Synthesis S. Wunder et al. Paper

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

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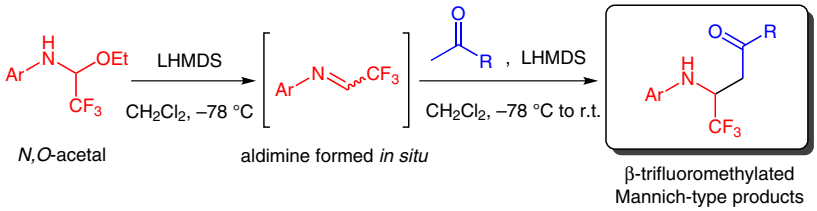
Dedicated to Professor Dr. Rolf Huisgen on the occasion of his 95th birthday



N,*O*-acetal — aldimine formed *in situ* — β-trifluoromethylated Mannich-type products

24 examples, up to 92% yield

Received: 05.11.2015
Accepted after revision: 15.12.2015
Published online: 26.01.2016
DOI: 10.1055/s-0035-1561324; Art ID: ss-2015-t0645-op

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

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

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

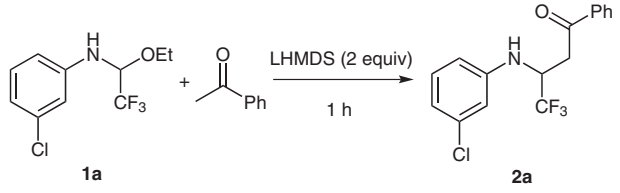
Mannich bases (β-amino ketones) are particularly useful building blocks[9] for the preparation of nitrogen containing biologically active compounds.[10] Their chemistry has been intensively studied and they can be easily converted into other multifunctional compounds (e.g., β-amino esters, γ-amino alcohols,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

thesis of β-amino-β-trifluoromethyl carbonyl compounds via Mannich-type nucleophilic addition reaction to various *N*-aryl *N*,*O*-acetals is highly desirable and presented herein.

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

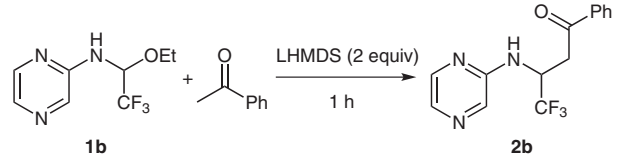
Having identified suitable conditions for the Mannich-type reaction, we briefly looked at its scope by varying the substitution pattern of the aromatic ring within the hemiaminal ether (Table 2). Thus it was found that electron-poor

Table 1 Optimization Studies



1a **2a**

Entry	Solvent	Temp (°C)	Yield (%)[a]
1	toluene	55	38
2	THF	55	26
3	CH_2Cl_2	55	46
4	MeCN	55	8
5	CH_2Cl_2	r.t.	61
6	CH_2Cl_2	0	38
7	CH_2Cl_2	–78 to r.t.	71

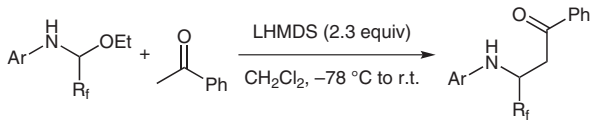


1b **2b**

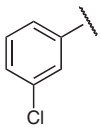
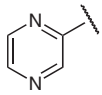
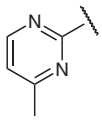
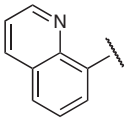
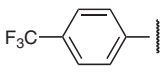
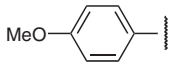
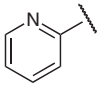
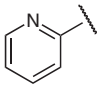
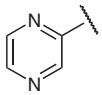
8	CH_2Cl_2	–78 to r.t.	92
9	THF	–78 to r.t.	89
10	Et_2O	–78 to r.t.	91

[a] Yield of isolated product after flash chromatography.

Table 2 Reaction of Acetophenone with Aromatic *N*,*O*-Acetals



1 **2**

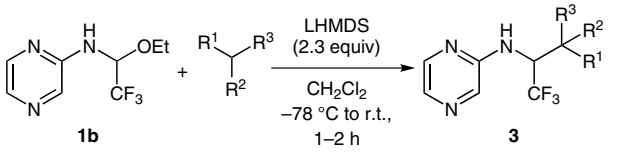
Entry	Ar	R_f	Time (h)	Yield (%)[a]	Product
1[b]		CF_3	1	71	**2a**
2		CF_3	1	92	**2b**
3		CF_3	1	72	**2c**
4		CF_3	0.3	92	**2d**
5		CF_3	1	52	**2e**
6		CF_3	2	64	**2f**
7		CF_3	1	78	**2g**
8		CF_2H	2	quant.	**2h**
9		CF_2CF_3	1	quant.	**2i**

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

N,*O*-acetals comprising pyrazine and quinoline groups are particularly well suited for this reaction and provide the target β-trifluoromethylated β-amino ketones **2b** and **2d** in high yields (Table 2, entries 2 and 4). Interestingly, the corresponding *N*,*O*-acetal featuring a (4-trifluoromethyl)phenyl substituent only afforded the desired reaction product **2e** with a moderate yield of 52% (entry 5), most presumably due to difficulties during the purification step. In contrast, difluoromethylated and pentafluoroethylated β-amino ketones are accessible in almost quantitative yields by subjecting the corresponding *N*,*O*-acetals **1h** and **1i** to the reaction conditions described above (entries 8 and 9).

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

Table 3 Reaction of Pyrazyl *N*,*O*-Acetals with Various Nucleophiles



1b **3**

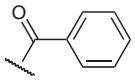
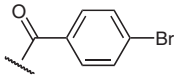
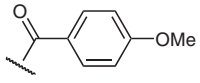
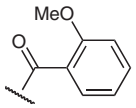
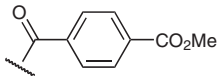
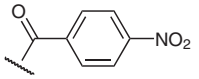
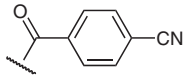
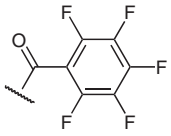
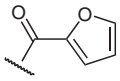
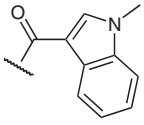
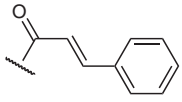
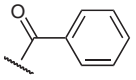
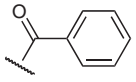
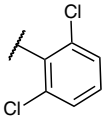
Entry	R^1	R^2	R^3	Yield (%)[a]	Product
1	H	H		92	**2b**
2	H	H		62	**3a**
3	H	H		90	**3b**

Table 3 (continued)

Entry	R^1	R^2	R^3	Yield (%)[a]	Product
4	H	H		88	**3c**
5	H	H		82	**3d**
6	H	H		75	**3e**
7	H	H		91	**3f**
8	H	H		35	**3g**
9	H	H		58	**3h**
10	H	H		67	**3i**
11	H	H		64	**3j**
12	H	Me		68	**3k**
13	Me	Me		22	**3l**
14	H	CN		60	**3m**
15	H	CO_2Et	CO_2Et	59	**3n**
16	H	H	CO_2Et	25	**3o**

[a] Yield of isolated product after flash chromatography.

In summary, we have devised an efficient one-pot procedure for the synthesis of a broad range of functionalized β-amino-β-trifluoromethyl carbonyl derivatives using readily accessible, shelf-stable *N*-aryl *N*,*O*-acetals and lithium enolates derived from ketones, esters, as well as nitriles. The reaction is easy to perform and allows rapid formation

of novel trifluoromethylated Mannich-type products, which are useful potential building blocks for pharmaceutical and biological applications. Moreover, the reaction protocol can be successfully applied to the synthesis of functionalized β-difluoromethylated and β-pentafluoroethylated Mannich-type products.

