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Catalytic Radical Intramolecular Aminoperfluoroalkylation and Aminodifluoromethylation of Unactivated Alkenes with Fluoroalkylsulfonyl Chlorides

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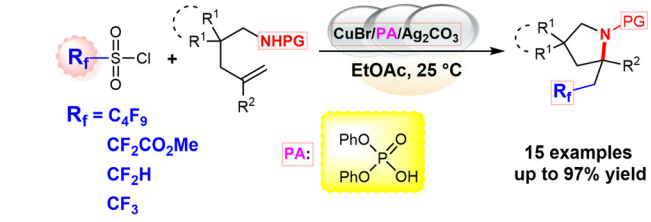

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Abstract The Cu(I)/phosphoric acid (PA) dual-catalyzed radical aminoperfluoroalkylation and aminodifluoromethylation of alkenes with commercially available fluoroalkylsulfonyl chlorides as the radical source is described. Functionalized α-tertiary pyrrolidines bearing four types of fluoroalkyl groups are obtained with moderate to excellent yields. The introduction of a Cu(I)/phosphoric acid dual catalytic system and the use of silver carbonate as a key additive to inhibit the side hydroamination reaction caused by the in situ generated HCl are crucial for the transformation.

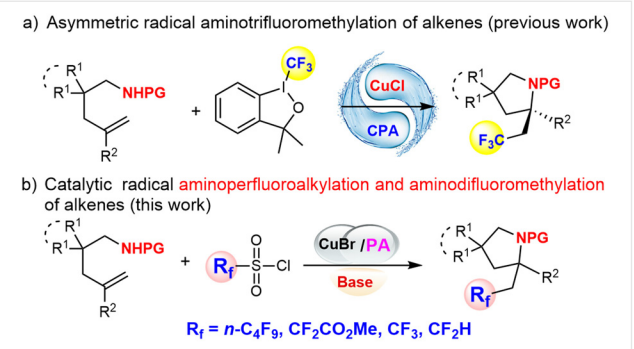
Key words fluoroalkylsulfonyl chlorides, aminodifluoromethylation, aminoperfluoroalkylation, radical, dual catalytic, pyrrolidines, unactivated alkenes

Azaheterocycles containing a fluoroalkyl group, such as perfluoroalkyl, trifluoromethyl, and difluoromethyl, as important synthetic building blocks,[1] have been extensively studied and widely applied as pharmaceutical and agricultural chemicals because these moieties can lead to intriguing alterations of the physical and biological properties of compounds.[2] For example, azaheterocycles bearing a difluoromethylene group (CF_2), which can function as a lipophilic hydrogen bond donor and as a bioisostere for a hydroxy or a mercapto group,[3] should be of great importance for medicinal chemistry. In view of the wide occurrence of the fluoroalkyl moiety in azaheterocycle pharmaceuticals and their unique physical and biological characteristics, tremendous efforts have been dedicated to the development of new protocols for the synthesis of azaheterocycles bearing different fluoroalkyl groups.[1] In this respect, Cho's group[4] have reported a photocatalyzed intramolecular perfluoroalkylation of terminal allylic amines with commercially available perfluoroalkyl iodides as the radical sources in the presence of a ruthenium complex as the photocatalyst to give various perfluoroalkylated aziridines.

Employing a similar strategy, Xiao's group[5] also disclosed photocatalytic radical trifluoromethylation of β,γ-unsaturated hydrazones with Umemoto's reagent to produce CF_3-containing dihydropyrazoles. Additionally, photocatalyzed intermolecular aminotrifluoromethylation of unactivated alkenes with Umemoto's reagent has been developed by the Akita[6] and Masson[7] groups. Compared with the recent use of Umemoto's reagent, Togni's reagent[1k] is more widespread as a trifluoromethylating reagent, reacting with diverse unsaturated carbon–carbon bonds to provide a convenient and powerful access to a wide array of functionalized CF_3-containing molecules via the use of different initiators. Recently, Sodeoka,[8] Wang[9] and our group[10] have independently developed copper-catalyzed intramolecular aminotrifluoromethylation of alkenes with diverse nitrogen-based nucleophiles using Togni's reagent as the CF_3 source, furnishing CF_3-containing aziridines, pyrrolidines, lactams and indolines. Additionally, Liu's group[11] recently disclosed copper-catalyzed intermolecular aminotrifluoromethylation of alkenes and azidotrifluoromethylation of alkynes with Togni's reagent for the synthesis of CF_3-substituted azirines and aziridines. Although significant progress toward CF_3 sources has been made, the transformation is mainly limited to the aminotrifluoromethylation of alkenes or alkynes employing expensive Togni's reagent or Umemoto's reagent as the CF_3 precursor, and leads to the generation of stoichiometric byproduct (dibenzothiophene from Umemoto's reagent). Thus, a commercially available, cheap and convenient CF_3 radical source is highly desirable. In this context, fluoroalkylsulfonyl chlorides[12] are generally considered to be suitable, highly reactive radical sources for the aminofluoroalkylation reaction by releasing SO_2 as a single byproduct, and significant progress has been made in the

direct 1,2-difunctionalization-type fluoroalkylation of alkenes by using stable fluoroalkylsulfonyl chlorides as the radical sources. More recently, Dolbier's group reported an elegant photoredox-catalyzed intramolecular aminodifluoromethylation of unactivated alkenes using HCF_2SO_2Cl as a source of HCF_2,[12e] but other fluoroalkylsulfonyl radical sources, such as *n*-$C_4F_9SO_2Cl$ and CF_3SO_2Cl, were incompatible with identical reaction conditions wherein their use led mainly to the products of simple atom transfer radical addition (ATRA) reactions.

