}), 8.00 ppm (s, 1H; NH); ^{13}C NMR (100.6 MHz): $\delta = 21.1$, 85.9 (dq, $^1J(C,F) = 205.2$ Hz, $^2J(C,F) = 33.6$ Hz), 120.7, 120.8 (qd, $^1J(C,F) = 282.8$ Hz, $^2J(C,F) = 25.9$ Hz), 130.0, 133.3, 136.0, 159.0 ppm (d, $^2J(C,F) = 18.1$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -200.70$ (dm, $^2J(F,H) = 46.8$ Hz, 1F, CHF), −76.31 ppm (dd, $^3J(F,F) = 9.8$ Hz, $^3J(F,H) = 7.4$ Hz, 3F, CF_3); IR (KBr): $\tilde{\nu} = 3331$, 3208, 3147, 2930, 1697, 1674, 1608, 1552, 1516, 1350, 1268, 1256, 1194, 1149, 1095, 870, 820 cm^{-1}; MS (70 eV, EI): m/z (%): 235 (100) $[M]^+$, 134 (62), 106 (99), 91 (37); EI-HRMS: m/z: calcd for $C_{10}H_9NOF_4$: 235.0620 $[M]^+$; found: 235.0617; elemental analysis calcd (%) for $C_{10}H_9NOF_4$ (235.2): C 51.07, H 3.86, N 5.96, F 32.31; found: C 50.79, H 4.01, N 5.86, F 32.49.

Compound 12: Pale yellow oil; ^{1}H NMR (400 MHz): $\delta = 2.31$ (s, 6H; CH_3), 5.62 (dq, $^2J(H,F) = 44.8$ Hz, $^3J(H,F) = 5.5$ Hz, 1H; CHF), 6.59 (s, 1H; NH), 6.62–6.85 (m, 2H; H_{ar}), 6.85–7.20 (m, 4H; H_{ar}), 7.54 ppm (d, $^3J(H,H) = 7.5$ Hz, 2H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 20.7$, 20.8, 80.9 (dq, $^1J(C,F) = 195.7$ Hz, $^2J(C,F) = 36.2$ Hz), 120.0, 120.6, 123.4 (qm, $^1J(C,F) = 231.9$ Hz), 129.4, 129.8, 132.6, 133.4, 135.9, 143.1 (d, $^2J(C,F) = 17.2$ Hz), 145.0 ppm; ^{19}F NMR (376.4 MHz): $\delta = -203.65$ (1F, dq, $^2J(F,H) = 44.8$ Hz, $^3J(F,F) = 12.8$ Hz, CHF), −76.22 ppm (3F, dd, $^3J(F,F) = 12.4$ Hz, $^3J(F,H) = 5.0$ Hz, CF_3); IR (film): $\tilde{\nu} = 3453$, 3027, 2924, 1658, 1601, 1535, 1504, 1320, 1266, 1197, 1146, 1077, 831, 814 cm^{-1}; MS (70 eV, EI): m/z (%): 324 (90) $[M]^+$, 218 (90), 107 (77), 91 (100); EI-HRMS: m/z: calcd for $C_{17}H_{16}N_2F_4$: 324.1250 $[M]^+$; found: 324.1244.

