PAPER

A facile preparation of trisubstituted amino-furan and -thiophene derivatives†

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β-Alkylation of amino-furan and -thiophene heterocycles is described through metal-, acid- and base-free carbon–carbon bond formation. The ability of both heterocycles to undergo selective β-alkylation is compared by mean of experimental and theoretical data. The presence of chiral amine substituents induced the diastereoselective generation of the newly formed additional stereocenter.

Introduction

Furans and thiophenes are among the most versatile five-membered heterocycles commonly found in natural products and widely used as building blocks in the synthesis of complex molecular architectures. Although 2,5-disubstituted furans and thiophenes are common compounds in these series, installation of an additional substituent is usually not trivial and often requires tedious procedures. 2,4,5-Trisubstituted analogues may be obtained either through the construction of the heterocycle from appropriate precursors or through additional substitution of parent 2,5-disubstituted furans.[1–15] In addition to traditional routes[1] using established Paal–Knorr[2] or Feist–Bénary[3] procedures, recent appealing papers by Li[4a] and Pirali[4b] described Pd/Cu-mediated cascade and multicomponent reaction sequences respectively that revived the interest for the polysubstituted targets. A phosphino-assisted cyclisation strategy was also recently described by Lin[5] *via* intramolecular Wittig-type reactions. Although undoubtedly useful for the construction of furans, these procedures were not applied to the analogous thiophene series. Although tremendous work has been done, the direct β-alkylation of preformed heterocycles, under classical metal-induced Friedel–Crafts conditions, suffers from a lack of generalisation and is strongly dependent on the substitution pattern.[6] Nucleophilic-based alkylation of electron-withdrawing group-substituted heterocycles such as 2-nitrofuran or 2-nitrothiophene[7] requires harsh conditions (strong base or acid). In contrast, fewer studies have been directed towards heterocycles bearing electron-donating substituents. β-Alkylation of 2-acetamidothiophene or 2-imidazolothiophene using the Vilsmeier–Haach reagent[8] or requiring the presence

of expensive metals[9] respectively is scarcely reported. In this context, the increase of the electronic density of the furan ring induced by the presence of electron-donating groups was shown to be beneficial to the overall reactivity of furans[10–14] allowing the selective synthesis of complex molecular architectures. Moreover, the presence of an amino substituent plausibly impacted the electron density at adjacent carbon atoms. This pseudo "enamine-type reactivity" was first evidenced by Boyd[15] some years ago with the formation of a C–N bond from aminofurylaryl derivatives and electrophilic nitrogen atom precursors. In contrast, attempts to generalise this methodology to the formation of C–C bonds failed.[15] The appealing "enamine-type property" of amino-furans and -thiophenes has until now been greatly under-exploited. Thus, the development of methods allowing the selective introduction of electrophiles at amino furans or thiophenes under mild conditions may open up new routes to polysubstituted heterocycles and more complex architectures. In this context we report herein the metal-, acid- and base-free electrophilic formation of carbon–carbon bonds on 5-amino-2-carbonylated furans or thiophenes. The behaviour of both heterocycles towards electrophiles is compared at experimental and theoretical levels.

Results and discussion

Preparation of starting materials

We first prepared six aminofurans **1a–f** and five aminothiophenes **2a–e** starting from their parent commercial bromide derivatives. If furans **1a–b** and thiophenes **2a–b** were synthesised as already stated in refluxing water or water–dioxane mixture,[11] the previous conditions were not suitable for obtaining all the furan or thiophene derivatives (Table 1). In fact, the introduction of prolinol and proline or pipecolic acid moieties at aminohetero-cycles required a further optimisation of the reaction conditions (refluxing water and ethanolic solution respectively)[16] Thus, new aminoheterocycles were obtained in fair to high yields under metal-free conditions.