More recently, we disclosed that a dual catalytic system of Cu(I) and a chiral phosphoric acid (CPA) catalyzed the asymmetric radical aminotrifluoromethylation of alkenes with Togni's reagent as the CF_3 radical source with excellent enantioselectivity[13] (Scheme 1, a). To address the existing limitations to enhance the synthetic utility of the dual catalytic methodology, we envisaged an immediate extension of the methodology established above to develop new and effective catalytic systems for efficient and general radical fluoroalkylation reactions with versatile fluoroalkylating reagents under mild conditions. Two challenges can be associated with this transformation: (1) it is very difficult to develop an integrated catalytic approach that is compatible with a variety of electronically distinct fluoroalkylsulfonyl chlorides, such as perfluoroalkyl, trifluoromethyl, difluoroacetyl, and even difluoromethyl radical precursors; (2) a competitive hydroamination[14] of the alkene may occur, as a stoichiometric amount of the strong Brønsted acid HCl would be generated in situ during the process. Herein, we report the catalytic radical intramolecular aminoperfluoroalkylation and aminodifluoromethylation of alkenes with various fluoroalkylsulfonyl chlorides via a dual catalytic system composed of Cu(I) and phosphoric acid, giving a practical access to diverse fluoroalkyl-containing pyrrolidines (Scheme 1, b).[15]



Scheme 1 Transition-metal-catalyzed aminotrifluoromethylation of unactivated alkenes

Encouraged by our recent success employing Cu(I) and a chiral phosphoric acid (CPA) as a dual catalytic system for the asymmetric radical aminotrifluoromethylation of alkenes with Togni's reagent,[13] we conducted our initial investigation by reacting *N*-alkenyl urea **1a** with *n*-$C_4F_9SO_2Cl$ (**2a**) as a model reaction. To our disappointment, the treatment of *N*-alkenyl urea **1a** with **2a** in the absence of a base under otherwise identical conditions gave the desired product **3A** in a poor yield, along with side hydroamination product **3AA** in 28% yield (Table 1, entry 1).

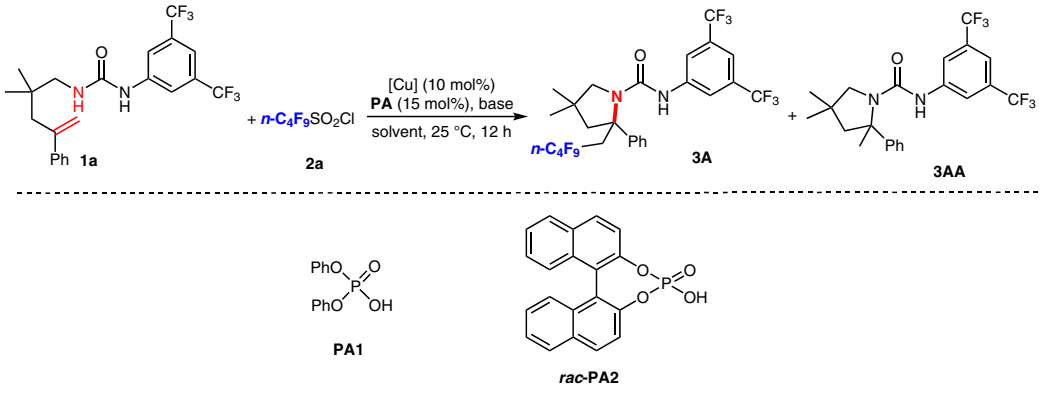
Among the different bases examined, Ag_2CO_3 was found to be particularly effective, giving **3A** in 98% yield (Table 1, entries 2–6). This can be attributed to the use of silver carbonate to quench the stoichiometric amount of HCl generated in situ,[12e] which could cause a side hydroamination reaction. Further investigation revealed that CuBr behaved as the most efficient catalyst after screening Cu(I) catalysts (Table 1, entries 7–9). Next, a solvent screen revealed that EtOAc was better than the other solvents, suggesting a significant solvent effect on this reaction (Table 1, entries 10–12). A change of **PA1** to **PA2** led to a dramatic decrease in the yield to 21% (Table 1, entry 13). Finally, a control experiment revealed that the reaction suffered a dramatic decrease in the product yield in the absence of **PA1** (Table 1, entry 14), revealing that a phosphoric acid in combination with Ag_2CO_3 is essential for this transformation.

To further investigate the substrate scope of the present catalytic system, we performed the catalytic radical fluoroalkylation of alkenes with various fluoroalkylsulfonyl chlorides. As summarized in Scheme 2, regardless of the position and electronic nature of the substituent on the phenyl ring, *N*-aryl urea derivatives reacted efficiently with *n*-$C_4F_9SO_2Cl$ to give the desired products in good to excellent yields. For example, a range of diversely functionalized alkenyl ureas **1**, including those having aryl groups with electron-withdrawing (CF_3, F, Cl, Br) or electron-donating groups (Me) at different positions (*ortho*, *meta* or *para*) on the aryl ring were well tolerated, affording the desired products **3A–G** in 88–97% yields. Gratifyingly, a variety of cyclic substrates containing three- to six-membered rings were all suitable for the transformation, providing a diverse set of perfluoroalkylated spiro products **3H–K** in 92–95% yields.

Even more remarkably, another protected amine was also found to be suitable for the transformation: the reaction of *N*-alkenyl tosyl **1l** proceeded well to afford the corresponding product **3L** in 70% yield under identical conditions (Scheme 2).

Inspired by the above success, we were naturally eager to extend the current protocol to other fluoroalkylsulfonyl chlorides to provide easy access to structurally diverse fluoroalkyl-containing pyrrolidines. To our delight, the reaction of *N*-alkenyl urea substrate **1a** with other fluoroalkylsulfonyl chlorides under the modified conditions furnished the corresponding products **4A–C** in moderate to good yields. The results showed that trifluoromethanesulfonyl chlorides as highly reactive, low-cost and simple to work-up CF_3 sources exhibit several advantages over Togni's reagent.