2-(2′-Quinolinyl)perfluoropropionic *N,N*-diethylamide (7aa): The title compound was prepared in analogous manner to **7d**, but the reaction with HFP was performed for 3 h at RT, and the second step (after evaporating the excess of HFP) was executed by adding neat diethylamine (347 mg, 493 μL, 4.75 mmol). Colourless crystalline solid, m.p. 88–89 °C (hexanes/Et_2O); ^{1}H NMR (400 MHz): $\delta = 0.93$ (t, $^3J(H,H) = 6.8$ Hz, 3H; CH_3), 1.21 (t, $^3J(H,H) = 7.2$ Hz, 3H; CH_3), 2.78 (m, 1H; CH_2), 3.08 (m, 1H; CH_2), 3.19 (m, 1H; CH_2), 3.72 (m, 1H; CH_2), 7.64 (ddd, $^3J(H,H) = 8.2$ Hz, 6.8 Hz, $^4J(H,H) = 1.1$ Hz, 1H; H_{ar}), 7.74–7.80 (m, 2H; H_{ar}), 7.88 (d, $^3J(H,H) = 8.1$ Hz, 1H; H_{ar}), 8.16 (d, $^3J(H,H) = 8.4$ Hz, 1H; H_{ar}), 8.32 ppm (d, $^3J(H,H) = 8.6$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 11.8$, 13.6 (d, $^5J(C,F) = 1.7$ Hz), 40.8, 41.5 (d, $^4J(C,F) = 8.7$ Hz), 94.8 (dq, $^1J(C,F) = 204.3$ Hz, $^2J(C,F) = 28.4$ Hz), 117.9 (d, $^3J(C,F) = 3.4$ Hz), 121.6 (qd, $^1J(C,F) = 285.4$ Hz, $^2J(C,F) = 31.0$ Hz), 127.6, 128.0, 128.1, 130.0, 130.4, 137.6, 147.2 (d, $^4J(C,F) = 1.7$ Hz), 150.3 (d, $^2J(C,F) = 23.3$ Hz), 162.0 ppm (d, $^2J(C,F) = 18.1$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -167.89$ (m, 1F, $CFCF_3$), −75.64 ppm (d, $^3J(F,F) = 7.0$ Hz, 3F, $CFCF_3$); IR (KBr): $\tilde{\nu} =$ 2973, 1671, 1462, 1291, 1213, 1163, 1094, 827, 769 cm^{-1}; MS (70 eV, EI): m/z (%): 328 (2) $[M]^+$, 308 (37), 237 (100), 229 (48), 209 (28), 178 (26), 128 (22), 100 (39), 72 (50); EI-HRMS: m/z: calcd for $C_{16}H_{16}N_2OF_4$: 328.1199 $[M]^+$; found: 328.1186; elemental analysis calcd (%) for $C_{16}H_{16}N_2OF_4$ (328.3): C 58.54, H 4.91, N 8.53, F 23.15; found: C 58.48, H 4.78, N 8.43, F 23.03.

General one-pot, two-step procedure for preparation of 2-heteroarylperfluoropropionic amides: Fluoroalkene (≈0.5 mL, 4 mmol) was condensed in a glass pressure tube at −78 °C under an argon atmosphere. DMF (2.4 mL) and *N*-oxide (0.95 mmol) were introduced, and the pressure tube was closed with a Teflon valve. The contents of the tube were stirred vigorously at 80 °C for 5 h. (or in some cases at RT, see Scheme 13). After cooling to RT, the pressure tube was opened, and the unreacted hexafluoropropene and products of its oligomerisation were removed under reduced pressure by using a water pump. The reaction mixture was subsequently cooled to 0 °C (argon atmosphere), and NEt_3 (192 mg, 265 μL, 1.9 mmol) and the appropriate primary or secondary amine (1.9 mmol) were added with stirring. The reaction mixture was allowed to slowly reach room temperature. After about 14 h, the mixture was poured into water (10 mL), and the products were isolated similarly to the procedure for 2-heteroarylperfluoropropionic methyl esters.

2-(2′-Pyridyl)perfluoropropionic *N*-*n*-butylamide (7c): Pale yellow oil; ^{1}H NMR (400 MHz): $\delta = 0.92$ (t, $^3J(H,H) = 7.3$ Hz, 3H; CH_3), 1.35 (m, 2H; CH_2), 1.55 (m, 2H; CH_2), 3.37 (m, 2H; NCH_2), 7.44 (ddd, $^3J(H,H) = 7.5$ Hz, 4.8 Hz, $^4J(H,H) = 1.3$ Hz, 1H; H_{ar}), 7.81 (dd, $^3J(H,H) = 8.1$ Hz, $^4J(H,H) = 0.9$ Hz, 1H; H_{ar}), 7.87 (td, $^3J(H,H) = 7.5$ Hz, $^4J(H,H) = 1.8$ Hz, H_{ar}), 8.68 ppm (dm, $^3J(H,H) = 4.8$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 13.5$, 19.8, 31.1, 39.6, 91.6 (dq, $^1J(C,F) = 197.4$ Hz, $^2J(C,F) = 31.0$ Hz), 121.1 (qd, $^1J(C,F) = 286.2$ Hz, $^2J(C,F) = 29.3$ Hz), 121.7 (d, $^3J(C,F) = 7.8$ Hz), 124.9, 137.6 (d, $^4J(C,F) = 1.7$ Hz), 148.8 (d, $^4J(C,F) = 1.7$ Hz), 150.1 (d, $^2J(C,F) = 24.1$ Hz), 161.5 ppm (d, $^2J(C,F) = 21.6$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -175.09$ (q, $^3J(F,F) = 8.8$ Hz, 1F, CF), −76.81 ppm (d, $^3J(F,F) = 8.8$ Hz, 3F, CF_3); IR (film): $\tilde{\nu} = 3333$, 2962, 1694, 1539, 1469, 1437, 1273, 1199, 754 cm^{-1}; MS (70 eV, EI): m/z (%): 278 (<1) $[M]^+$, 263 (3), 235 (7), 206 (13), 179 (100), 159 (55); EI-HRMS: m/z: calcd for $C_{12}H_{14}N_2OF_4$: 278.1042 $[M]^+$; found: 278.1048; elemental analysis calcd (%) for $C_{12}H_{14}N_2OF_4$ (278.2): C 51.80, H 5.07, N 10.07, F 27.31; found: C 51.99, H 5.05, N 9.95, F 27.10.