All reactions were carried out under an argon atmosphere using dried glassware. Commercially available reagents and solvents were used without further purification. Dry CH_2Cl_2 (SeccoSolv®) was purchased from Merck KGaA. *N*,*O*-Acetal substrates were synthesized according to standard procedures from 1-ethoxy-2,2,2-trifluoroethanol and the corresponding amines using PTSA in EtOH.[17] Purification was performed by flash chromatography and *N*,*O*-acetal substrates were dried under reduced pressure prior to use. Reactions were monitored by TLC with precoated silica gel 60 F254 aluminum plates (Merck KGaA) using UV light as the visualizing agent. The crude β-amino-β-trifluoromethyl carbonyl compounds were purified by MPLC with a CombiFlash Rf Teledyne ISCO or by standard flash chromatography using silica gel (35–70 µm) from Acros Organics. Analytical RP-HPLC was measured on a JASCO system with a Phenomenex Luna C18 column (5 µm, 250 × 4.6 mm). HR-EI mass spectra were recorded on a Finnigan MAT95Q or on a Finnigan MAT90. HR-ESI mass spectra were recorded on a Thermo Finnigan LTQ FT or on a Bruker maXis equipped with a Waters Acquity UPLC using a Kinetex C18 column (2.6 µ, 100 A) at 40 °C and HPLC-MS was performed on Agilent 1100 and Agilent 1200 systems using Chromolith Speed ROD RP-18e columns. In all cases, mixtures of H_2O (eluent A) and MeCN (eluent B) were used as solvents; if required, 0.05% formic acid or 0.1% TFA was added. ^1H, ^{13}C, and ^{19}F spectra were recorded on a Varian 400 MHz, 600 MHz and 800 MHz spectrometer or on a Bruker Avance II 300 MHz, 400 MHz, and 500 MHz spectrometer in DMSO-d_6 or $CDCl_3$. The chemical shifts are reported in ppm relative to the signal of the deuterated solvent. Standard abbreviations were used to denote the signal multiplicities. Melting points were measured on a Melting Point B-540 Büchi apparatus.

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

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

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

According to the general procedure, 3-chloro-*N*-(1-ethoxy-2,2,2-trifluoroethyl)aniline (**1a**; 150 mg, 0.59 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.18 mL, 1.18 mmol), and reacted with acetophenone (0.10 mL, 0.89 mmol). After stirring at r.t. (2 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 9:1), and recrystallization (^{c}hex), the β-amino ketone **2a** (138 mg, 0.42 mmol, 71%) was obtained as a colorless crystalline solid; mp 98 °C; R_f = 0.61 (^{c}hex/EtOAc, 2:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 8.07–7.93 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.73–7.62 [m, 1 H, $H4_{ph}$], 7.55 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 7.11 [t, *J*(H5,H4/H6) = 8.1 Hz, 1 H, H5], 6.77 [br s, 1 H, H2], 6.65 [m, 2 H, H4, H6], 6.30 [d, *J*(NH,CH) = 8.4 Hz, 1 H, NH], 4.87–4.76 [m, 1 H, CH], 3.62 [dd, *J*(CH_2,CH_2) = 17.8 Hz, *J*(CH_2,CH) = 10.0 Hz, 1 H, CH_2], 3.44 [dd, *J*(CH_2,CH_2) = 17.8 Hz, *J*(CH_2,CH) = 2.5 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.97 [C=O], 148.96 [C1], 136.13 [$C1_{ph}$], 133.55 [C3], 133.52 [$C4_{ph}$] 130.34 [C5], 128.73 [$C3_{ph}$, $C5_{ph}$], 128.09 [$C2_{ph}$, $C6_{ph}$], 126.58 [q, ^1J(C,F) = 283.8 Hz, CF_3], 116.47 [C4], 111.93 [C2], 111.35 [C6], 50.16 [q, ^2J(C,F) = 29.7 Hz, CH], 37.54 [CH_2].

^{19}F NMR (376 MHz, DMSO-d_6): δ = −74.25 [d, *J*(CF_3,CH) = 7.4 Hz, CF_3].

HR-EI-MS: *m*/*z* calcd for $C_{16}H_{13}ClF_3NO^+$ $[M]^+$: 327.0638; found: 327.0641.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.98 min, λ = 220 nm.

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

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (**1b**; 100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with acetophenone (0.08 mL, 0.68 mmol). After stirring at r.t. (1 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), and recrystallization (^{c}hex), the β-amino ketone **2b** (123 mg, 0.42 mmol, 92%) was obtained as a colorless crystalline solid; mp 128 °C; R_f = 0.20 (^{c}hex/EtOAc, 2:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 8.04 [dd, *J*(H6,H5) = 2.8 Hz, *J*(H6,H3) = 1.5 Hz, 1 H, H6], 8.01–7.94 [m, 3 H, H3, $H2_{ph}$, $H6_{ph}$], 7.82 [d, *J*(H5,H6) = 2.8 Hz, 1 H, H5], 7.70–7.63 [m, 1 H, $H4_{ph}$], 7.58–7.51 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 7.48 [d, *J*(NH,CH) = 8.2 Hz, 1 H, NH], 5.50–5.38 [m, 1 H, CH], 3.65 [dd, *J*(CH_2,CH_2) = 17.8 Hz, *J*(CH_2,CH) = 9.8 Hz, 1 H, CH_2], 3.52 [dd, *J*(CH_2,CH_2) = 17.8 Hz, *J*(CH_2,CH) = 3.3 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 195.03 [C=O], 153.90 [C2], 141.26 [C6], 136.08 [$C1_{ph}$], 133.55 [C5], 133.02 [$C4_{ph}$], 132.91 [C3], 128.74 [$C3_{ph}$, $C5_{ph}$], 128.07 [$C2_{ph}$, $C6_{ph}$], 126.22 [q, ^1J(C,F) = 282.8 Hz, CF_3] 47.17 [q, ^2J(C,F) = 30.5 Hz, CH], 37.12 [CH_2].

^{19}F NMR (376 MHz, DMSO-d_6): δ = −74.37 [d, *J*(CF_3,CH) = 7.9 Hz, CF_3].

HR-EI-MS: *m*/*z* calcd for $C_{14}H_{12}F_3N_3O^+$ $[M]^+$: 295.0932; found: 295.0931.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.59 min, λ = 220 nm.

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

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-methylpyrimidin-2-amine (**1c**; 100 mg, 0.43 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 0.98 mL, 0.98 mmol), and reacted with acetophenone (0.08 mL, 0.64 mmol). After stirring at r.t. (2 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), and recrystallization (^{c}hex), the β-amino ketone **2c** (97 mg, 0.31 mmol, 72%) was obtained as a colorless crystalline solid; mp 109 °C; R_f = 0.35 (^{c}hex/EtOAc, 2:1).

^1H NMR (400 MHz, DMSO-d_6): δ = 8.19 [br s, 1 H, H6], 8.00–7.91 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.65 [tt, *J*($H4_{ph}$,$H3_{ph}$/$H5_{ph}$) = 7.4 Hz, *J*($H4_{ph}$,$H2_{ph}$/$H6_{ph}$) = 1.1 Hz, 1 H, $H4_{ph}$], 7.53 [m, 3 H, NH, $H3_{ph}$, $H5_{ph}$],

6.60 [d, J(H5,H6) = 5.0 Hz, 1 H, H5], 5.54–5.39 [m, 1 H], 3.74 [dd, J(CH_2,CH_2) = 17.7 Hz, J(CH_2,CH) = 10.3 Hz, 1 H, CH_2], 3.39 [dd, J(CH_2,CH_2) = 17.6 Hz, J(CH_2,CH) = 2.9 Hz, 1 H, CH_2], 2.25 [s, 3 H, CH_3].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 195.89 [C=O], 167.89 [C4], 162.05 [C2], 157.85 [C6], 136.70 [$C1_{ph}$], 134.02 [$C4_{ph}$], 129.24 [$C2_{ph}$, $C6_{ph}$], 128.19 [$C3_{ph}$, $C5_{ph}$], 126.78 [q, ^1J(C,F) = 283.1 Hz, CF_3], 111.53 [C5], 48.51 [q, ^2J(C,F) = 30.2 Hz, CH], 37.21 [CH_2], 24.00 [CH_3].

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.48 [br s, CF_3].

HRMS (ESI+): m/z calcd for $C_{15}H_{15}F_3N_3O^+$ [M + H]$^+$: 310.1162; found: 310.1162.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 13.93 min, λ = 214 nm.