Table 1 Screening of the Reaction Conditions[a]

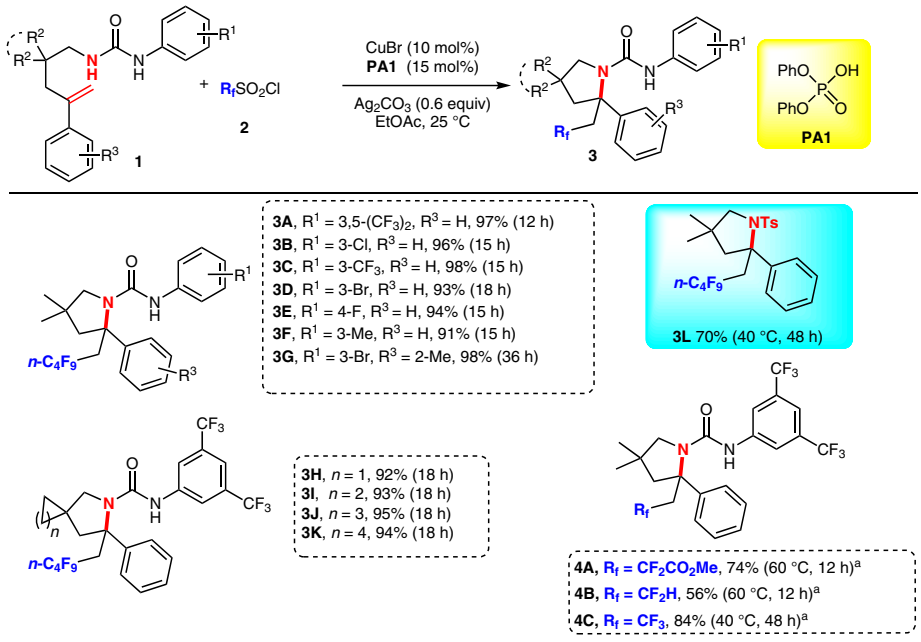


Entry	[Cu]	Base (equiv)	PA[b]	Solvent	Yield (%)[c]	
					3A	**3AA**
1	CuBr	–	**PA1**	EtOAc	18	28
2	CuBr	$NaHCO_3$ (1.2)	**PA1**	EtOAc	17	0
3	CuBr	Na_2CO_3 (0.6)	**PA1**	EtOAc	11	0
4	CuBr	K_2CO_3 (0.6)	**PA1**	EtOAc	10	trace
5	CuBr	KH_2PO_4 (1.2)	**PA1**	EtOAc	26	trace
6	CuBr	Ag_2CO_3 (0.6)	**PA1**	EtOAc	98	0
7	CuI	Ag_2CO_3 (0.6)	**PA1**	EtOAc	94	0
8	CuCl	Ag_2CO_3 (0.6)	**PA1**	EtOAc	97	0
9	CuOAc	Ag_2CO_3 (0.6)	**PA1**	EtOAc	39	0
10	CuBr	Ag_2CO_3 (0.6)	**PA1**	CH_2Cl_2	28	0
11	CuBr	Ag_2CO_3 (0.6)	**PA1**	THF	53	0
12	CuBr	Ag_2CO_3 (0.6)	**PA1**	*n*-hexane	NR	NR
13	CuBr	Ag_2CO_3 (0.6)	**PA2**[d]	EtOAc	21	0
14	CuBr	Ag_2CO_3 (0.6)	–	EtOAc	17	trace

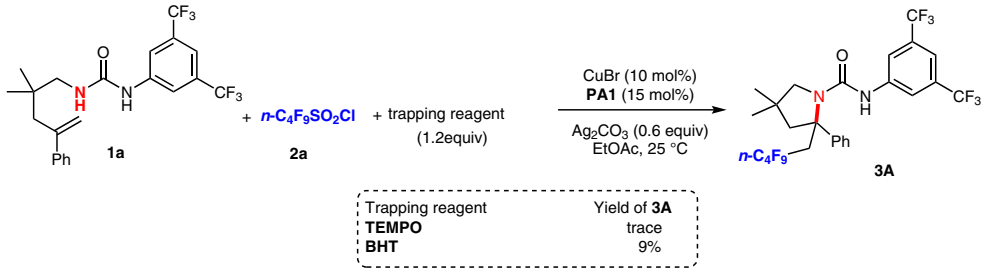
[a] Reaction conditions: **1a** (0.05 mmol), **2a** (0.06 mmol), [Cu] (10 mol%), base, **PA1** (15 mol%), solvent (0.5 mL), 25 °C, 12 h, Ar atm.
[b] PA = phosphoric acid.
[c] Yield based on ^1H NMR analysis of the crude product using CH_2Br_2 as an internal standard. NR = no reaction.
[d] **PA2** (25 mol%) was used.

Given the broad scope of fluoroalkyl radicals, the current reaction system represents a more appealing alternative to the previous protocols.[10,12e]

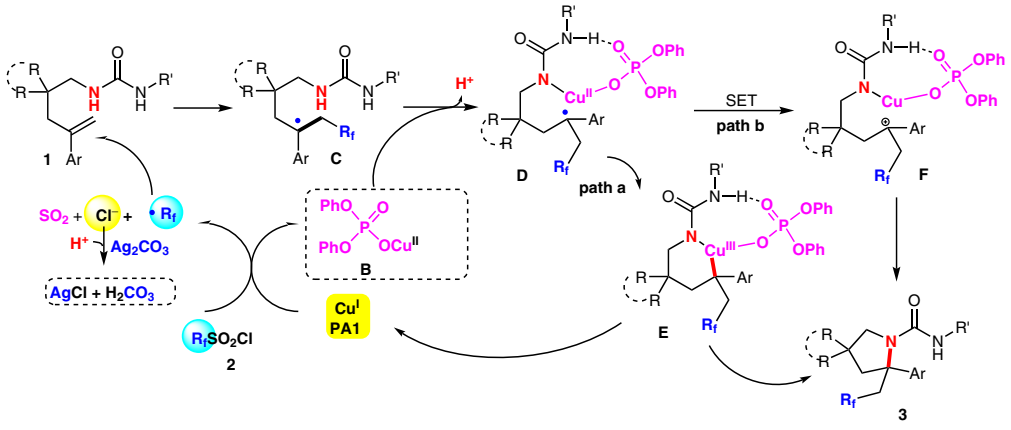
To gain some insights into the reaction mechanism, radical-trapping experiments using 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) as radical scavengers were carried out, and it was found that the present reaction was significantly inhibited by these reagents (Scheme 3). On the basis of the above mechanistic investigations and previous studies,[12e,13,16] a plausible mechanism for the catalytic radical aminofluoroalkylation of alkenes is shown in Scheme 4. Initially, the reaction of R_fSO_2Cl with CuBr and the phosphoric acid could generate an R_f radical and phosphate Cu(II) **B** via a single-electron transfer (SET) process along with the generation of SO_2 and a chloride anion; at the same time, Ag_2CO_3 could quench the stoichiometric amount of HCl generated in situ. Subsequently, the R_f radical could attack the alkene **1** to generate the α-R_f alkyl radical **C**, which could coordinate to Cu(II) phosphate **B** to form a Cu(II) species **D** via both hydrogen-bonding and ion-pairing interactions.[13] The alkyl radical intermediate could then be trapped by the Cu(II) phosphate to afford Cu(III) phosphate **E**[13,16,17] via a concerted transition state (path a), followed by reductive elimination to afford the final product **3** along with the regeneration of Cu(I) and the phosphoric acid.