Amide 7ka: Colourless crystalline solid, m.p. 131–132 °C (hexanes/Et_2O); ^{1}H NMR (400 MHz): $\delta = 1.96$ (s, 1H; CH_3), 2.12 (s, 1H; CH_3), 4.58 (dd, $^2J(H,H) = 14.7$ Hz, $^3J(H,H) = 4.2$ Hz, 1H; $NHCH_2$), 4.82 (dd, $^2J(H,H) = 14.7$ Hz, $^3J(H,H) = 6.6$ Hz, 1H; $NHCH_2$), 5.05 (d, $^2J(H,H) = 17.0$ Hz, 1H; CH_2Ph), 5.33 (d, $^2J(H,H) = 16.9$ Hz, 1H; CH_2Ph), 6.89 (d, $^3J(H,H) = 6.8$ Hz, 2H; Ph), 7.19–7.34 (m, 4H; H_{ar}), 7.44 (td, $^3J(H,H) = 7.7$ Hz, $^4J(H,F) = 5.3$ Hz, 1H; H_{ar}), 7.50 (d, $^3J(H,H) = 7.7$ Hz, 1H; H_{ar}), 9.14 ppm (t, $^3J(H,H) = 5.3$ Hz, 1H; NH); ^{13}C NMR (100.6 MHz): $\delta = 8.7$, 12.4, 34.1, 48.4 (d, $^3J(C,F) = 9.5$ Hz), 90.0 (dq, $^1J(C,F) = 194.8$ Hz, $^2J(C,F) = 32.8$ Hz), 119.6 (d, $^2J(C,F) = 23.3$ Hz), 120.8 (qd, $^1J(C,F) = 287.1$ Hz, $^2J(C,F) = 30.2$ Hz), 121.9 (m), 122.5 (dm, $^2J(C,F) = 19.0$ Hz), 123.4 (qm, $^1J(C,F) = 273.3$ Hz), 125.5, 127.3, 127.5, 128.7, 130.0 (d, $^3J(C,F) = 9.5$ Hz), 130.0 (qd, $^2J(C,F) = 31.0$ Hz, $^3J(C,F) = 3.4$ Hz), 133.4 (d, $^2J(C,F) = 24.1$ Hz), 135.9, 160.3 (d, $^2J(C,F) = 23.3$ Hz), 161.9 ppm (d, $^1J(C,F) = 250.9$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -170.88$ (q, $^3J(F,F) = 11.7$ Hz, 1F, $CFCF_3$), −113.33 (m, 1F, C(sp^2)-F), −76.90 ppm (d, $^3J(F,F) = 11.7$ Hz, 3F, $CFCF_3$), −59.41 (s, 3F, CF_3); IR (KBr): $\tilde{\nu} = 3328$, 3070, 2918, 1685, 1540, 1471, 1452, 1431, 1367, 1323, 1216, 1183, 1170, 1138, 1118, 1069, 957, 934, 799, 724 cm^{-1}; MS (70 eV, EI): m/z (%): 505 (28) $[M]^+$, 286 (58), 195 (81), 91 (100); EI-HRMS: m/z: calcd for $C_{23}H_{19}N_3OF_8$: 505.1400 $[M]^+$; found: 505.1413; elemental analysis calcd (%) for $C_{23}H_{19}N_3OF_8$ (505.4): C 54.66, H 3.79, N 8.31, F 30.07; found: C 54.53, H 3.91, N 8.32, F 31.01.