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

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)quinolin-8-amine (**1d**; 100 mg, 0.37 mmol) was dissolved in dry CH_2Cl_2 (5 mL), treated with LHMDS (1.0 M solution in toluene, 0.85 mL, 0.85 mmol), and reacted with acetophenone (0.65 mL, 0.56 mmol). After stirring at r.t. (20 min), aqueous workup, and flash chromatography (^{c}hex → ^{c}hex/EtOAc, 9:1), the β-amino ketone **2d** (117 mg, 0.34 mmol, 92%) was obtained as a light yellow oil; R_f = 0.50 (^{c}hex/EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.68 [dd, J(H2,H3) = 4.2 Hz, J(H2,H4) = 1.7 Hz, 1 H, H2], 8.06 [dd, J(H4,H3) = 8.2 Hz, J(H4,H2) = 1.7 Hz, 1 H, H4], 7.99–7.93 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.62–7.54 [m, 1 H, $H4_{ph}$], 7.51–7.40 [m, 3 H, H6, $H3_{ph}$, $H5_{ph}$], 7.36 [dd, J(H3,H4) = 8.2 Hz, J(H3,H2) = 4.2 Hz, 1 H, H3], 7.16 [dd, J(H5,H6) = 8.2 Hz, J(H5,H7) = 1.1 Hz, 1 H, H5], 7.07 [d, J(H7,H6) = 7.6 Hz, 1 H, H7], 6.44 [d, J(NH,CH) = 9.9 Hz, 1 H, NH], 5.10 [dtd, J(CH,NH) = 9.9 Hz, J(CH,CF_3) = 7.2 Hz, J(CH,CH_2) = 4.7 Hz, 1 H, CH], 3.63–3.49 [m, 2 H, CH_2].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.05 [C=O], 147.32 [C2], 142.75 [C4a], 138.16 [C8a], 136.42 [$C1_{ph}$], 136.20 [C4], 133.82 [$C4_{ph}$], 128.91 [$C3_{ph}$, $C5_{ph}$], 128.73 [C8], 128.34 [$C2_{ph}$, $C6_{ph}$], 127.71 [C6], 126.40 [q, ^1J(C,F) = 283.3 Hz, CF_3], 121.61 [C3], 116.12 [C5], 106.54 [C7], 51.40 [q, ^2J(C,F) = 30.5 Hz, CCF_3], 39.06 [CH_2].

^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.63 [d, J(CF_3,CH) = 7.1 Hz, CF_3].

HRMS (ESI+): m/z calcd for $C_{19}H_{16}F_3N_2O^+$ [M + H]$^+$: 345.1209; found: 345.1210.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 18.93 min, λ = 214 nm.

4,4,4-Trifluoro-1-phenyl-3-{[4-(trifluoromethyl)phenyl]amino}butan-1-one (2e)

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-(trifluoromethyl)aniline (**1e**; 50 mg, 0.17 mmol) was dissolved in dry CH_2Cl_2 (5 mL), treated with LHMDS (1.0 M solution in toluene, 0.40 mL, 0.40 mmol), and reacted with acetophenone (0.03 mL, 0.26 mmol). After stirring at r.t. (1 h), aqueous workup and flash chromatography (^{c}hex → ^{c}hex/EtOAc, 5:1), the β-amino ketone **2e** (33 mg, 0.09 mmol, 52%) was obtained as a light brown solid; mp 127 °C; R_f = 0.46 (^{c}hex/EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.92 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.65–7.59 [m, 1 H, $H4_{ph}$], 7.50 [dd, J = 8.3 Hz, J = 7.1 Hz, 2 H, $H3_{ph}$, $H5_{ph}$], 7.44 [d, J(H3,H2) = J(H5,H6) = 8.5 Hz, 2 H, H3, H5], 6.79 [d, J(H2,H3) = J(H6,H5) = 8.4 Hz, 2 H, H2, H6], 4.87 [dtd, J(CH,NH) = 9.6 Hz, J(CH,CF_3) = 7.2 Hz, J(CH,CH_2) = 4.3 Hz, 1 H, CH], 4.14 [d, J(NH,CH) = 9.9 Hz, 1 H, NH], 3.45–3.37 [m, 2 H, CH_2].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 194.90 [C=O], 148.67 [C1], 136.16 [$C1_{ph}$], 134.14 [$C4_{ph}$], 129.05 [$C3_{ph}$, $C5_{ph}$], 128.31 [$C2_{ph}$, $C6_{ph}$], 126.92 [q, ^3J(C,F) = 3.8 Hz, C3, C5], 125.97 [q, ^1J(C,F) = 283.2 Hz, CF_3], 124.77 [d, ^1J(C,F) = 270.6 Hz, CF_3], 121.15 [q, ^2J(C,F) = 32.8 Hz, C4], 113.19 [C2, C6], 51.80 [q, ^2J(C,F) = 30.7 Hz, CCF_3], 38.34 [CH_2].

^{19}F NMR (376 MHz, $CDCl_3$): δ = –61.40 [CF_3], –75.66 [d, J(CF_3,CH) = 7.1 Hz, CF_3].

HRMS (ESI–): m/z calcd for $C_{17}H_{12}F_6NO^-$ [M – H]$^-$: 360.0828; found: 360.0835.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 19.85 min, λ = 214 nm.

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

Following the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)-4-methoxyaniline (**1f**; 170 mg, 0.68 mmol) was dissolved in dry CH_2Cl_2 (10 mL), treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol), and reacted with acetophenone (0.12 mL, 1.02 mmol). After stirring at r.t. (2 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), and recrystallization (^{c}hex) the β-amino ketone **2f** (140 mg, 0.43 mmol, 64%) was obtained as a colorless crystalline solid; mp 90 °C; R_f = 0.53 (^{c}hex/EtOAc, 4:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.95 [m, 1 H, $H2_{ph}$/$H6_{ph}$], 7.94 [m, 1 H, $H2_{ph}$/$H6_{ph}$], 7.60 [m, 1 H, $H4_{ph}$], 7.51–7.46 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 6.80–6.76 [m, 2 H, H2, H6], 6.76–6.72 [m, 2 H, H3, H5], 4.69 [m, 1 H, CH], 3.74 [s, 3 H, OCH_3], 3.40–3.29 [m, 2 H, CH_2].

^{13}C NMR (151 MHz, $CDCl_3$): δ = 195.53 [C=O], 153.58 [C4], 139.93 [C1], 136.48 [$C1_{ph}$], 133.85 [$C4_{ph}$], 129.94 [$C2_{ph}$, $C6_{ph}$], 128.29 [$C3_{ph}$, $C5_{ph}$], 126.34 [q, ^1J(C,F) = 283.5 Hz, CF_3], 116.13 [$C3_{ph}$, $C5_{ph}$], 114.98 [$C2_{ph}$, $C1_{ph}$], 55.79 [OCH_3], 53.97 [q, ^2J(C,F) = 29.5 Hz, CCF_3], 38.47 [CH_2].

^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.48 [CF_3].

HRMS (ESI+): m/z calcd for $C_{17}H_{17}F_3NO_2^+$ [M + H]$^+$: 324.1206; found: 324.1210.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 18.43 min, λ = 214 nm.

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

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyridin-2-amine (**1g**; 100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with acetophenone (0.08 mL, 0.68 mmol). After stirring at r.t. (1 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), and recrystallization (^{c}hex), the β-amino ketone **2g** (104 mg, 0.35 mmol, 78%) was obtained as a colorless crystalline solid; mp 124 °C; R_f = 0.46 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 [dd, J(H6,H5) = 5.0 Hz, J(H6,H4) = 1.2 Hz, 1 H, H6], 8.00–7.95 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.69–7.63 [m, 1 H, $H4_{ph}$], 7.56–7.51 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 7.41 [ddd, J(H4,H3) = 8.8 Hz, J(H4,H5) = 7.1 Hz, J(H4,H6) = 1.9 Hz, 1 H, H4], 6.94 [d, J(NH,CH) = 8.4 Hz, 1 H, NH], 6.59 [ddd, J(H5,H4) = 7.0 Hz, J(H5,H6) = 5.1 Hz, J(H5,H3) = 0.8 Hz, 1 H, H5], 6.51 [d, J(H3,H4) = 8.4 Hz, 1 H, H3], 5.60–5.44 [m, 1 H, CH], 3.60 [dd, J(CH_2,CH_2) = 17.5 Hz, J(CH_2,CH) = 9.6 Hz, 1 H, CH_2], 3.43 [dd, J(CH_2,CH_2) = 17.5 Hz, J(CH_2,CH) = 3.5 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 195.50 [C=O], 157.47 [C1], 147.33 [C6], 137.18 [C4], 136.34 [$C1_{ph}$], 133.67 [$C4_{ph}$], 128.92 [$C3_{ph}$, $C5_{ph}$], 128.21 [$C2_{ph}$, $C6_{ph}$], 126.59 [q, ^1J(C,F) = 283.8 Hz, CF_3], 113.32 [C5], 108.74 [C3], 47.56 [q, ^2J(C,F) = 30.0 Hz, CH], 37.55 [CH_2].