Scheme 2 Substrate scope for the aminofluoroalkylation of alkenyl ureas **1**. All the reactions were conducted on 0.2 mmol scale. Yields are those of isolated products based on **1**. [a] **PA1** (30 mol%) was used.



Scheme 3 Mechanistic studies. *Reagents and conditions*: **1a** (0.05 mmol), **2a** (0.06 mmol), CuBr (10 mol%), Ag_2CO_3 (0.03 mmol), trapping reagent (0.06 mmol), **PA1** (15 mol%), EtOAc (0.5 mL), 25 °C, 12 h, Ar atm.



Scheme 4 A mechanistic proposal

On the other hand, intermediate **D** could also be further converted into the corresponding carbocation intermediate **F**[12e] via a single-electron transfer process. Intermediate **F** then undergoes C–N bond formation to give product **3**. This alternative mechanism (path b) could not be excluded at the present stage.

In conclusion, we have developed a new copper(I)/phosphoric acid catalyzed radical aminoperfluoroalkylation and aminodifluoromethylation of alkenes with commercially available fluoroalkylsulfonyl chlorides, allowing efficient access to four types of structurally diverse fluoroalkyl-containing pyrrolidines bearing an α-tertiary stereocenter. The process exhibits excellent functional group tolerance and provides a valuable alternative to previous methodologies. Importantly, the newly presented aminotrifluoromethylation of alkenes with CF_3SO_2Cl as the CF_3 source represents a useful complement to the existing approach.[10] Further studies involving the development of a more challenging catalytic asymmetric version are ongoing in our laboratory.

All reagents were obtained from commercial sources and used without further purification, unless otherwise stated. Ethyl acetate (EtOAc) was purchased from Adamas-beta®. CuBr and Ag_2CO_3 were purchased from Sigma-Aldrich. Methyl 2-(chlorosulfonyl)-2,2-difluoroacetate and difluoromethylsulfonyl chloride were purchased from 9dingchem (China). TLC was performed on adsorbent plates (Tsingdao silica gel). Silica Gel 200–300F (Tsingdao silica gel) was used for column chromatography. ^{1}H NMR spectra were recorded in $CDCl_3$ at ambient temperature on Bruker DRX-500 and DPX 400 spectrometers at 500 or 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on Bruker DRX-500 and DPX 400 spectrometers at 126 or 100 MHz. ^{19}F NMR spectra were recorded in $CDCl_3$ at ambient temperature on a Bruker DPX 400 spectrometer at 376 MHz. The chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and Hz, respectively. Data for ^{1}H NMR spectra are indicated as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ). Mass spectrometric data were recorded using a Bruker Apex IV RTMS spectrometer. Melting points were recorded on a Hanon H450 auto melting point system.

Aminoperfluoroalkylation of Alkenes; General Procedure

An oven-dried Schlenk tube with a magnetic stir bar was charged with urea substrate **1a** (0.2 mmol, 1.0 equiv), phosphoric acid **PA1** (7.5 mg, 0.03 mmol, 15 mol%), CuBr (2.86 mg, 0.02 mmol, 10 mol%), Ag_2CO_3 (33.09 mg, 0.12 mmol, 0.6 equiv), *n*-$C_4F_9SO_2Cl$ (**2a**) (76.3 mg, 0.24 mmol, 1.2 equiv) and EtOAc (2.0 mL) under an atmosphere of dry argon. The mixture was then stirred at 25 °C. Upon completion (monitored by TLC), the mixture was purified directly by silica gel chromatography [eluent: PE/EtOAc = 100:0 to 5:1, initially using PE (100%) to remove the solvent (EtOAc)] to afford the desired product **3**.

N-[3,5-Bis(trifluoromethyl)phenyl]-4,4-dimethyl-2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-phenylpyrrolidine-1-carboxamide (3A)

White solid; yield: 129.8 mg (97%); mp 150-152 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.83 (s, 2 H), 7.45 (s, 1 H), 7.39–7.29 (m, 4 H), 7.26–7.24 (m, 1 H), 6.82 (s, 1 H), 3.82 (dd, *J* = 35.0, 14.0 Hz, 1 H), 3.59–3.42 (m, 2 H), 2.85–2.83 (m, 1 H), 2.78 (d, *J* = 13.5 Hz, 1 H), 2.24 (d, *J* = 13.5 Hz, 1 H), 1.12 (s, 3 H), 0.87 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.2, 145.5, 140.2, 131.9 (q, *J* = 33.3 Hz), 128.3, 127.1, 125.7, 123.1 (q, *J* = 272.7 Hz), 119.6 (d, *J* = 4.0 Hz), 116.3 (quin, *J* = 3.8 Hz), 121.2–106.8 (m), 68.9, 61.2, 53.1, 36.5, 36.2 (t, *J* = 18.4 Hz), 28.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.2 (s, 6 F), –81.2 (t, *J* = 9.8 Hz, 3 F), –107.3 (AB, d, $J_{F–F}$ = 270.7 Hz, 1 F), –117.1 (AB, d, $J_{F–F}$ = 271.9 Hz, 1 F), –124.5 (s, 2 F), –125.7 to –125.8 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{22}F_{15}N_2O$: 663.1493; found: 663.1487.