With the aim of investigating the diastereoselective formation of the C–C bond and the role of the protected-free hydroxyl group, we further extended the range of reactants to the *O*-protected

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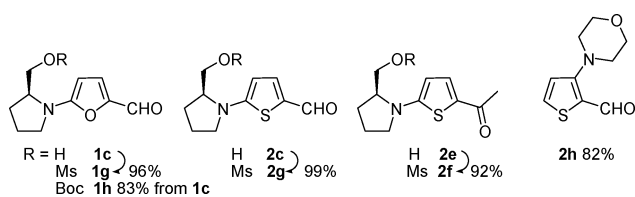
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Table 1 Preparation of 2-carbonylated 5-aminoheterocycles **1a–f** & **2a–e**

Scheme:

Br–(X ring)–Y + R²R¹NH →(Reflux) R²R¹N–(X ring)–Y

X = O, S
Y = CHO, COMe

X = O **1a-f**
S **2a-e**

Entry	X	Y	R²R¹NH	Product	Yield (%)[c]
1[a]	O	CHO	Morpholine	**1a**	98 [17]
2[a]	O	CHO	Piperidine	**1b**	80 [17]
3[c]	O	CHO	(S)-Prolinol	**1c**	50
4[d]	O	CHO	(L)-(−)-Proline	**1d**	73
5[d]	O	CHO	(±)-Pipecolic acid	**1e**	65
6[b]	O	CHO	N-Methylallylamine	**1f**	78 [11d]
7[a]	S	CHO	Morpholine	**2a**	73 [17]
8[c]	S	CHO	Piperidine	**2b**	64 [18]
9[c]	S	CHO	(S)-Prolinol	**2c**	23
10[d]	S	CHO	(L)-(−)-Proline	**2d**	40
11[e]	S	COMe	(S)-Prolinol	**2e**	43

[a] Amine (2 eq), NEt₃ (3 eq) in refluxing water. [b] Amine (2 eq), NEt₃ (3 eq) in refluxing dioxane : water (9 : 1). [c] Aminoalcohol (1.5 eq), NEt₃ (2 eq) in refluxing water. [d] Aminoacid (1.01 eq), NaHCO₃ (4 eq) in refluxing EtOH : H₂O (1 : 1). [e] Amine (2 eq), NEt₃ (3 eq) in water under pressure.

Table 2 C–C bond formations with the furan derivatives **1a–h**

Scheme:

R²R¹N–(furan)–CHO + R³C(=O)R⁴ → HO–C(R⁴)(R³)–(furan, R²R¹N)–CHO **3a-h** (α to γ)

1a-h

R³, R⁴ =
CF₃, CO₂Me   α
CF₃, CF₃   β
CF₂Cl, CF₂Cl   γ

Entry	Furan 1	R³	R⁴	Time (h)	Product 3	Yield (%)	dr[d]
1	**1a**	CF₃	CO₂Me	18	**3aα**	90[a]	—
2	**1a**	CF₃	CO₂Me	18	**3aα**	91[b]	—
3	**1a**	CF₃	CF₃	18	**3aβ**	85[a]	—
4	**1a**	CF₂Cl	CF₂Cl	48	**3aγ**	78[a]	—
5	**1a**	CF₃	CH₃	18	—	nr[a]	—
6	**1a**	CH₃	CO₂Me	18	—	nr[a]	—
7	**1b**	CF₃	CF₃	24	**3bβ**	42[a]	—
8	**1d**	CF₃	CO₂Me	18	**3dα**	50[b]	6 : 1
9	**1e**	CF₃	CO₂Me	18	**3eα**	79[b]	1 : 1
10	**1f**	CF₃	CF₃	20	**3fβ**	57[a]	—
11	**1g**	CF₃	CO₂Me	18	**3gα**	39[c]	2 : 1
12	**1g**	CF₃	CO₂Me	16	**3gα**	72[a]	2 : 1
13	**1h**	CF₃	CO₂Me	16	**3hα**	62[b]	5 : 1
14	**1h**	CF₃	CF₃	16	Degradation[a]	—	—

[a] Experiment conducted in refluxing toluene. [b] Experiment conducted in CH₂Cl₂ at rt. [c] Experiment conducted in CH₂Cl₂ at reflux. [d] dr measured in ¹H NMR spectroscopy on the isolated product mixture.

substrates. Although *O*-benzylated and *O*-silylated derivatives could not be isolated, generating both side products and degradation upon purification, *O*-mesylated heterocycles **1g**, **2g**, **2f** could be obtained in very good yields, starting from the parent prolinol reactants (Fig. 1). On the other hand 3-morpholino-2-thiophenecarboxaldehyde **2h** was synthesised from its 3-bromide parent in 82% yield.[17] Thus, cyclic, acyclic, chiral functionalised amines were introduced iton 2-carbonylated furans or thiophenes giving a wide variety of potent nucleophilic heterocycles.

Fig. 1 Further functionalisation of heterocycles **1g–h** and **2f–h**.