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.34 [d, J(CF_3,CH) = 8.0 Hz, CF_3].

HR-EI-MS: m/z calcd for $C_{15}H_{13}F_3N_2O^+$ [M]$^+$: 294.0980; found: 294.0977.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.25 min, δ = 220 nm.

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

According to the general procedure, *N*-(1-ethoxy-2,2-difluoroethyl)pyridin-2-amine (**1h**; 100 mg, 0.49 mmol) was dissolved in dry CH_2Cl_2 (5 mL), treated with LHMDS (1.0 M solution in toluene, 1.13 mL, 1.13 mmol), and reacted with acetophenone (0.09 mL, 0.74 mmol). After stirring at r.t. (2 h), aqueous workup, and flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), the β-amino ketone **2h** (136 mg, 0.49 mmol, quant.) was obtained as a light brown solid; mp 115 °C; R_f = 0.24 (^{c}hex/EtOAc, 3:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 [ddd, J(H6,H5) = 5.1 Hz, J(H6,H4) = 1.9 Hz, J(H6,H3) = 0.9 Hz, 1 H, H6], 8.00–7.92 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.65–7.54 [m, 1 H, $H4_{ph}$], 7.53–7.44 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 7.40 [ddd, J(H4,H3) = 8.4 Hz, J(H4,H5) = 7.1 Hz, J(H4,H6) = 1.9 Hz, 1 H, H4], 6.62 [ddd, J(H5,H4) = 7.1 Hz, J(H5,H6) = 5.1 Hz, J(H5,H3) = 0.9 Hz, 1 H, H5], 6.48 [dt, J(H3,H4) = 8.3 Hz, J(H3,H5) = 0.9 Hz, 1 H, H3], 6.20 [td, J(CHF_2,CHF_2) = 56.7 Hz, J(CHF_2,CH) = 3.1 Hz, 1 H, CHF_2], 5.08–4.91 [m, 1 H, CH], 4.89 [d, J(NH,CH) = 9.0 Hz, 1 H, NH], 3.46–3.38 [m, 2 H, CH_2].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.85 [C=O], 157.16 [C2], 147.97 [C6], 137.61 [C4], 136.58 [$C1_{ph}$], 133.76 [$C4_{ph}$], 128.89 [$C3_{ph}$, $C5_{ph}$], 128.34 [$C2_{ph}$, $C6_{ph}$], 115.45 [t, ^1J(CHF_2,CHF_2) = 244.9 Hz, CHF_2], 113.02 [C5], 108.87 [C3], 49.94 [dd, ^2J(CH,CHF_2) = 24.5 Hz, ^2J(CH,CHF_2) = 22.8 Hz, CH], 36.73 [CH_2].

^{19}F NMR (376 MHz, $CDCl_3$): δ = –125.78 [ddd, J(CHF_2,CHF_2) = 281.1 Hz, J(CHF_2,CHF_2) = 56.4 Hz, J(CHF_2,CH) = 10.4 Hz, CHF_2], –128.96 [ddd, J(CHF_2,CHF_2) = 281.1 Hz, J(CHF_2,CHF_2) = 56.9 Hz, J(CHF_2,CH) = 16.0 Hz, CHF_2].

HRMS (ESI+): m/z calcd for $C_{15}H_{15}F_2N_2O^+$ [M + H]$^+$: 277.1147; found: 277.1146.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 10.23 min, λ = 214 nm.

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

Following the general procedure, *N*-(1-ethoxy-2,2,3,3,3-pentafluoropropyl)pyrazin-2-amine (**1i**; 100 mg, 0.37 mmol) was dissolved in dry CH_2Cl_2 (5 mL), treated with LHMDS (1.0 M solution in toluene, 0.85 mL, 0.85 mmol), and reacted with acetophenone (0.07 mL, 0.55 mmol). After stirring at r.t. (1 h), aqueous workup, and flash chromatography (^{c}hex → ^{c}hex/EtOAc, 2:1), the β-amino ketone **2i** (130 mg, 0.37 mmol, quant.) was obtained as a light yellow solid; mp 105 °C; R_f = 0.23 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 [dd, J(H6,H5) = 2.8 Hz, J(H6,H3) = 1.5 Hz, 1 H, H6], 7.99 [d, J(H3,H6) = 1.5 Hz, 1 H, H3], 7.95–7.91 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.90 [m, 1 H, H5], 7.60 [m, 1 H, $H4_{ph}$], 7.48 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 5.73 [m, 1 H, CH], 5.06 [d, J(NH,CH) = 10.0 Hz, 1 H, NH], 3.51–3.46 [m, 2 H, CH_2].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 195.68 [C=O], 152.61 [C2], 141.68 [C6], 136.31 [$C1_{ph}$], 134.84 [C5], 134.01 [$C4_{ph}$], 132.96 [C3], 129.01 [$C3_{ph}$, $C5_{ph}$], 128.27 [$C2_{ph}$, $C6_{ph}$], 46.94 [dd, ^2J(CH,CF_2) = 27.1 Hz, ^2J(CH,CF_2) = 21.4 Hz, CH], 37.07 [CH_2].

^{19}F NMR (376 MHz, $CDCl_3$): δ = –81.84 [CF_3], –118.54 [dd, J(CF_2,CF_2) = 273.6 Hz, J(CF_2,CF_3) = 7.3 Hz, CF_2], –124.82 [dd, J(CF_2,CF_2) = 273.6 Hz, J(CF_2,CF_3) = 19.8 Hz, CF_2].

HRMS (ESI+): m/z calcd for $C_{15}H_{13}F_5N_3O^+$ [M + H]$^+$: 346.0973; found: 346.0973.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 16.28 min, λ = 214 nm.

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

According to the general procedure, *N*-(1-ethoxy-2,2,2-trifluoroethyl)pyrazin-2-amine (**1b**; 150 mg, 0.68 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol), and reacted with 4-bromoacetophenone (203 mg, 1.02 mmol). After stirring at 40 °C (2 h), aqueous workup, flash chromatography (^{c}hex/EtOAc, 3:1 → 2:1), and recrystallization (^{c}hex/EtOAc, 9:1), the β-amino ketone **3a** (157 mg, 0.42 mmol, 62%) was obtained as a colorless crystalline solid; mp 112 °C; R_f = 0.24 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.04 [dd, J(H6,H5) = 2.7 Hz, J(H6,H3) = 1.4 Hz, 1 H, H6], 7.96 [d, J(H3,H6) = 1.4 Hz, 1 H, H3], 7.94–7.89 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.82 [d, J(H5,H6) = 2.7 Hz, 1 H, H5], 7.78–7.73 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 7.46 [d, J(NH,CH) = 8.2 Hz, 1 H, NH], 5.48–5.35 [m, 1 H, CH], 3.62 [dd, J(CH_2,CH_2) = 17.8 Hz, J(CH_2,CH) = 9.8 Hz, 1 H, CH_2], 3.52 [dd, J(CH_2,CH_2) = 17.8 Hz, J(CH_2,CH) = 3.3 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.57 [C=O], 154.01 [C2], 141.46 [C6], 135.19 [C1], 133.13 [C3], 133.09 [C5], 131.98 [$C3_{ph}$, $C5_{ph}$], 130.26 [$C2_{ph}$, $C6_{ph}$], 127.87 [CBr], 126.29 [q, ^1J(C,F) = 282.8 Hz, CF_3], 47.26 [q, ^2J(C,F) = 30.3 Hz, CH], 37.28 [CH_2].

^{19}F NMR (471 MHz, DMSO-d_6): δ = –74.37 [d, J(CF_3,CH) = 7.6 Hz, CF_3].