N-(3-Chlorophenyl)-4,4-dimethyl-2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-phenylpyrrolidine-1-carboxamide (3B)

White solid; yield: 107.6 mg (96%); mp 142-144 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (s, 1 H), 7.38–7.36 (m, 4 H), 7.28–7.24 (m, 2 H), 7.20 (t, *J* = 8.0 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.45 (s, 1 H), 3.82 (dd, *J* = 36.0, 14.5 Hz, 1 H), 3.55–3.50 (m, 2 H), 2.95–2.73 (m, 2 H), 2.25 (d, *J* = 13.5 Hz, 1 H), 1.19 (s, 3 H), 0.92 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.6, 146.2, 140.4, 134.8, 130.1, 128.6, 127.2, 126.2, 123.4, 120.3, 118.2, 121.2–106.8 (m), 68.9, 61.4, 53.5, 36.8, 36.6 (t, *J* = 18.5 Hz), 28.7, 28.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.8 to –81.3 (m, 3 F), –107.7 (AB, d, $J_{F–F}$ = 269.2 Hz, 1 F), –116.4 (AB, d, $J_{F–F}$ = 268.8 Hz, 1 F), –124.0 (s, 2 F), –125.6 to –125.7 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}ClF_9N_2O$: 561.1355; found: 561.1350.

4,4-Dimethyl-2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-phenyl-*N*-[3-(trifluoromethyl)phenyl]pyrrolidine-1-carboxamide (3C)

White solid; yield: 116.6 mg (98%); mp 148-149 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 (s, 2 H), 7.40–7.30 (m, 5 H), 7.30–7.19 (m, 2 H), 6.56 (s, 1 H), 3.88–3.78 (m, 1 H), 3.55–3.48 (m, 2 H), 2.92–2.62 (m, 2 H), 2.24 (d, *J* = 13.5 Hz, 1 H), 1.16 (s, 3 H), 0.89 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.4, 145.8, 139.3, 131.1 (q, *J* = 32.3 Hz), 129.3, 128.2, 126.9, 125.8, 124.0 (q, *J* = 272.4 Hz), 123.1, 119.6 (q, *J* = 3.8 Hz), 116.6 (q, *J* = 4.0 Hz), 121.1–106.5 (m), 68.6, 61.1, 53.1, 36.4, 36.2 (t, *J* = 18.2 Hz), 28.24, 28.21.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.7 (s, 3 F), –81.1 (t, *J* = 9.8 Hz, 3 F), –107.4 (AB, d, $J_{F–F}$ = 270.3 Hz, 1 F), –116.7 (AB, d, $J_{F–F}$ = 270.7 Hz, 1 F), –124.5 (s, 2 F), –125.1 to –126.2 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{23}F_{12}N_2O$: 595.1619; found: 595.1613.

N-(3-Bromophenyl)-4,4-dimethyl-2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-phenylpyrrolidine-1-carboxamide (3D)

White solid; yield: 112.6 mg (93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (s, 1 H), 7.42–7.35 (m, 4 H), 7.33–7.31 (m, 1 H), 7.28–7.24 (m, 1 H), 7.21–7.07 (m, 2 H), 6.43 (s, 1 H), 3.82 (dd, *J* = 36.5, 15.0 Hz, 1 H), 3.58–3.45 (m, 2 H), 2.91–2.72 (m, 2 H), 2.25 (d, *J* = 13.5 Hz, 1 H), 1.19 (s, 3 H), 0.92 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.6, 146.2, 140.5, 130.4, 128.6, 127.2, 126.4, 126.2, 123.1, 122.8, 118.7, 121.5–106.5 (m), 68.9, 61.4, 53.5, 36.8, 36.6 (t, *J* = 18.3 Hz), 28.7, 28.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.0 (d, *J* = 9.8 Hz, 3 F), –107.7 (AB, d, $J_{F–F}$ = 269.2 Hz, 1 F), –116.4 (AB, d, $J_{F–F}$ = 268.8 Hz, 1 F), –122.4 (s, 2 F), –124.9 to –126.5 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}BrF_9N_2O$: 605.0850; found: 605.0845.

N-(4-Fluorophenyl)-4,4-dimethyl-2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-phenylpyrrolidine-1-carboxamide (3E)

White solid; yield: 102.4 mg (94%); mp 132-133 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.32 (m, 6 H), 7.27–7.23 (m, 1 H), 7.02–6.97 (m, 2 H), 6.35 (s, 1 H), 3.83 (dd, *J* = 37.5, 15.0 Hz, 1 H), 3.58–3.46 (m, 2 H), 2.89–2.73 (m, 2 H), 2.26 (d, *J* = 13.5 Hz, 1 H), 1.19 (s, 3 H), 0.92 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.3 (d, *J* = 241.8 Hz), 154.1, 146.4, 135.0 (d, *J* = 2.7 Hz), 128.5, 127.1, 126.3, 122.5 (d, *J* = 7.9 Hz), 115.7 (d, *J* = 22.3 Hz), 121.5–106.9 (m), 68.8, 61.4, 53.5, 36.7, 36.6 (t, *J* = 18.9 Hz), 28.7, 28.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.0 to –81.1 (m, 3 F), –107.5 (AB, d, $J_{F–F}$ = 268.8 Hz, 1 F), –116.6 (AB, d, $J_{F–F}$ = 267.7 Hz, 1 F), –119.9 (m, 1 F), –124.4 (s, 2 F), –125.5 to –125.8 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{23}F_{10}N_2O$: 545.1651; found: 545.1645.