Amide 7kb: Obtained as a 6.7:1 (from ^{1}H NMR) mixture of diastereoisomers, only the major one could be isolated in a pure form. White needles, m.p. 136–138 °C (hexanes/Et_2O); ^{1}H NMR (400 MHz): $\delta = 1.49$ (d, $^3J(H,H) = 6.9$ Hz, 3H; $CHCH_3$), 1.96 (s, 3H; CH_3), 2.17 (s, 3H; CH_3), 5.06 (d, $^2J(H,H) = 17.0$ Hz, 1H; NCH_2), 5.11 (p, $^3J(H,H) = 7.3$ Hz, 1H; $NCHCH_3$), 5.29 (d, $^2J(H,H) = 17.0$ Hz, 1H; NCH_2), 6.90 (d, $^3J(H,H) = 6.7$ Hz, 2H; Ph), 7.20–7.38 (m, 8H; 2×Ph), 9.05 ppm (d, $^3J(H,H) = 7.8$ Hz, 1H; NH); ^{13}C NMR (100.6 MHz): $\delta = 8.9$, 12.6, 22.1, 44.5 (d, $^4J(C,F) = 9.0$ Hz), 49.9, 90.0 (dq, $^1J(C,F) = 194.4$ Hz, $^2J(C,F) = 32.3$ Hz), 120.9 (qd, $^1J(C,F) = 286.6$ Hz, $^2J(C,F) = 30.2$ Hz), 125.6, 126.0, 127.2, 127.4, 127.5, 128.6, 128.7, 133.8 (d, $^2J(C,F) = 24.1$ Hz), 134.0, 135.9, 142.3, 159.9 ppm (d, $^2J(C,F) = 23.3$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -171.07$ (q, $^3J(F,F) = 11.2$ Hz, 1F, CF), −76.67 ppm (d, $^3J(F,F) = 11.8$ Hz, 3F, CF_3); IR (KBr): $\tilde{\nu} = 3312$, 3031, 2981, 2975, 1677, 1537, 1431, 1212, 1171, 1132, 1068, 750, 699 ppm; MS (70 eV, EI): m/z (%): 433 (7) $[M]^+$, 418 (2), 286 (62), 285 (53), 195 (68), 105 (30), 91 (100); EI-HRMS: m/z: calcd for $C_{23}H_{23}N_3OF_4$: 433.1777 $[M]^+$; found: 433.1771; elemental analysis calcd (%) for $C_{23}H_{23}N_3OF_4$ (433.4): C 63.73, H 5.35, N 9.69, F 17.53; found: C 63.45, H 5.61, N 9.44, F 17.42.

Amide 7m: Pale yellow crystals, m.p. 113–114 °C (Et_2O); ^{1}H NMR (400 MHz): $\delta = 7.39$ (ddd, $^3J(H,H) = 7.5$ Hz, 4.8 Hz, $^4J(H,H) = 1.1$ Hz, 1H; H_{ar}), 7.71 (dd, $^3J(H,H) = 8.8$ Hz, $^4J(H,H) = 2.6$ Hz, 1H; H_{ar}), 7.84 (ddd, $^3J(H,H) = 7.9$ Hz, $^4J(H,H) = 2.0$ Hz, $^5J(H,H) = 0.9$ Hz, 1H; H_{ar}), 7.91 (td, $^3J(H,H) = 7.5$ Hz, $^4J(H,H) = 1.8$ Hz, 1H; H_{ar}), 8.04 (t, $^3J(H,H) = 8.0$ Hz, 1H; H_{ar}), 8.23 (dd, $^3J(H,H) = 8.8$ Hz, $^5J(H,H) = 0.7$ Hz, 1H; H_{ar}), 8.28 (dd, $^4J(H,H) = 2.6$ Hz, $^5J(H,H) = 0.7$ Hz, 1H; H_{ar}), 8.62 (dt, $^3J(H,H) = 8.0$ Hz, $^4J(H,H) = 1.0$ Hz, 1H; H_{ar}), 8.63 (dd, $^3J(H,H) = 8.0$ Hz, $^4J(H,H) = 0.9$ Hz, 1H; H_{ar}), 8.71 (ddd, $^3J(H,H) = 4.8$ Hz, $^4J(H,H) = 1.8$ Hz, $^5J(H,H) = 0.9$ Hz, 1H; H_{ar}), 10.76 ppm (s, 1H; CONH); ^{13}C NMR