R = H **1c**; Ms **1g** 96%; Boc **1h** 83% from **1c**

H **2c**; Ms **2g** 99%

H **2e**; Ms **2f** 92%

2h 82%

Enaminic behavior in the furan series

We next focused our attention to the formation[15] of carbon–carbon bonds in the furan series (Table 2). We anticipated that strong electrophilic partners would be able to induce carbon–carbon bonds with aminoheterocycle substrates. In fact, preliminary results with **1a** and *tert*-butyl chloride or 2-nitrobenzaldehyde gave unsatisfactory results. We decided to use methyl trifluoropyruvate as a better electrophile.[19]

5-Morpholino-2-furancarboxaldehyde **1a** reacted with methyl trifluoropyruvate at rt in DCM giving **3aα** with 91% yield (entry 2). Moving from trifluoropyruvate reactant to hexafluoroacetone gave a surprising result showing a lesser reactivity (85%) even in refluxing toluene (entry 3). This difference was more pronounced with the substrate **1g** which reacted with methyl trifluoropyruvate at rt whereas no reaction occurred with hexafluoroacetone at 110° (entry 10). This behavior was likely due to the sesquihydrate form of hexafluoroacetone decreasing the electrophilicity (*vide infra*).

The use of additional MgSO₄ and/or Dean–Stark apparatus and/or a closed vessel gave similar results. As expected, the use of the lesser electrophilic dichlorotetrafluoroketone with **1a** required a prolonged reaction time (48 h) for completion. Nevertheless the corresponding alcohol **3aγ** was isolated in 78% yield (entry 4). As a minimum, the presence of the both α-polyfluorinated and other electron-withdrawing moieties that substituted the ketone were required to get the corresponding product. In fact, 1,1,1-trifluoropropanone or methyl pyruvate were revealed to be inactive with **1a** (entries 5 and 6). Thus the enaminic character was illustrated by methyl trifluoropyruvate with the furans **1d**, **1e**, **1h** giving the tertiary alcohols **3dα**, **3eα**, **3hα** respectively (entries 8, 9, 13).

Interestingly, the C–C bond formation gave a mixture of inseparable diastereomers **3** starting from an unsymmetrical electrophile. The diastereomeric ratio was determined by NMR spectroscopies analysis based on the displacements in each diastereomers. The relative intensity of the singlet signal of the methyl carboxylate group was compared for the two diastereomers in ¹H NMR spectroscopy and then corroborated in ¹⁹F NMR spectroscopy by the relative intensity of the two signals of the trifluoromethyl moiety. Low to moderate dr were observed depending on the chiral amine residue.

The use of the (L)-(−)-proline furan derivative induced the diastereoselective introduction in a 6 : 1 ratio that could not be increased by modifications of the reaction conditions (Table 2, entry 8). In contrast, moving from proline to pipecolic acid or to mesylated prolinol dramatically affected the diastereoselectivity of the reaction (entry 9). It is worth noting that the *O*-Boc protective group similarly allowed a good 5 : 1 dr to be maintained (entry 13).

Table 3 C–C bond formation with the thiophene derivatives **2a–g**

Entry	Thiophene **2**	Time (h)	Product	Yield (%)	dr[d]
1	**2a**	66	**4a**	40[c]	—
2	**2a**	66	**4a**	84[a]	—
3	**2b**	18	**4b**	66[a]	—
4	**2d**	18	**4d**	50[b]	2 : 1
5	**2d**	42	**4d**	99[b]	2 : 1
6	**2f**	18	**4f**	89[a]	1 : 1
7	**2g**	24	**4g**	69[a]	2 : 1

[a] Experience conducted in refluxing toluene. [b] Experience conducted in CH$_2$Cl$_2$ at rt. [c] Experience conducted in CH$_2$Cl$_2$ at reflux. [d] dr measured in ^{1}H NMR spectroscopy on the isolated product mixture.