4,4-Dimethyl-2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-phenyl-*N*-(*m*-tolyl)pyrrolidine-1-carboxamide (3F)

White solid; yield: 98.4 mg (91%); mp 134-135 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.32 (m, 5 H), 7.26 (tt, *J* = 7.0, 3.5 Hz, 1 H), 7.22–7.17 (m, 2 H), 6.93–6.86 (m, 1 H), 6.36 (s, 1 H), 3.97–3.75 (m, 1 H), 3.63–3.45 (m, 2 H), 2.92–2.74 (m, 2 H), 2.35 (s, 3 H), 2.26 (d, *J* = 13.5 Hz, 1 H), 1.20 (s, 3 H), 0.93 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.0, 146.5, 139.09, 139.07, 129.0, 128.5, 127.1, 126.3, 124.3, 121.0, 117.3, 121.2–106.3 (m), 68.8, 61.4, 53.5 (d, *J* = 5.6 Hz), 36.7, 36.6 (t, *J* = 18.2 Hz), 28.7, 28.6, 21.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.0 (t, *J* = 9.8 Hz, 3 F), –107.5 (AB, d, $J_{F–F}$ = 267.7 Hz, 1 F), –116.3 (AB, d, $J_{F–F}$ = 270.0 Hz, 1 F), –124.4 (s, 2 F), –125.5 to –125.7 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{26}F_9N_2O$: 541.1901; found: 541.1896.

N-(3-Bromophenyl)-4,4-dimethyl-2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-(*o*-tolyl)pyrrolidine-1-carboxamide (3G)

White solid; yield: 121.4 mg (98%); mp 146-147 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (s, 1 H), 7.46–7.45 (m, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.24–7.10 (m, 5 H), 6.45 (s, 1 H), 4.19–3.94 (m, 1 H), 3.62–3.38 (m, 2 H), 2.96 (ddd, *J* = 31.5, 15.5, 8.0 Hz, 1 H), 2.84 (d, *J* = 13.0 Hz, 1 H), 2.48 (s, 3 H), 2.32 (d, *J* = 13.0 Hz, 1 H), 1.21 (s, 3 H), 0.90 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.0, 143.2, 140.8, 133.6, 133.3, 130.7, 128.05, 127.98, 126.7, 126.1, 123.4, 123.1, 119.0, 122.1–107.1 (m), 70.1, 61.4, 51.6, 37.3, 33.5 (t, *J* = 17.8 Hz), 29.4, 29.1, 23.1.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –80.9 to –81.0 (m, 3 F), –107.1 (AB, d, $J_{F–F}$ = 268.8 Hz, 1 F), –116.8 (AB, d, $J_{F–F}$ = 268.5 Hz, 1 F), –124.6 (d, *J* = 8.3 Hz, 2 F), –125.4 to –125.7 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{25}BrF_9N_2O$: 619.1007; found: 619.1017.

N-[3,5-Bis(trifluoromethyl)phenyl]-6-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-6-phenyl-5-azaspiro[2.4]heptane-5-carboxamide (3H)

White solid; yield: 115.2 mg (92%); mp 150-151 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (s, 2 H), 7.50–7.26 (m, 6 H), 6.83 (br s, 1 H), 3.96–3.70 (m, 2 H), 3.34 (d, *J* = 8.5 Hz, 1 H), 3.16–2.95 (m, 2 H), 1.80 (d, *J* = 13.0 Hz, 1 H), 0.64–0.54 (m, 2 H), 0.55–0.49 (m, 1 H), 0.24–0.16 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 152.5, 145.1, 140.2, 131.7 (q, *J* = 33.3 Hz), 128.6, 127.3, 124.6, 123.1 (q, *J* = 272.6 Hz), 119.5 (d, *J* = 3.0 Hz), 116.1 (q, *J* = 3.8 Hz), 122.0–106.5 (m), 67.9, 55.9, 48.3, 34.6 (t, *J* = 18.7 Hz), 18.2, 15.6, 5.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.3 (s, 6 F), –79.0 to –86.1 (m, 3 F), –108.8 (AB, d, $J_{F–F}$ = 246.5 Hz, 1 F), –115.7 (AB, d, $J_{F–F}$ = 241.3 Hz, 1 F), –124.5 (s, 2 F), –125.7 to –125.8 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{20}F_{15}N_2O$: 661.1336; found: 661.1331.

N-[3,5-Bis(trifluoromethyl)phenyl]-7-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-7-phenyl-6-azaspiro[3.4]octane-6-carboxamide (3I)

White solid; yield: 119.2 mg (93%); mp 133-134 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.85 (s, 2 H), 7.48 (s, 1 H), 7.40–7.32 (m, 2 H), 7.31–7.24 (m, 3 H), 6.79 (br s, 1 H), 4.02–3.78 (m, 2 H), 3.64 (d, *J* = 8.5 Hz, 1 H), 2.91–2.81 (m, 1 H), 2.76 (d, *J* = 13.0 Hz, 1 H), 2.50 (d, *J* = 13.0 Hz, 1 H), 2.09–2.00 (m, 2 H), 1.85–1.70 (m, 3 H), 1.29 (s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.1, 144.6, 140.6, 132.3 (q, *J* = 33.2 Hz), 128.7, 127.6, 125.7, 123.5 (q, *J* = 272.8 Hz), 119.8 (d, *J* = 3.9 Hz), 116.7–116.4 (m), 121.5–106.8 (m), 68.5, 60.3, 51.8, 42.7, 36.0, 35.5 (t, *J* = 18.4 Hz), 30.2, 16.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.2 (s, 6 F), –81.0 to –81.5 (t, *J* = 9.8 Hz, 3 F), –106.8 (AB, d, $J_{F–F}$ = 270.0 Hz, 1 F), –117.7 (AB, d, $J_{F–F}$ = 269.6 Hz, 1 F), –124.5 (d, *J* = 10.4 Hz, 2 F), –125.5 to –126.0 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{22}F_{15}N_2O$: 675.1493; found: 675.1487.