(100.6 MHz): $\delta = 91.3$ (dq, $^1J(C,F) = 198.3$ Hz, $^2J(C,F) = 31.0$ Hz), 114.9, 121.0 (qd, $^1J(C,F) = 286.2$ Hz, $^2J(C,F) = 29.3$ Hz), 121.5, 121.6, 122.8, 124.6, 127.8, 137.3, 138.1, 139.1 (d, $^4J(C,F) = 1.7$ Hz), 146.9, 148.5, 148.8 (d, $^2J(C,F) = 25.9$ Hz), 149.3, 154.1, 155.9 (d, $^3J(C,F) = 2.6$ Hz), 159.4 ppm (d, $^2J(C,F) = 23.3$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -175.59$ (q, $^3J(F,F) = 8.6$ Hz, 1F, CF), -76.58 ppm (d, $^3J(F,F) = 8.6$ Hz, 3F, CF_3); IR (KBr): $\tilde{\nu} = 3212, 3036, 1720, 1585, 1546, 1461, 1435, 1377, 1307, 1265, 1220, 1196, 1184, 1159, 1146, 1083, 972, 835, 779$ cm^{-1}; MS (70 eV, EI): m/z (%): 256 (100), 236 (14), 206 (8); ESI-HRMS: calcd for $C_{18}H_{11}N_4OClF_4Na$: 433.0450 $[M+Na]^+$; found: 433.0458; elemental analysis calcd (%) for $C_{18}H_{11}N_4OClF_4$ (410.8): C 52.63, H 2.70, N 13.64, Cl 8.63, F 18.50; found: C 52.27, H 2.57, N 13.82, Cl 8.69, F 18.70.

Amide 7b: Pale yellow oil; ^{1}H NMR (400 MHz): $\delta = 1.20$ (t, $^3J(H,H) = 7.1$ Hz, 3H; CH_3), 1.20 (t, $^3J(H,H) = 7.1$ Hz, 3H; CH_3), 1.62–1.68 (m, 4H; $2\times CH_2$), 3.35–3.43 (m, 2H; NCH_2), 3.43–3.53 (m, 2H; OCH_2), 3.57–3.68 (m, 2H; OCH_2), 3.99 (s, 3H; OCH_3), 4.48 (m, 1H; $CH(OEt)_2$), 7.62 (s, 1H; NH), 7.92 (d, $^3J(H,H) = 8.2$ Hz, 1H; H_{ar}), 8.44 (dd, $^3J(H,H) = 8.2$ Hz, $^4J(H,H) = 2.0$ Hz, 1H; H_{ar}), 9.25 ppm (m, 1H; H_{ar}); ^{19}F NMR (376.4 MHz): $\delta = -174.63$ (q, $^3J(F,F) = 8.7$ Hz, 1F, $CFCF_3$), -76.39 (d, $^3J(F,F) = 8.7$ Hz, 3F, $CFCF_3$); EI-HRMS: m/z: calcd for $C_{18}H_{24}N_2O_5F_4$: 447.1511 $[M+Na]^+$; found: 447.1514.

Amide 7b′: Pale yellow oil; ^{1}H NMR (400 MHz): $\delta = 1.20$ (t, $^3J(H,H) = 7.1$ Hz, 6H; $2\times CH_3$), 1.60–1.80 (m, 4H; $2\times CH_2$), 3.46–3.55 (m, 2H; NCH_2), 3.60–3.67 (m, 2H; OCH_2), 3.98–4.06 (m, 1H; OCH_2), 4.08–4.17 (m, 1H; OCH_2), 4.52 (t, $^3J(H,H) = 5.3$ Hz,1H; $CH(OEt)_2$), 7.71 (dd, $^3J(H,H) = 7.9$ Hz, 4.8 Hz, H_{ar}), 8.55 (m, 1H; H_{ar}), 9.03 ppm (dd, $^3J(H,H) = 4.8$ Hz, $^4J(H,H) = 1.8$ Hz, H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 15.3$, 18.4, 20.2, 23.1, 30.8, 40.8, 41.6, 61.3, 87.0 (dq, $^1J(C,F) = 206.9$ Hz, $^2J(C,F) = 32.3$ Hz), 102.3, 126.5, 137.1, 146.5 (d, $^2J(C,F) = 17.2$ Hz), 154.8, 161.5, 162.7 ppm (d, $^2J(C,F) = 21.6$ Hz), 200.5; ^{19}F NMR (376.4 MHz): $\delta = -178.47$ (q, $^3J(F,F) = 12.3$ Hz, 1F, $CFCF_3$), -77.73 (d, $^3J(F,F) = 11.6$ Hz, 3F, $CFCF_3$).