Enaminic behavior in the thiophene series

The thiophene series was slightly less reactive. Although the reaction with **2a** and methyl trifluoropyruvate took place in DCM at 40°, refluxing toluene was required to obtain a good yield (Table 3, entries 1 and 2). Surprisingly, the C–C bond formation was easily exemplified with thiophenes **2d** and **2g** after prolonged reaction times leading to **4d** and **4g** in 99 and 69% yield respectively (entries 5 and 7). This was an expected result since 5-amino-2-thiophenecarboxaldehydes did not display Diels–Alder reactivity unlike the furan series.[11]

The keto substrate **2f** yielded **4f** in high yield and thus compared favorably to the carboxaldehyde analogue (entries 6 and 7). The influence of the position of the amino moiety was next examined. No reaction occurred between 3-morpholino-2-thiophenecarboxaldehyde **2h** and methyl trifluoropyruvate even under harsh conditions for prolonged reaction time (toluene, 110°, 66 h) confirming a similar enaminic-type behaviour between both amino heterocycles *vis-à-vis* electrophiles such as α-polyhalogenated ketones. Moving from the furan to thiophene series gave a decrease of the stereoinduction (Table 3, entries 4 and 5 compared to Table 2, entry 8). In addition, alkylation of mesyl protected thiophenes **2g**, **2f** led to low dr (Table 3, entries 6 and 7) indicating a similar trend in the stereoinduction regardless of the heterocycle.

Calculations

In order to gain more information and insight in regard to the β-alkylation results, calculations have been performed. The experimental results were compared to calculations, on the one hand, to verify the reactivity order, and on the other hand to investigate the enaminic character. The geometry optimisations and energies of aminoheterocycles **1d**, **1e**, **1g**, **2d**, **2g**, as well as of the electrophiles, were performed in the gas phase at a B3LYP/6-311+G(d,p) level of theory[20] with standard parameters for both reactants using the Gaussian 09 Package software.[21] The main calculations results are gathered in Table 4, Fig. 2 and Table 5, Fig. 3 for the electrophiles and the heterocycles respectively.

**Table 4** Calculation results for the electrophiles

Entry	Compound	LUMO[a]
1	1,1,1-Trifluoropropanone	−2.10
2	Methyl pyruvate	−2.33
3	Hexafluoroacetone·H$_2$O	−2.81
4	Hexafluoroacetone·2 H$_2$O	−3.07
5	Methyl trifluoropyruvate (α)	−3.35
6	1,3-Dichloro-1,3-tetrafluoroacetone (γ)	−3.37
7	Hexafluoroacetone	−3.48

[a] Energy of the Lowest Unoccupied Molecular Orbital (eV).

Table 5 Calculation results for the nucleophiles

Entry	Compound	HOMO[a]	Exp. result[b]	Conditions
1	2-*N*-(Prolino)furan	−5.11	—	—
2	**1d**	−5.72	50	DCM, 20 °C
3	**1e**	−5.77	79	DCM, 20 °C
4	**2d**	−5.78	50	DCM, 20 °C
5	**1g**	−6.01	39	DCM, 40 °C
6	2-Furaldehyde	−7.21	No reaction	Tol, 110 °C

[a] Energy of the Highest Occupied Molecular Orbital (eV). [b] Yield obtained with methyl trifluoropyruvate during 18 h.
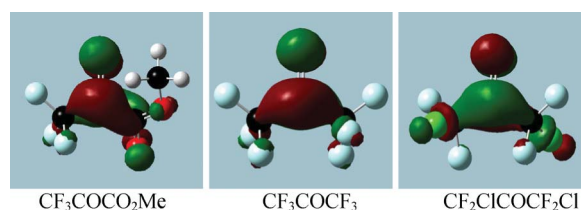
Fig. 2 LUMO representation for an isovalue at 95%.
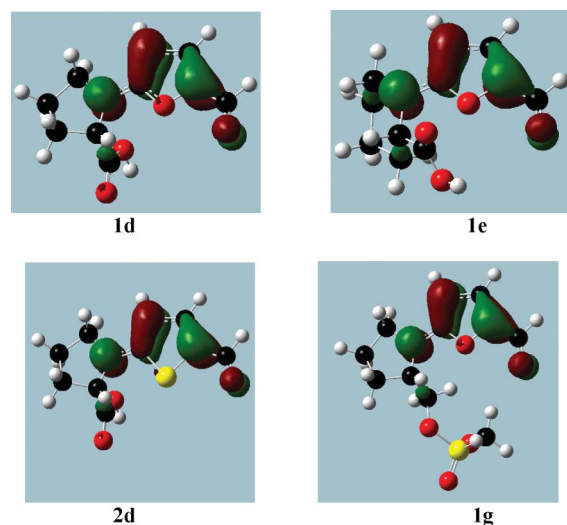
Fig. 3 HOMO representation for an isovalue at 95%.

We have first checked that the shape of the LUMOs of the electrophiles presented adequate symmetry to interact with the HOMOs of the substrates (Fig. 2 and 3).