N-[3,5-Bis(trifluoromethyl)phenyl]-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-phenyl-2-azaspiro[4.4]nonane-2-carboxamide (3J)

Clear semi-solid; yield: 124.4 mg (95%); mp 137-138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.84 (s, 2 H), 7.46 (s, 1 H), 7.37–7.31 (m, 4 H), 7.26 (t, *J* = 7.0 Hz, 1 H), 6.79 (br s, 1 H), 3.96–3.76 (m, 1 H), 3.66–3.52 (m, 2 H), 2.99–2.68 (m, 2 H), 2.30 (d, *J* = 13.0 Hz, 1 H), 1.62 (s, 2 H), 1.53 (s, 4 H), 1.44–1.37 (m, 1 H), 0.97–0.95 (m, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.3, 145.2, 140.7, 132.1 (q, *J* = 33.2 Hz), 128.6, 127.5, 126.1, 123.5 (q, *J* = 272.6 Hz), 120.0, 116.7–116.5 (m), 121.5–106.5 (m), 68.6, 60.4, 51.6, 47.4, 39.2, 38.6, 36.2 (t, *J* = 18.3 Hz), 25.3, 24.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.1 (s, 6 F), –81.1 (t, *J* = 9.9 Hz, 3 F), –106.6 (AB, d, $J_{F–F}$ = 270.9 Hz, 1 F), –117.6 (AB, d, $J_{F–F}$ = 269.6 Hz, 1 F), –124.5 (s, 2 F), –125.6 to –125.8 (m, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{24}F_{15}N_2O$: 689.1649; found: 689.1644.

N-[3,5-Bis(trifluoromethyl)phenyl]-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-3-phenyl-2-azaspiro[4.5]decane-2-carboxamide (3K)

Clear semi-solid; yield: 125.8 mg (94%); mp 138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 2 H), 7.50 (s, 1 H), 7.40–7.30 (m, 4 H), 7.27 (t, *J* = 7.5 Hz, 1 H), 6.81 (br s, 1 H), 3.81 (dd, *J* = 35.0, 14.0 Hz, 1 H), 3.70 (d, *J* = 8.5 Hz, 1 H), 3.49 (d, *J* = 8.5 Hz, 1 H), 2.94–2.77 (m, 1 H), 2.66 (d, *J* = 13.5 Hz, 1 H), 2.44 (d, *J* = 13.5 Hz, 1 H), 1.53–1.20 (m, 10 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.5, 146.0, 140.6, 132.3 (q, *J* = 33.3 Hz), 128.8, 127.4, 125.8, 123.5 (q, *J* = 273.2 Hz), 120.0, 116.8–116.5 (m), 121.5–106.8 (m), 68.5, 59.4, 51.2, 40.7, 38.7, 36.6 (t, *J* = 18.2 Hz), 36.2, 25.8, 24.2, 22.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.1 (s, 6 F), –81.2 (t, *J* = 9.7 Hz, 3 F), –107.5 (AB, d, $J_{F–F}$ = 268.9 Hz, 1 F), –116.8 (AB, d, $J_{F–F}$ = 270.4 Hz, 1 F), –124.5 (s, 2 F), –125.77 (d, *J* = 11.4 Hz, 2 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{26}F_{15}N_2O$: 703.1806; found: 703.1800.

4,4-Dimethyl-2-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-2-phenyl-1-tosylpyrrolidine (3L)

White solid; yield: 80.6 mg (70%); mp 139-141 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2 H), 7.27–7.15 (m, 3 H), 7.04 (s, 4 H), 4.23 (ddd, *J* = 33.0, 16.5, 4.5 Hz, 1 H), 3.50 (d, *J* = 9.0 Hz, 1 H), 3.15 (d, *J* = 9.0 Hz, 1 H), 3.11–2.92 (m, 1 H), 2.59 (d, *J* = 14.5 Hz, 1 H), 2.50 (d, *J* = 14.5 Hz, 1 H), 2.36 (s, 3 H), 1.30 (s, 3 H), 1.16 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 142.6, 141.9, 136.3, 129.0, 127.9, 127.5, 127.0, 126.8, 120.8–106.6 (m), 69.7, 61.8, 53.7 (d, *J* = 4.3 Hz), 39.8 (t, *J* = 19.8 Hz), 36.8, 28.7, 27.3, 21.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.0 (t, *J* = 2.9 Hz, 3 F), –104.0 (AB, dd, *J* = 274.5, 15.7 Hz, 1 F), –108.0 (AB, d, *J* = 273.4 Hz, 1 F), –124.1 (d, *J* = 8.6 Hz, 2 F), –125.5 (dd, *J* = 17.6, 9.3 Hz, 1 F), –125.7 (t, *J* = 14.2 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{25}F_9NO_2S$: 562.1462; found: 562.1471.

Methyl 3-(1-{[3,5-Bis(trifluoromethyl)phenyl]carbamoyl}-4,4-dimethyl-2-phenylpyrrolidin-2-yl)-2,2-difluoropropanoate (4A)

An oven-dried Schlenk tube with a magnetic stir bar was charged with urea substrate **1a** (0.2 mmol, 1.0 equiv), phosphoric acid **PA1** (15 mg, 0.06 mmol, 30 mol%), CuBr (2.86 mg, 0.02 mmol, 10 mol%), Ag_2CO_3 (33.09 mg, 0.12 mmol, 0.6 equiv), $MeO_2CCF_2SO_2Cl$ (**2b**) (50 mg, 0.24 mmol, 1.2 equiv) and EtOAc (2.0 mL) under an atmosphere of dry argon. The mixture was then stirred at 60 °C for 12 h. Upon completion (monitored by TLC), the mixture was cooled to r.t. and directly purified by silica gel chromatography [eluent: PE/EtOAc = 100:0 to 5:1, initially using PE (100%) to remove the solvent (EtOAc)] to afford the desired product **4A**.