HRMS (ESI+): m/z calcd for $C_{14}H_{12}BrF_3N_3O^+$ [M + H]$^+$: 374.0110; found: 374.0112.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.74 min, λ = 220 nm.

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

According to the general procedure, **1b** (150 mg, 0.68 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol), and reacted with 4-methoxyacetophenone (153 mg, 1.02 mmol). After stirring at r.t. (2 h), aqueous workup, flash chromatography (^{c}hex/EtOAc, 3:1 → 2:1), and recrystallization (^{c}hex/EtOAc, 9:1), the β-amino ketone **3b** (199 mg, 0.61 mmol, 90%) was obtained as a colorless crystalline solid; mp 135 °C; R_f = 0.11 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.03 [dd, J(H6,H5) = 2.6 Hz, J(H6,H3) = 1.4 Hz, 1 H, H6], 7.99–7.93 [m, 3 H, H3, $H2_{ph}$, $H6_{ph}$], 7.81 [d, J(H5,H6) = 2.8 Hz, 1 H, H5], 7.47 [d, J(NH,CH) = 8.3 Hz, 1 H, NH], 7.05 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 5.52–5.34 [m, 1 H, CH], 3.85 [s, 3 H, OCH_3], 3.57 [dd, J(CH_2,CH_2) = 17.5 Hz, J(CH_2,CH) = 9.9 Hz, 1 H, CH_2], 3.42 [dd, J(CH_2,CH_2) = 17.5 Hz, J(CH_2,CH) = 3.2 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 193.51 [C=O], 163.59 [$COCH_3$], 154.04 [C2], 141.47 [C6], 133.10 [C3], 133.01 [C5], 130.64 [$C2_{ph}$, $C6_{ph}$], 129.17 [$C1_{ph}$], 126.40 [q, ^1J(C,F) = 283.0 Hz, CF_3], 114.11 [$C3_{ph}$, $C5_{ph}$], 55.73 [OCH_3], 47.36 [q, ^2J(C,F) = 30.3 Hz, CH], 36.84 [CH_2].

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.34 [d, J(CF_3,CH) = 7.8 Hz, CF_3].

HR-EI-MS: m/z calcd for $C_{15}H_{14}F_3N_3O_2^+$ [M]$^+$: 325.1038; found: 325.1043.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.60 min, λ = 220 nm.

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

According to the general procedure, **1b** (150 mg, 0.68 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol), and reacted with 2-methoxyacetophenone (0.14 mL, 1.02 mmol). After stirring at r.t. (2 h), aqueous workup, flash chromatography (^{c}hex/EtOAc, 3:1 → 2:1), and recrystallization (^{c}hex/EtOAc, 9:1), the β-amino ketone **3c** (194 mg, 0.59 mmol, 88%) was obtained as a colorless crystalline solid; mp 134 °C; R_f = 0.14 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.97 [dd, J(H6,H5) = 2.7 Hz, J(H6,H3) = 1.5 Hz, 1 H, H6], 7.95 [d, J(H3,H6) = 1.5 Hz, 1 H, H3], 7.79 [d, J(H5,H6) = 2.8 Hz, 1 H, H5], 7.60–7.49 [m, 3 H, $H2_{ph}$, $H4_{ph}$, $H5_{ph}$], 7.20 [d, J(NH,CH) = 8.2 Hz, 1 H, NH], 7.03–6.97 [m, 1 H, $H3_{ph}$], 5.47–5.37 [m, 1 H, CH], 3.91 [s, 3 H, OCH_3], 3.46 [dd, J(CH_2,CH_2) = 17.4 Hz, J(CH_2,CH) = 4.2 Hz, 1 H, CH_2], 3.40 [dd, J(CH_2,CH_2) = 17.4 Hz, J(CH_2,CH) = 9.2 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 196.16 [C=O], 158.68 [$COCH_3$], 153.95 [C2], 141.39 [C6], 134.64 [$C4_{ph}$], 133.16 [C3], 132.95 [C5], 129.99 [$C2_{ph}$], 126.51 [$C1_{ph}$], 126.30 [q, ^1J(C,F) = 282.9 Hz, CF_3] 120.71 [$C3_{ph}$], 112.68 [$C5_{ph}$], 55.97 [OCH_3], 47.31 [q, ^2J(C,F) = 30.1 Hz, CH], 42.49 [CH_2].

^{19}F NMR (471 MHz, DMSO-d_6): δ = –74.52 [d, J(CF_3,CH) = 7.7 Hz, CF_3].

HR-EI-MS: m/z calcd for $C_{15}H_{14}F_3N_3O_2^+$ $[M]^+$: 325.1038; found: 325.1044.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.62 min, λ = 220 nm.

Methyl 4-[4,4,4-Trifluoro-3-(pyrazin-2-ylamino)butanoyl]benzoate (3d)

According to the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with methyl 4-acetylbenzoate (120 mg, 0.68 mmol). After stirring at r.t. (2.5 h), aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), and recrystallization (^{c}hex), the desired β-amino ketone **3d** (130 mg, 0.37 mmol, 82%) was obtained as a colorless crystalline solid; mp 121 °C; R_f = 0.17 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10 [d, J($H2_{ph}$,$H3_{ph}$) = J($H5_{ph}$,$H6_{ph}$) = 2.1 Hz, 4 H, $H2_{ph}$, $H3_{ph}$, $H5_{ph}$, $H6_{ph}$], 8.04 [dd, J(H6,H5) = 2.8 Hz, J(H6,H3) = 1.5 Hz, 1 H, H6], 7.96 [d, J(H3,H6) = 1.5 Hz, 1 H, H3], 7.82 [d, J(H5,H6) = 2.8 Hz, 1 H, H5], 7.46 [d, J(NH,CH) = 8.2 Hz, 1 H, NH], 5.49–5.36 [m, 1 H, CH], 3.69 [dd, J(CH_2,CH_2) = 17.9 Hz, J(CH_2,CH) = 9.7 Hz, 1 H, CH_2], 3.59 [dd, J(CH_2,CH_2) = 17.5 Hz, J(CH_2,CH) = 3.1 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.84 [C=O], 165.46 [CO_2Me], 153.85 [C2], 141.22 [C6], 139.39 [$C1_{ph}$], 133.47 [C5], 133.00 [$C4_{ph}$], 132.96 [C3], 129.42 [$C3_{ph}$, $C5_{ph}$], 128.38 [$C2_{ph}$, $C6_{ph}$], 52.47 [CH_3], 47.12 [q, ^2J(C,F) = 30.5 Hz, CH], 37.50 [CH_2]. Due to low intensity, the signal for CF_3 could not be observed.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.38 [d, J(CF_3,CH) = 8.0 Hz, CF_3].

HRMS (ESI+): m/z calcd for $C_{16}H_{15}F_3N_3O_3^+$ $[M + H]^+$: 354.1060; found: 354.1061.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.62 min, λ = 220 nm.

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

According to the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with 4′-nitroacetophenone (111 mg, 0.68 mmol). After stirring at r.t. (1 h) followed by stirring at 40 °C (2 h), TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to –78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at –78 °C for 10 min, 4′-nitroacetophenone (75 mg, 0.45 mmol) was added, and the reaction mixture was stirred at 40 °C (20 h). Subsequent aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), and recrystallization (^{c}hex/EtOAc, 9:1) furnished the β-amino ketone **3e** (115 mg, 0.34 mmol, 75%) as a yellow crystalline solid; mp 163 °C; R_f = 0.14 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.41–8.30 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 8.26–8.18 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 8.04 [dd, J(H6,H5) = 2.8 Hz, J(H6,H3) = 1.5 Hz, 1 H, H6], 7.96 [d, J(H3,H6) = 1.5 Hz, 1 H, H3], 7.83 [d, J(H5,H6) = 2.8 Hz, 1 H, H5], 7.47 [d, J(NH,CH) = 8.1 Hz, 1 H, NH], 5.52 – 5.33 [m, 1 H, CH], 3.77–3.60 [m, 2 H, 2 × CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.63 [C=O], 154.01 [C2], 150.24 [CNO_2], 141.46 [C6], 140.72 [C3], 133.17 [C5], 129.70 [$C2_{ph}$, $C6_{ph}$], 126.23 [q, ^1J(C,F) = 282.8 Hz, CF_3] 123.98 [$C3_{ph}$, $C5_{ph}$], 47.25 [q, ^2J(C,F) = 30.5 Hz, CH], 37.90 [CH_2].