One-step preparation of 2-heteroarylperfluoropropionic amides: These reactions were performed analogously to the syntheses of 2-heteroarylperfluoropropionic methyl esters by using reagent quantities and conditions specified in Scheme 14 and Scheme 16.

2-(2′-Quinolinyl)perfluoropropionic *N*-ethyl-*N*-phenylamide (7ab): Colourless crystalline solid, m.p. 133–135 °C (cyclohexane/Et_2O); ^{1}H NMR (400 MHz): $\delta = 1.17$ (t, $^3J(H,H) = 7.2$ Hz, 3H; CH_3), 3.72–3.87 (m, 2H; CH_2), 7.06 (m, 3H; H_{ar}), 7.20–7.45 (m, 3H; H_{ar}), 7.62 (tm, $^3J(H,H) = 7.2$ Hz, 1H; H_{ar}), 7.75–7.83 (m, 2H; H_{ar}), 7.98 (d, $^3J(H,H) = 8.7$ Hz, H_{ar}), 8.20 ppm (d, $^3J(H,H) = 8.4$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 12.2$, 46.3, 94.6 (dq, $^1J(C,F) = 205.2$ Hz, $^2J(C,F) = 28.4$ Hz), 117.3 (d, $^3J(C,F) = 6.9$ Hz), 121.5 (qd, $^1J(C,F) = 285.3$ Hz, $^2J(C,F) = 30.2$ Hz), 127.4, 127.7, 127.8, 128.2, 129.2, 129.8, 129.9, 130.2, 136.9, 139.3 (d, $^4J(C,F) = 2.5$ Hz), 146.8 (d, $^4J(C,F) = 2.5$ Hz), 151.1 (d, $^2J(C,F) = 25.0$ Hz), 161.6 ppm (d, $^2J(C,F) = 18.1$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -165.63$ (m, 1F, $CFCF_3$), -75.90 ppm (d, $^3J(F,F) = 6.3$ Hz, 3F, $CFCF_3$); IR (KBr): $\tilde{\nu} = 3055, 2979, 1679, 1593, 1496, 1408, 1287, 1215, 1165, 1105, 829, 769, 704$ cm^{-1}; MS (70 eV, EI): m/z (%): 376 (14) $[M]^+$, 356 (3), 229 (76), 120 (100); EI-HRMS: m/z: calcd for $C_{20}H_{16}N_2OF_4$: 376.1199 $[M]^+$; found: 376.1210; elemental analysis calcd (%) for $C_{20}H_{16}N_2OF_4$ (376.4): C 63.83, H 4.29, N 7.44, F 20.19; found: C 63.92, H 4.24, N 7.45, F 20.30.

Amide 7kc: Colourless crystalline solid, m.p. 152–154 °C (cyclohexane/CH_2Cl_2); ^{1}H NMR (400 MHz): $\delta = 2.08$ (s, 3H; CH_3), 2.20 (s, 3H; CH_3), 2.90 (t, $^3J(H,H) = 8.2$ Hz, 2H; CH_2CH_2N), 3.46 (m, 1H; CH_2CH_2N), 3.76 (m, 1H; CH_2CH_2N), 5.25 (AB, $^2J(H,H) = 2$H; 17.1 Hz), 6.90 (d, $^3J(H,H) = 6.8$ Hz, 2H; H_{ar}), 7.04 (td, $^3J(H,H) = 7.3$ Hz, $^4J(H,H) = 0.9$ Hz, 1H; H_{ar}), 7.08–7.18 (m, 3H; H_{ar}), 7.18–7.24 (m, 2H; H_{ar}), 8.17 ppm (d, $^3J(H,H) = 8.1$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 9.0$, 12.9, 28.3 (d, $^5J(C,F) = 2.2$ Hz), 47.6 (d, $^4J(C,F) = 10.3$ Hz), 48.1 (d, $^4J(C,F) = 2.6$ Hz), 92.3 (dq, $^1J(C,F) = 201.7$ Hz, $^2J(C,F) = 30.6$ Hz), 118.3, 121.4 (qd, $^1J(C,F) = 286.2$ Hz, $^2J(C,F) = 31.5$ Hz), 124.3, 124.9, 125.3, 127.4, 127.4, 127.5, 128.6, 131.1, 133.3 (d, $^2J(C,F) = 23.7$ Hz), 135.2, 136.0, 142.6, 159.1 ppm (d, $^2J(C,F) = 19.8$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -166.12$ (q, $^3J(F,F) = 5.6$ Hz, 1F, CF), -75.01 ppm (d, $^3J(F,F) = 9.1$ Hz, 3F, CF_3); IR (KBr): $\tilde{\nu} = 3035, 2924, 1684, 1598, 1481, 1461, 1437, 1407, 1282, 1210, 1172, 1130, 1073, 997, 760, 743, 720, 687$ cm^{-1}; MS (70 eV, EI): m/z (%): 431 (4) $[M]^+$, 411 (9), 340 (4), 314 (11), 294 (100), 285 (31), 195 (24), 91 (67); EI-HRMS: m/z: calcd for $C_{23}H_{21}N_3OF_4$: 431.1621 $[M]^+$; found: 431.1632; elemental analysis calcd (%) for $C_{23}H_{21}N_3OF_4$ (431.4): C 64.03, H 4.91, N 9.74, F 17.61; found: C 64.14, H 4.84, N 9.89, F 17.61.