The examination of the calculated LUMO values and the experimental results allowed to distinguish two classes of electrophiles: i) unreactive electrophiles (1,1,1-trifluoropropanone and methyl pyruvate), ii) reactive ones **α**, **β** and **γ**, associating both halogenated

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moiety and another withdrawing group with the ketone. The latter combination ensured the closest electrophile LUMO and substrate HOMO values (Table 4, entries 5, 6 and 7). Interestingly, the presence of surrounding water molecules in hexafluoroacetone affected the LUMO energy level ranging from −3.48 to −2.81 eV (entries 3, 4 and 7) and explained the hexafluoroacetone sesquihydrate poor reactivity observed (*vide supra*).

Considering the frontier molecular orbital theory, the introduction of an amino group clearly confirmed the increase of the energy level of the HOMO compared to the unsubstituted 2-furaldehyde in which case no reaction occurred (Table 5, entry 6). The HOMO levels were roughly equal between **1d**, **1e**, **2d** (compare entries 2, 3, 4). In contrast, **1g** exhibited a slightly lower HOMO level (entry 5). This marked difference was in good agreement with the yields observed and the experimental conditions employed. As shown in Fig. 3, the increase of the C-4 relative coefficient in **1d**, **1e**, **2d**, **1g** highlighted the enaminic character of the N–C5–C4 bond sequence. The latter enaminic character is likely due to the presence of the amine moiety that induced a strong modification of the balance symmetry of the π-aromatic orbital system and thus resulted in an enhanced reactivity toward electrophiles. It is worth noting that the enaminic character is similar moving from furan to thiophene (entries 2 and 4). In contrast to the marked difference of reactivity between amino-furans and -thiophenes as dienes in Diels–Alder reactions,[11] the present study evidenced a similar behaviour for both heterocycles.

Synthesis of furan-fused oxazepin(on)e

Amino heterocycles bearing adjacent substituents in positions 4 and 5 are of particular interest. Indeed, formation of a fused seven membered ring may result from intramolecular etherification or lactonisation processes of substrates bearing adequate combination of functional groups. Taking into account that fused heterocycles based on a 7-membered central ring and/or a fluorinated moiety such as Chloropramine or Telcagepant are pharmaceutically-relevant compounds,[22] new access to such architectures from easily accessible building-blocks is of high interest.[23] The joint presence of OMs and OH or COOH and OH groups in **3gα** and **4f** or **3dα** and **4g** may generate the formation of oxazepine or oxazepinone rings respectively. Surprisingly, both heterocycles did not exhibit similar behaviour. Indeed, extensive attempts to promote both etherification and lactonisation starting from thiophenes **4d**, **4f**, **4g** failed. In contrast, etherification and lactonisation gratifyingly led to the fused tricyclic targets (Scheme 1). The *O*-mesylated compound **3gα** reacted with sodium hydride in THF to cleanly afford oxazepine **5** in 52% yield. In addition, oxazepinone **6** could be obtained under classical coupling conditions from carboxylic acid **3dα** in 60% yield.

Conclusions

In conclusion, we succeeded in the selective β-alkylation of 5-amino-2-carbonylated furans or thiophenes by a convenient atom economical procedure. Both experimental and theoretical data suggested that furans and thiophenes behave similarly towards functionalised electrophiles. The presence of chiral amine substituents induced the diastereoselective formation of neighbouring carbon–carbon bonds. Unprecedented furan-fused
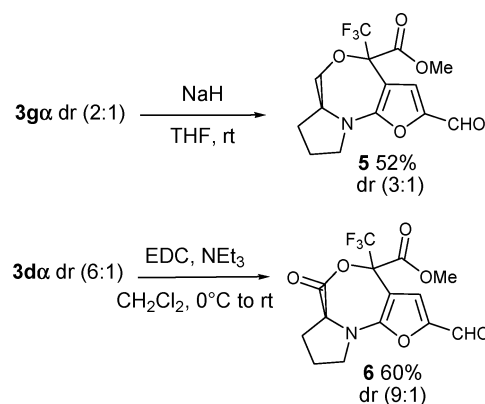
Scheme 1 Access to furan-fused oxazepin(on)es **5** and **6**.

tricyclic oxazepine and oxazepinone could be obtained through intramolecular etherification and lactonisation processes.