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.47 [d, J(CF_3,CH) = 7.8 Hz, CF_3].

HRMS (ESI+): m/z calcd for $C_{14}H_{12}F_3N_4O_3^+$ $[M + H]^+$: 341.0856; found: 341.0859.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.62 min, λ = 220 nm.

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

According to the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with 4′-cyanoacetophenone (99 mg, 0.68 mmol). After stirring at r.t. (1 h) followed by stirring at 40 °C (1 h) TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to –78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at –78 °C (10 min), 4′-cyanoacetophenone (65 mg, 0.45 mmol) was added and the reaction mixture was stirred at 40 °C (1 h). Subsequent aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), and recrystallization (^{c}hex) furnished the β-amino ketone **3f** (131 mg, 0.41 mmol, 91%) as a colorless crystalline solid; mp 185 °C; R_f = 0.37 (^{c}hex/EtOAc, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.18–8.09 [m, 2 H, $H3_{ph}$, $H5_{ph}$], 8.05–8.02 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 8.01 [m, 1 H, H6], 7.96 [d, J(H3,H6) = 1.4 Hz, 1 H, H3], 7.82 [d, J(H5,H6) = 2.8 Hz, 1 H, H5], 7.46 [d, J(NH,CH) = 8.1 Hz, 1 H, NH], 5.53–5.28 [m, 1 H, CH], 3.68 [dd, J(CH_2,CH_2) = 18.1 Hz, J(CH_2,CH) = 9.3 Hz, 1 H, CH_2], 3.61 [dd, J(CH_2,CH_2) = 18.0 Hz, J(CH_2,CH) = 3.9 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 194.84 [C=O], 154.01 [C2], 141.45 [C6], 139.30 [$C1_{ph}$], 133.16 [C3], 133.15 [C5], 132.94 [$C2_{ph}$, $C6_{ph}$], 128.88 [$C3_{ph}$, $C5_{ph}$], 126.24 [q, ^1J(C,F) = 282.7 Hz, CF_3], 118.22 [C≡N], 115.61 [CCN], 47.24 [q, ^2J(C,F) = 30.5 Hz, CH], 37.69 [CH_2].

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.37 [d, J(CF_3,CH) = 7.9 Hz, CF_3].

HRMS (ESI+): m/z calcd for $C_{15}H_{12}F_3N_4O^+$ $[M + H]^+$: 321.0958; found: 321.0959.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.56 min, λ = 220 nm.

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

According to the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with 2′,3′,4′,5′,6′-pentafluoroacetophenone (0.10 mL, 0.68 mmol). After stirring at r.t. (1 h) followed by stirring at 40 °C (2 h), TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to −78 °C before LHMDS (1.0 M solution in toluene, 0.45 mL, 0.45 mmol) was added. Stirring was continued at −78 °C (10 min), 2′,3′,4′,5′,6′-pentafluoroacetophenone (0.07 mL, 0.45 mmol) was added and the reaction mixture was stirred at 40 °C (20 h). Subsequent aqueous workup, flash chromatography (^{c}hex → ^{c}hex/EtOAc, 4:1), and recrystallization (^{c}hex/EtOAc, 9:1) furnished the β-amino ketone **3g** (61 mg, 0.16 mmol, 35%) as a light yellow solid; mp 115 °C; R_f = 0.30 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03–7.97 [m, 2 H, H6, H3], 7.84 [d, J(H5,H6) = 2.3 Hz, 1 H, H5], 7.70 [d, J(NH,CH) = 8.8 Hz, 1 H, NH], 5.51–5.37 [m, 1 H, CH], 3.55 [dd, J(CH_2,CH_2) = 17.7 Hz, J(CH_2,CH) = 4.0 Hz, 1 H, CH_2], 3.40 [dd, J(CH_2,CH_2) = 17.7 Hz, J(CH_2,CH) = 9.7 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 189.83 [C=O], 153.88 [C2], 146.07–145.78 [m, CF], 144.42–144.10 [m, CF], 143.55–143.31 [m, CF], 141.56 [C6], 139.00–138.65 [m, CF], 136.52–136.16 [m, C–F], 133.64 [C5], 133.49 [C3], 126.01 [q, ^1J(C,F) = 283.0 Hz, CF_3], 113.99–113.63 [m, CF], 47.15 [q, ^2J(C,F) = 30.8 Hz, CH], 43.49 [CH_2].

^{19}F NMR (376 MHz, DMSO-d_6): δ = −74.68 [d, J(CF_3,CH) = 7.8 Hz, CF_3], −140.87 to −141.17 [m, F2, F6], −149.30 [tt, J(F4,F3) = J(F4,F5) = 22.2 Hz, J(F4,F2) = J(F4,F6) = 4.4 Hz, F4], −160.93 to −161.21 [m, F3, F5].

HRMS (ESI+): m/z calcd for $C_{14}H_8F_8N_3O^+$ [M + H]$^+$: 386.0534; found: 386.0534.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.74 min, λ = 220 nm.

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

According to the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMSD (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with 2-acetylfuran (75 mg, 0.68 mmol). After stirring at r.t. (2 h), aqueous workup, and column chromatography (^{c}hex/EtOAc, 1.5:1 → 1:1), the β-amino ketone **3h** (75 mg, 0.26 mmol, 58%) was obtained as a light yellow oil; R_f = 0.32 (^{c}hex/EtOAc, 1:1).

^{1}H NMR (800 MHz, DMSO-d_6): δ = 8.02 [dd, J(H6,H5) = 2.8 Hz, J(H6,H3) = 1.5 Hz, 1 H, H6], 8.00 [dd, J($H5_{furan}$,$H4_{furan}$) = 1.7 Hz, J($H5_{furan}$,$H3_{furan}$) = 0.7 Hz, 1 H, $H5_{furan}$], 7.95 [d, J(H3,H6) = 1.5 Hz, 1 H, H3], 7.80 [d, J(H5,H6) = 2.8 Hz, 1 H, H5], 7.57 [d, J(NH,CH) = 8.5 Hz, 1 H, NH], 7.52 [dd, J($H3_{furan}$,$H4_{furan}$) = 3.6 Hz, J($H3_{furan}$,$H5_{furan}$) = 0.7 Hz 1 H, $H3_{furan}$], 6.73 [dd, J($H4_{furan}$,$H3_{furan}$) = 3.6 Hz, J($H4_{furan}$,$H5_{furan}$) = 1.7 Hz, 1 H, $H4_{furan}$], 5.47–5.29 [m, 1 H, CH], 3.43–3.37 [m, 1 H, CH_2], 3.31 [dd, J(CH_2,CH_2) = 17.1 Hz, J(CH_2,CH) = 3.8 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 183.44 [C=O], 153.91 [C2], 151.57 [$C2_{furan}$], 148.36 [$C5_{furan}$], 141.45 [C6], 133.15 [C3, C5], 129.19 [q, ^1J(C,F) = 282.8 Hz, CF_3], 119.42 [$C3_{furan}$], 112.92 [$C4_{furan}$], 47.02 [q, ^2J(C,F) = 30.5 Hz, CH], 36.95 [CH_2].

^{19}F NMR (376 MHz, DMSO-d_6): δ = −74.52 [d, J(CF_3,CH) = 7.9 Hz, CF_3].

HRMS (ESI+): m/z calcd for $C_{12}H_{11}F_3N_3O_2^+$ [M + H]$^+$: 286.0798; found: 286.0797.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 12.68 min, λ = 214 nm.