2,3,3,3-Tetrafluoropropionic amide (13): Colourless crystalline solid, m.p. 101–102 °C (hexanes/Et_2O); ^{1}H NMR (400 MHz): $\delta = 3.24$ (t, $^3J(H,H) = 8.6$ Hz, 2H; CH_2CH_2N), 4.16–4.31 (m, 2H; CH_2CH_2N), 5.37 (dq, $^2J(H,F) = 46.4$ Hz, $^3J(H,F) = 6.2$ Hz, 1H; CHF), 7.13 (td, $^3J(H,H) = 7.5$ Hz, $^4J(H,H) = 0.9$ Hz, 1H; H_{ar}), 7.21–7.29 (m, 2H; H_{ar}), 8.23 ppm (d, $^3J(H,H) = 8.6$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 28.3$ (d, $^5J(C,F) = 1.7$ Hz), 47.6 (d, $^4J(C,F) = 7.8$ Hz), 85.2 (dq, $^1J(C,F) = 200.9$ Hz, $^2J(C,F) = 34.0$ Hz), 117.9, 121.0 (qd, $^1J(C,F) = 282.8$ Hz, $^2J(C,F) = 26.3$ Hz), 124.7, 125.5, 127.7, 131.3, 142.0, 158.4 ppm (d, $^2J(C,F) = 19.8$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -200.32$ (dq, $^2J(F,H) = 46.2$ Hz, $^3J(F,F) = 12.3$ Hz, 1F, CF), -75.66 ppm (dd, $^3J(F,F) = 13.1$ Hz, $^3J(F,H) = 6.2$ Hz, 3F, CF_3); IR (KBr): $\tilde{\nu} = 2923, 1677, 1598, 1486, 1433, 1350, 1260, 1196, 1151, 1121, 868, 757$ cm^{-1}; MS (70 eV, EI): m/z (%): 247 (100) $[M]^+$, 146 (55), 128 (52), 118 (99), 91 (82); EI-HRMS: m/z: calcd for $C_{11}H_9NOF_4$: 247.0620 $[M]^+$; found: 247.0629; elemental analysis calcd (%) for $C_{11}H_9NOF_4$ (247.2): C 53.45, H 3.67, N 5.67, F 30.74; found: C 53.57, H 3.53, N 5.71, F 30.70.