Experimental

General methods

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. Petroleum ether was distilled under Argon. Toluene was used without distillation. All reactions were carried out under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was purified by silica gel flash chromatography using an ethyl acetate–petroleum ether mixture as the eluent unless specified otherwise. NMR spectra were recorded on 300 MHz and 200 MHz spectrometers. Chemical shifts were reported in ppm relative to the residual solvent peak (7.26 ppm for CHCl$_3$, 2.05 ppm for acetone-d_6, 3.31 ppm for CD$_3$OD) for ^{1}H spectra and (77.0 ppm for CDCl$_3$, 206.0 ppm for acetone-d_6, 49.0 ppm for CD$_3$OD) for ^{13}C spectra. Melting points were measured on a Melting-Point B-545 device and were uncorrected. High Resolution Mass spectroscopy data in electronic impact were recorded with a resolution of 5000 RP at 5%. Electronic impact (EI) and chemical ionisation (CI) mass spectroscopies were recorded on a HP5989 B device. Electrospray ionisation (ESI) mass spectroscopy was recorded on an UPLC Waters device (in positive mode unless otherwise noted). Infrared spectra were recorded on a FT IR spectrometer in KBr for liquid and solid compounds. TLC was carried out on Silica Gel 60 F$_{254}$ (0.5 mm thickness).

(*S*)-5-(2-Hydroxymethyl)pyrrolidin-1-yl-2-furancarboxaldehyde (1c)

Following the general procedure for amination,[11d] 5-bromo-2-furancarboxaldehyde led to **1c** as an yellow solid (50%) after silica gel flash chromatography (petroleum ether : MeOH 9.5 : 0.5). R$_f$: 0.12 (petroleum ether : EtOAc 2 : 8); 0.22 (petroleum ether : EtOAc : MeOH 4.5 : 5 : 0.5). Mp: 119.3–120.1 °C. [α]$_D$$^{20\,°C}$ = × 153 ± 8 (*c* = 0.116; CHCl$_3$). IR (KBr, *v*, cm^{-1}): 3446, 3113, 2950, 2874, 1637, 1584, 1405, 1278, 1246, 1160, 1141, 1048, 1025, 942, 793, 756. ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 2.01–2.06 (m, 4H, NCH$_2$C$_2$H$_4$), 3.00 (brs, 1H, OH), 3.39–3.45 (m, 1H, NC*H*$_2$), 3.54–3.56 (m, 1H, NC*H*$_2$), 3.69 (d, ^{3}*J* = 5.4 Hz, 2H, NCHC*H*$_2$OH), 4.00–4.04 (m, 1H, NC*H*CH$_2$OH), 5.29 (d, ^{3}*J* = 3.9 Hz, 1H,

HC≡CN), 7.19 (d, ^3J = 3.1 Hz, 1H, HC=CCHO), 8.89 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.9 (NCH$_2$$CH_2CH_2$), 28.4 (NCH$_2CH_2CH_2$), 48.8 (N$CH_2CH_2CH_2$), 61.3 (NC$HCH_2$OH), 63.7 (NCH$CH_2$OH), 87.3 (H$C$≡CN), 132.1 (H$C$=CCHO), 144.4 (HC=$C$N), 162.6 (HC=$C$CHO), 170.5 (CHO). MS (CI, NH$_3$) m/z (rel int): 196.1 (50, M + H$^+$), 218.1 (100, M + Na$^+$). MS (ESI, CH$_3$CN) m/z (rel int): 196.0 (20, M + H$^+$), 218.0 (100, M + Na$^+$), 279.1 (65). HRMS (ESI, CH$_3$CN) m/z: calcd for (M + Na$^+$) C$_{10}$H$_{13}$NO$_3$Na 218.0793; found 218.0775.

(*S*)-1-(5-Formylfuran-2-yl)pyrrolidine-2-carboxylic acid (1d)