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

According to the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with 1-(1-methyl-1*H*-indol-3-yl)ethan-1-one (117 mg, 0.68 mmol). After stirring at r.t. (2 h), aqueous workup, flash chromatography [CH_2Cl_2 → CH_2Cl_2/(CH_2Cl_2/MeOH, 10:1), 7:3] and recrystallization (^{c}hex), the β-amino ketone (105 mg, 0.30 mmol, 67%) was obtained as a colorless solid; mp 198 °C; R_f = 0.17 (^{c}hex/EtOAc, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.46 [s, 1 H, $H2_{in}$], 8.12 [d, J($H7_{in}$,$H6_{in}$) = 7.6 Hz, 1 H, $H7_{in}$], 8.03 [dd, J(H6,H5) = 2.8 Hz, J(H6,H3) = 1.5 Hz, 1 H, H6], 7.98 [d, J(H3,H6) = 1.5 Hz, 1 H, H3], 7.79 [d, J(H5,H6) = 2.8 Hz, 1 H, H5], 7.54 [m, 2 H, NH, $H4_{in}$], 7.32–7.25 [m, 1 H, $H5_{in}$], 7.21 [td, J($H6_{in}$,$H7_{in}$/$H5_{in}$) = 7.6 Hz, ^4J($H6_{in}$,$H4_{in}$) = 1.0 Hz, 1 H, $H6_{in}$], 5.59–5.41 [m, 1 H, CH], 3.89 [s, 3 H, NCH_3], 3.45 [dd, J(CH_2,CH_2) = 16.5 Hz, J(CH_2,CH) = 9.8 Hz, 1 H, CH_2], 3.26 [dd, J(CH_2,CH_2) = 16.5 Hz, J(CH_2,CH) = 3.5 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 188.98 [C=O], 154.06 [C2], 141.51 [C6], 138.37 [$C2_{in}$], 137.39 [C_{quat}N], 133.11 [C3], 132.92 [C5], 126.53 [q, ^1J(C,F) = 283.0 Hz, CF_3] 125.75 [$C3_{in}$], 123.21 [$C5_{in}$], 122.46 [$C6_{in}$], 121.47 [$C7_{in}$], 115.00 [C_{quat}], 110.81 [$C4_{in}$], 47.42 [q, ^2J(C,F) = 30.1 Hz, CH], 37.64 [CH_2], 33.35 [CH_3].

^{19}F NMR (376 MHz, DMSO-d_6): δ = −74.34 [d, J(CF_3,CH) = 8.0 Hz, CF_3].

HRMS (ESI+): m/z calcd for $C_{17}H_{16}F_3N_4O^+$ [M + H]$^+$: 349.1271; found: 349.1273.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.60 min, λ = 220 nm.

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

According to the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with (*E*)-4-phenylbut-3-en-2-one (99 mg, 0.68 mmol). After stirring at r.t. (2 h), aqueous workup, and column chromatography (^{c}hex/EtOAc, 3:1 → 1:1), the β-amino ketone (92 mg, 0.29 mmol, 64%) was obtained as a yellow oil; R_f = 0.55 (^{c}hex/EtOAc, 1:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.03 [dd, J(H6,H5) = 2.8 Hz, J(H6,H3) = 1.5 Hz, 1 H, H6], 7.99 [d, J(H3,H6) = 1.5 Hz, 1 H, H3], 7.80 [d, J(H5,H6) = 2.8 Hz, 1 H, H5], 7.74–7.70 [m, 2 H, $H2_{ph}$, $H6_{ph}$], 7.67 [d, J(H_a,H_b) = 16.3 Hz, 1 H, H_a], 7.53 [d, J(NH,CH) = 8.5 Hz, 1 H, NH], 7.47–7.42 [m, 3 H, $H3_{ph}$, $H4_{ph}$, $H5_{ph}$,], 6.96 [d, J(Ha,Hb) = 16.3 Hz, 1 H, H_b], 5.48–5.31 [m, 1 H, CH], 3.32–3.24 [m, 1 H, CH_2], 3.19 [dd, J(CH_2,CH_2) = 17.3 Hz, J(CH_2,CH) = 3.6 Hz, 1 H, CH_2].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 195.11 [C=O], 154.02 [C2], 143.33 [C_a], 141.45 [C6], 134.32 [$C1_{ph}$], 133.18 [C3], 133.05 [C5], 130.88 [$C4_{ph}$], 129.16 [$C3_{ph}$, $C5_{ph}$], 128.68 [$C2_{ph}$, $C6_{ph}$], 126.31 [q, ^1J(C,F) = 282.8 Hz, CF_3] 126.10 [C_b], 47.20 [q, ^2J(C,F) = 30.3 Hz, CH].

^{19}F NMR (376 MHz, DMSO-d_6): δ = −74.50 [d, J(CF_3,CH) = 7.9 Hz, CF_3].

HRMS (ESI+): m/z calcd for $C_{16}H_{15}F_3N_3O^+$ [M + H]$^+$: 322.1162; found: 322.1160.

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

Following the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with propiophenone (0.09 mL, 0.68 mmol). After stirring at r.t. (2 h), aqueous workup, and column chromatography (^{c}hex/EtOAc, 3:1 → 2:1), the β-amino ketone **3k** (95 mg, 0.31 mmol, 68%) was obtained as a colorless solid (mixture of diastereomers); mp 95 °C; R_f = 0.37 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05–7.98 [m, 4 H, H6, H3, H2$_{ph}$, H6$_{ph}$], 7.80 [d, *J*(H5,H6) = 2.8 Hz, 1 H, H5], 7.71–7.65 [m, 1 H, H4$_{ph}$], 7.60–7.53 [m, 3 H, H3$_{ph}$, H5$_{ph}$, NH], 5.36–5.23 [m, 1 H, CH], 4.17 [dq, *J*(*CH*CH$_3$,CH) = 14.2 Hz, *J*(*CH*CH$_3$,CH$_3$) = 7.0 Hz 1 H, *CH*CH$_3$], 1.25 [dd, *J*(CH$_3$,*CH*CH$_3$) = 7.0 Hz, *J*(CH$_3$,CF$_3$) = 1.1 Hz 3 H, CH$_3$].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 199.81 [C=O], 153.69 [C2], 141.17 [C6], 135.21 [C1$_{ph}$], 133.65 [C5], 133.12 [C4$_{ph}$], 132.96 [C3], 128.90 [C3$_{ph}$, C5$_{ph}$], 128.43 [C2$_{ph}$, C6$_{ph}$], 126.13 [q, ^{1}*J*(C,F) = 284.3 Hz, CF$_3$], 52.21 [q, ^{2}*J*(C,F) = 28.8 Hz, CH], 26.32 [*C*HCH$_3$], 14.60 [d, ^{4}*J*(C,F) = 1.9 Hz, CH$_3$].

^{19}F NMR (376 MHz, DMSO-d_6): δ = –69.65 [dd, *J*(CF$_3$,CH) = 8.4 Hz, *J*(CF$_3$,CH$_3$) = 1.1 Hz, CF$_3$].

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{15}F_3N_3O^+$ [M + H]$^+$: 310.1162; found: 310.1160.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 15.79 min, 15.97 min, λ = 214 nm.

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

Following the general procedure, **1b** (100 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.04 mL, 1.04 mmol), and reacted with 2-methyl-1-phenylpropan-1-one (0.1 mL, 0.68 mmol). After stirring at r.t. (3 h), aqueous workup, and column chromatography (^{c}hex/EtOAc, 3:1 → 2:1), the β-amino ketone **3l** (32 mg, 0.10 mmol, 22%) was obtained as a light yellow solid; mp 130 °C; R_f = 0.29 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.20 [d, *J*(H3,H6) = 1.5 Hz, 1 H, H3], 8.00 [dd, *J*(H6,H5) = 2.8 Hz, *J*(H6,H3) = 1.5 Hz, 1 H, H6], 7.82 [d, *J*(H5,H6) = 2.8 Hz, 1 H, H5], 7.75–7.68 [m, 1 H, H4$_{ph}$], 7.67–7.61 [m, 2 H, H2$_{ph}$, H6$_{ph}$], 7.58–7.51 [m, 1 H, NH], 7.47 [m, 2 H, H3$_{ph}$, H5$_{ph}$], 6.01 [m, 1 H, CH], 1.40 [s, 3 H, CH$_3$], 1.27 [s, 3 H, CH$_3$].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 206.17 [C=O], 154.05 [C2], 141.02 [C6], 137.80 [C1$_{ph}$], 133.52 [C5], 133.14 [C4$_{ph}$], 131.20 [C3], 128.36 [C3$_{ph}$, C5$_{ph}$], 127.29 [C2$_{ph}$, C6$_{ph}$], 125.73 [q, ^{1}*J*(C,F) = 284.7 Hz, CF$_3$], 54.13 [q, ^{2}*J*(C,F) = 27.6 Hz, CH], 49.48 [*C*(CH$_3$)$_2$], 24.02 [CH$_3$], 20.37 [d, ^{4}*J*(C,F) = 1.1 Hz, CH$_3$].