Clear semi-solid; yield: 78.8 mg (74%); mp 160-161 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.91 (s, 2 H), 7.49 (s, 1 H), 7.39–7.30 (m, 4 H), 7.27–7.22 (m, 1 H), 6.82 (br s, 1 H), 3.74–3.57 (m, 5 H), 3.53 (d, *J* = 8.5 Hz, 1 H), 2.95 (q, *J* = 16.0 Hz, 1 H), 2.83 (d, *J* = 13.5 Hz, 1 H), 2.22 (d, *J* = 13.5 Hz, 1 H), 1.17 (s, 3 H), 0.89 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.7 (t, *J* = 33.0 Hz), 153.4, 145.7, 140.5, 131.9 (q, *J* = 33.4 Hz), 128.3, 126.9, 125.6, 123.2 (q, *J* = 272.5 Hz), 119.5, 116.1, 115.8 (t, *J* = 253.0 Hz), 68.8, 61.3, 53.8, 53.4, 41.7 (t, *J* = 20.6 Hz), 36.4, 28.4, 28.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.0 (s, 6 F), –95.8 (d, *J* = 262.1 Hz, 1 F), –108.4 (d, *J* = 260.8 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{25}F_8N_2O_3$: 553.1737; found: 553.1732.

N-[3,5-Bis(trifluoromethyl)phenyl]-2-(2,2-difluoroethyl)-4,4-dimethyl-2-phenylpyrrolidine-1-carboxamide (4B)

An oven-dried Schlenk tube with a magnetic stir bar was charged with urea substrate **1a** (0.2 mmol, 1.0 equiv), phosphoric acid **PA1** (15 mg, 0.06 mmol, 30 mol%), CuBr (2.86 mg, 0.02 mmol, 10 mol%), Ag_2CO_3 (33.09 mg, 0.12 mmol, 0.6 equiv), HCF_2SO_2Cl (**2c**) (36.0 mg, 0.24 mmol, 1.2 equiv) and EtOAc (2.0 mL) under an atmosphere of dry argon. The mixture was then stirred at 60 °C for 12 h. Upon completion (monitored by TLC), the mixture was cooled to r.t. and directly purified by silica gel chromatography [eluent: PE/EtOAc = 100:0 to 5:1, initially using PE (100%) to remove the solvent (EtOAc)] to afford the desired product **4B**

Clear semi-solid; yield: 51.6 mg (56%); mp 147-148 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (s, 2 H), 7.52 (s, 1 H), 7.37 (t, *J* = 7.5 Hz, 2 H), 7.33–7.23 (m, 3 H), 6.74 (s, 1 H), 6.11–5.84 (m, 1 H), 3.61–3.53 (m, 2 H), 3.22–3.04 (m, 1 H), 2.84–2.72 (m, 1 H), 2.64 (d, *J* = 13.5 Hz, 1 H), 2.25 (d, *J* = 13.5 Hz, 1 H), 1.19 (s, 3 H), 0.92 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 153.0, 145.6, 140.2, 132.1 (q, *J* = 33.3 Hz), 128.5, 127.0, 125.3, 123.2 (d, *J* = 272.8 Hz), 119.4 (t, *J* = 4.0 Hz), 116.4 (t, *J* = 241.2 Hz), 116.4–116.3 (m), 68.4, 61.8, 54.8, 43.1 (t, *J* = 19.9 Hz), 36.3, 28.8, 28.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.0 (s, 6 F), –112.2 (ddt, *J* = 290.7, 55.8, 12.8 Hz, 1 F), –114.3 (d, *J* = 290.1 Hz, 1 F).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{23}F_8N_2O$: 495.1683; found: 495.1677.

N-[3,5-Bis(trifluoromethyl)phenyl]-4,4-dimethyl-2-phenyl-2-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (4C)

An oven-dried Schlenk tube with a magnetic stir bar was charged with urea substrate **1a** (0.2 mmol, 1.0 equiv), phosphoric acid **PA1** (15 mg, 0.06 mmol, 30 mol%), CuBr (2.86 mg, 0.02 mmol, 10 mol%), Ag_2CO_3 (33.09 mg, 0.12 mmol, 0.6 equiv), CF_3SO_2Cl (**2d**) (40.32 mg, 0.24 mmol, 1.2 equiv) and EtOAc (2.0 mL) under an atmosphere of dry argon. The mixture was then stirred at 40 °C for 48 h. Upon completion (monitored by TLC), the reaction mixture was cooled to r.t. and directly purified by silica gel chromatography [eluent: PE/EtOAc = 100:0 to 5:1, initially using PE (100%) to remove the solvent (EtOAc)] to afford the desired product **4C**.

White solid; yield: 80.4 mg (84%); mp 145-146 °C.

^{1}H NMR (500 MHz, acetone-d_6): δ = 8.40 (s, 1 H), 8.34 (s, 2 H), 7.59 (s, 1 H), 7.48 (d, *J* = 10.0 Hz, 2 H), 7.33 (t, *J* = 5.0 Hz, 2 H), 7.22 (t, *J* = 5.0 Hz, 1 H), 3.85 (d, *J* = 10.0 Hz, 1 H), 3.82–3.72 (m, 1 H), 3.61 (d, *J* = 5.0 Hz, 1 H), 3.20–3.10 (m, 1 H), 2.72 (d, *J* = 10.0 Hz, 1 H), 2.25 (d, *J* = 15.0 Hz, 1 H), 1.16 (s, 3 H), 0.89 (s, 3 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 154.7, 147.1, 143.6, 132.3 (q, *J* = 37.5 Hz), 128.8, 127.7 (q, *J* = 275.0 Hz), 127.5, 127.2, 124.7 (q, *J* = 275.0 Hz), 120.2 (q, *J* = 2.5 Hz), 115.6 (quin, *J* = 3.8 Hz), 69.2 (q, *J* = 1.3 Hz), 61.9, 53.5 (q, *J* = 2.5 Hz), 40.7 (q, *J* = 25.0 Hz), 37.0, 28.8, 28.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –59.6 (t, *J* = 7.5 Hz, 3 F), –62.9 (s, 6 F)

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}F_9N_2O$: 513.1588; found: 513.1583.

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Supporting Information

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