3,3,3-Trifluoro-2-(2′-quinolinyl)propionic *N*-ethyl-*N*-phenylamide (8a): Colourless crystalline solid, m.p. 97–99 °C (benzene/Et_2O); ^{1}H NMR (400 MHz): $\delta = 1.11$ (t, $^3J(H,H) = 7.2$ Hz, 3H; CH_3), 3.75 (dq, $^2J(H,H) = 13.4$ Hz, $^3J(H,H) = 7.2$ Hz, 1H; NCH_2), 3.82 (dq, $^2J(H,H) = 13.4$ Hz, $^3J(H,H) = 7.2$ Hz, 1H; NCH_2), 4.79 (q, $^3J(H,F) = 8.6$ Hz, 1H; $CHCF_3$), 6.95 (m, 2H; H_{ar}), 7.36 (m, 3H; H_{ar}), 7.56 (ddd, $^3J(H,H) = 8.2$ Hz, 6.9 Hz, $^4J(H,H) = 1.2$ Hz, 1H; H_{ar}), 7.70 (ddd, $^3J(H,H) = 8.5$ Hz, 6.9 Hz, $^4J(H,H) = 1.5$ Hz, 1H; H_{ar}), 7.83 (d, $^3J(H,H) = 8.4$ Hz, 2H; H_{ar}), 7.95 (dd, $^3J(H,H) = 7.9$ Hz, $^4J(H,H) = 0.4$ Hz, 1H; H_{ar}), 8.17 ppm (d, $^3J(H,H) = 8.6$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 12.7$, 44.8, 56.1 (q, $^2J(C,F) = 26.8$ Hz), 120.9, 124.0 (q, $^1J(C,F) = 281.1$ Hz), 127.1, 127.5, 127.6, 128.7, 129.4, 129.6, 129.8, 129.8, 136.8, 140.7, 147.6, 151.0 (q, $^3J(C,F) = 2.6$ Hz), 164.0 ppm (q, $^3J(C,F) = 1.7$ Hz); ^{19}F NMR (376.4 MHz): $\delta = -65.94$ ppm (d, $^3J(F,H) = 8.6$ Hz, CF_3); IR (KBr): $\tilde{\nu} = 3067, 2986, 2935, 1676, 1595, 1494, 1411, 1341, 1301, 1263, 1177, 1160, 1105, 825, 777, 757, 709$ cm^{-1}; MS (70 eV, EI): m/z (%): 358 (8) $[M]^+$, 238 (18), 211 (100), 191 (20), 128 (18), 120 (52); EI-HRMS: m/z: calcd for $C_{20}H_{17}N_2OF_4$: 358.1293 $[M]^+$; found: 358.1282; elemental analysis calcd (%) for $C_{20}H_{17}N_2OF_3$ (358.4): C 67.03, H 4.78, N 7.82, F 15.90; found: C 67.04, H 4.85, N 7.86, F 15.90.

Thioester 6e: This compound was prepared analogously to amide **7d** by adding *p*-chlorothiophenol (275 mg, 1.9 mmol) to the DMF solution of acyl fluoride **9e** instead of the amine. Pale yellow oil; ^{1}H NMR (400 MHz): $\delta = 7.35$ (d, $^3J(H,H) = 8.7$ Hz, 2H; C_6H_4), 7.42 (d, $^3J(H,H) = 8.7$ Hz, 2H; C_6H_4), 7.47 (dd, $^3J(H,H) = 5.2$ Hz, $^4J(H,H) = 1.8$ Hz, 1H; H_{ar}), 7.77 (s, 1H; H_{ar}), 8.63 ppm (d, $^3J(H,H) = 5.2$ Hz, 1H; H_{ar}); ^{13}C NMR (100.6 MHz): $\delta = 96.0$ (m), 120.3 (qd, $^1J(C,F) = 286.2$ Hz, $^2J(C,F) = 28.4$ Hz), 122.3 (d, $^3J(C,F) = 7.8$), 122.9 (d, $^4J(C,F) = 6.0$), 125.8, 129.8, 136.0, 136.9, 145.8, 150.1 (d, $^2J(C,F) = 24.1$), 150.6 (d, $^3J(C,F) = 1.7$), 188.7 ppm (d, $^2J(C,F) = 30.2$); ^{19}F NMR (376.4 MHz): $\delta = -170.28$ (q, $^3J(F,F) = 8.7$ Hz, 1F, $CFCF_3$), -75.67 ppm (d, $^3J(F,F) = 8.7$ Hz, 3F, $CFCF_3$); IR (film): $\tilde{\nu} = 3063, 1723, 1575, 1478, 1391, 1280, 1212, 1188, 1144, 1014, 821, 750$ cm^{-1}; MS (70 eV, EI): m/z (%): 383 (3) $[M]^+$, 240 (100), 212 (89), 162 (25), 143 (21), 108 (15); EI-HRMS: m/z: calcd for $C_{14}H_7NOSCl_2F_4$: 382.9562 $[M]^+$; found: 382.9556; elemental analysis calcd (%) for $C_{14}H_7NOSCl_2F_4$ (384.2): C 43.77, H 1.83, N 3.65, S 8.35, Cl 18.46, F 19.78; found: C 43.67, H 1.66, N 3.78, S 8.63, Cl 18.44, F 19.78.

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