^{19}F NMR (376 MHz, DMSO-d_6): δ = –67.66 [d, *J*(CF$_3$,CH) = 8.9 Hz, CF$_3$].

HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{17}F_3N_3O^+$ [M + H]$^+$: 324.1318; found: 324.1318.

HPLC (0.1% TFA; 0 min, 4% B → 15 min, 100% B, flow: 1 mL/min): t_R = 15.83 min, λ = 214 nm.

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

Following the general procedure, **1b** (150 mg, 0.68 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.56 mL, 1.56 mmol), and reacted with 2,6-dichlorophenylacetonitrile (202 mg, 1.09 mmol). After stirring at r.t. (2.5 h), aqueous workup, column chromatography (^{c}hex/EtOAc, 5:1 → 3:1), and washing with toluene, the β-amino ketone **3m** (148 mg, 0.41 mmol, 60%) was obtained as a colorless solid (mixture of diastereomers).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 [d, *J*(H3$_{ar}$,H4$_{ar}$) = 9.6 Hz, 1 H, H3$_{ar}$], 8.18 [d, *J*(H3,H6) = 1.5 Hz, 1 H, H3], 8.09 [dd, *J*(H6,H5) = 2.7 Hz, *J*(H6,H3) = 1.5 Hz, 1 H, H6], 7.94 [d, *J*(H5,H6) = 2.7 Hz, 1 H, H5], 7.65 [s, 2 H, NH, H5$_{ar}$], 7.53 [t, *J*(H4$_{ar}$,H3$_{ar}$/H5$_{ar}$) = 8.1 Hz, 1 H, H4$_{ar}$], 6.22–6.07 [m, 1 H, CH], 5.51 [d, *J*(CHCN,CH) = 10.5 Hz, 1 H, CHCN].

^{13}C NMR (75 MHz, DMSO-d_6): δ = 152.60 [C2], 140.63 [C6], 135.21 [C1$_{ph}$], 133.83 [C5], 132.89 [C3], 131.79 [C2$_{ph}$, C6$_{ph}$], 129.30 [C4$_{ph}$], 128,21 [q, ^{1}*J*(C,F) = 283.9 Hz, CF$_3$], 126.23 [C3$_{ph}$, C5$_{ph}$], 114.98 [C≡N], 50.71 [q, ^{2}*J*(C,F) = 30.2 Hz, *C*CF$_3$], 32.00 [*C*CN].

^{19}F NMR (471 MHz, DMSO-d_6): δ = –71.63 [br s, CF$_3$].

HR-EI-MS: *m*/*z* calcd for $C_{14}H_9Cl_2F_3N_4^+$ [M]$^+$: 360.0156; found: 360.0177.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.68 min, 1.73 min, λ = 220 nm.

Diethyl 2-[2,2,2-Trifluoro-1-(pyrazin-2-ylamino)ethyl]malonate (3n)

According to the general procedure, **1b** (150 mg, 0.68 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 1.42 mL, 1.42 mmol), and reacted with diethyl malonate (0.16 mL, 1.02 mmol). After stirring at r.t. (2 h), TLC and LC-MS control showed that large amounts of starting material remained. The reaction mixture was cooled to –78 °C before LHMDS (1.0 M solution in toluene, 0.68 mL, 0.68 mmol) was added. Stirring was continued at –78 °C (10 min), diethyl malonate (0.1 mL, 0.68 mmol) was added, and the reaction mixture was stirred at 40 °C (2 h). Subsequent aqueous workup and column chromatography (^{c}hex/EtOAc, 3:1) furnished the desired β-amino ketone **3n** (134 mg, 0.40 mmol, 59%) as a light yellow oil; R_f = 0.31 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.09 [d, *J*(H3,H6) = 1.5 Hz, 1 H, H3], 8.07 [dd, *J*(H6,H5) = 2.7 Hz, *J*(H6,H3) = 1.5 Hz, 1 H, H6], 7.87 [d, *J*(H5,H6) = 2.7 Hz, 1 H, H5], 7.71 [d, *J*(NH,CH) = 9.5 Hz, 1 H, NH], 5.73–5.59 [m, 1 H, CH], 4.23–3.94 [m, 4 H, 2 × CH$_2$], 1.16 [t, *J*(CH$_3$,CH$_2$) = 7.1 Hz, 3 H, CH$_3$], 1.01 [t, *J*(CH$_3$,CH$_2$) = 7.1 Hz, 3 H, CH$_3$].

^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.19 [C=O], 164.99 [C=O], 153.23 [C2], 141.06 [C6], 133.57 [C5], 133.31 [C3], 124.90 [q, ^{1}*J*(C,F) = 283.5 Hz, CF$_3$], 61.97 [CH$_2$], 61.70 [CH$_2$], 51.66 [*C*H(CO$_2$Et)$_2$], 49.70 [q, ^{2}*J*(C,F) = 30.5 Hz, CH], 13.63 [CH$_3$], 13.51 [CH$_3$].

^{19}F NMR (282 MHz, DMSO-d_6): δ = –72.79 [d, *J*(CF$_3$,CH) = 7.9 Hz, CF$_3$].

HR-EI-MS: *m*/*z* calcd for $C_{13}H_{16}F_3N_3O_4^+$ [M]$^+$: 335.1093; found: 335.1104.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.62 min, λ = 220 nm.

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

Following the general procedure, **1b** (90 mg, 0.41 mmol) was dissolved in dry CH_2Cl_2 (7 mL), treated with LHMDS (1.0 M solution in toluene, 0.94 mL, 0.94 mmol), and reacted with EtOAc (0.06 mL, 0.62 mmol). After stirring at r.t. (1 h), aqueous workup, and flash chromatography (^{c}hex → ^{c}hex/EtOAc, 3:1), the β-amino ester **3o** (27 mg, 0.10 mmol, 25%) was obtained as a light yellow oil; R_f = 0.15 (^{c}hex/EtOAc, 2:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.12–7.91 [m, 2 H, H6, H3], 7.82 [d, J(H5,H6) = 2.3 Hz, 1 H, H5], 7.65 [d, J(NH,CH) = 8.9 Hz, 1 H, NH], 5.40–5.18 [m, 1 H, CH], 4.03 [m, 2 H, OCH_2], 2.92 [dd, $J(CH_2,CH_2)$ = 16.2 Hz, $J(CH_2,CH)$ = 4.2 Hz, 1 H, CH_2], 2.72 [dd, $J(CH_2,CH_2)$ = 16.2 Hz, $J(CH_2,CH)$ = 10.0 Hz, 1 H, CH_2], 1.06 [t, $J(CH_3,CH_2)$ = 7.1 Hz, 3 H, CH_3].

^{13}C NMR (101 MHz, DMSO-d_6): δ = 168.76 [C=O], 153.64 [C2], 141.15 [C6], 133.11 [C5], 133.06 [C3], 125.57 [q, ^1J(C,F) = 283.2 Hz, CF_3], 60.47 [OCH_2], 47.83 [q, ^2J(C,F) = 30.7 Hz, CH], 33.58 [CH_2], 13.76 [CH_3].

^{19}F NMR (376 MHz, DMSO-d_6): δ = –74.89 [d, $J(CF_3,CH)$ = 7.9 Hz, CF_3].

HR-EI-MS: m/z calcd for $C_{10}H_{12}F_3N_3O_2^+$ $[M]^+$: 263.0882; found: 263.0898.

HPLC-MS (0.05% formic acid; 0 min, 0% B → 2.0 min, 100% B, flow: 3.3 mL/min): t_R = 1.43 min, λ = 220 nm.

Acknowledgment

Support of the work by the Excellence Cluster *Center of Integrated Protein Science Munich (CIPS^M)* and the GRK 2062 *Molecular Principles of Synthetic Biology* is gratefully acknowledged. The authors thank Antje Schöneberg and Doris Weidenkopf-Look (Merck) for laboratory support and Christian von der Heyden and Markus Knoth (Merck) for NMR support and fruitful discussions.

Supporting Information

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

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