In a 25 mL round-bottom flask were mixed 5-bromo-2-furancarboxaldehyde (500.0 mg, 2.86 mmol, 1 eq), (−)-(L)-proline (334.0 mg, 2.89 mmol, 1.1 eq) and NaHCO$_3$ (729.0 mg, 17.13 mmol, 3 eq) in a mixture of water : ethanol 1 : 1 (30 mL). The mixture was heated at reflux for 6 h. The mixture was allowed to cool to rt and then a HCl solution (1 N) was added until pH ≈ 3 (15 mL). The mixture was extracted with EtOAc (4 × 100 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (CH$_2$Cl$_2$: MeOH 9 : 1) to afford 441.4 mg of **1d** as a blue powder (74%). R$_f$: 0.13 (CH$_2$Cl$_2$: MeOH 9 : 1). Mp: 171.6–172.2 °C. The solution was too dark therefore the optical rotation could not be measured. IR (KBr, v, cm^{-1}): 3436, 3132, 2957, 2883, 1721, 1644, 1569, 1412, 1345, 1292, 1225, 1152, 1044, 915, 769. ^{1}H NMR (CD$_3$OD, 300 MHz) δ 2.03–2.47 (m, 4H, NCH$_2$C$_2$$H_4$), 3.54–3.72 (m, 2H, NC$H_2$), 4.50 (dd, ^3J = 8.7 and 3.1 Hz, 1H, NCHCOOH), 5.43 (d, ^3J = 4.2 Hz, 1H, HC≡CN), 7.48 (d, ^3J = 4.1 Hz, 1H, HC=CCHO), 8.75 (s, 1H, CHO). ^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.04–2.19 (m, 2H, NCH$_2$C$_2$$H_4$), 2.23–2.39 (m, 2H, NCH$_2C_2$$H_4$), 3.39–3.51 (m, 1H, NC$H_2$), 3.62–3.73 (m, 1H, NC$H_2$), 4.78 (t, ^3J = 5.1 Hz, 1H, NCHCOOH), 4.16 (d, ^3J = 4.2 Hz, 1H, HC=CCHO), 5.50–6.00 (brm, 1H, OH), 7.28 (d, ^3J = 4.3 Hz, 1H, HC=CCHO), 8.69 (s, 1H, CHO). ^{13}C NMR (CD$_3$OD, 75 MHz) δ 24.8 (NCH$_2$$CH_2CH_2$), 31.7 (NCH$_2CH_2$$CH_2$), 49.4 (N$CH_2CH_2CH_2$), 61.9 (NCHCOOH), 89.3 (HC≡CN), 135.4 (HC=CCHO), 146.0 (HC=CN), 164.0 (HC=CCHO), 171.7 (CHO), 175.3 (COOH). MS (ESI, CH$_3$CN) m/z (rel int): 210.0 (40, M + H$^+$), 232.0 (100, M + Na$^+$), 441.1 (30, 2M + Na$^+$). HRMS (ESI, CH$_3$CN) m/z: calcd for (M + Na$^+$) C$_{10}$H$_{11}$NO$_4$Na 232.0586; found 232.0562.

1-(5-Formylfuran-2-yl)piperidine-2-carboxylic acid (1e)

In a 25 mL round-bottom flask were mixed 5-bromo-2-furancarboxaldehyde (200.0 mg, 1.149 mmol, 1 eq), pipecolic acid (149.8 mg, 1.160 mmol, 1 eq) and NaHCO$_3$ (288.0 mg, 3.428 mmol, 3 eq) in a mixture of water : ethanol 1 : 1 (20 mL). The mixture was heated at reflux for 6 h. The mixture was allowed to cool to rt and then a HCl solution (1 N) was added until pH ≈ 3. The mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (CH$_2$Cl$_2$: MeOH 97.5 : 2.5 to 92 : 8) to afford 165.2 mg of **1e** as a green oil (65%). R$_f$: 0.14 (CH$_2$Cl$_2$: MeOH 95 : 5). IR (KBr, v, cm^{-1}): 2952, 2861, 1715, 1532, 1331, 1258, 1178, 1030, 982, 888, 776, 749. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.45–1.62 (m, 2H, NCH$_2$CH_2), 1.75–1.86 (m, 3H, NC$_2$H$_4$CH_2CHH), 2.38–

2.45 (m, 1H, NC$_2$H$_4$CH$_2$CHH), 3.43–3.51 (m, 2H, NCH_2), 5.04 (d, ^3J = 4.2 Hz, 1H, NCHCOOH), 5.41 (d, ^3J = 4.1 Hz, 1H, HC≡CN), 7.28 (d, ^3J = 4.2 Hz, 1H, HC=CCHO), 8.70 (s, 1H, CHO), 9.41 (brs, 1H, COOH). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 20.0 (NCH$_2$$CH_2CH_2$), 24.3 (NCH$_2CH_2$$CH_2$), 26.6 (NC$_2H_4CH_2CH_2$), 44.1 (N$CH_2CH_2CH_2$), 55.3 (N$CH$COOH), 88.9 (H$C$≡CN), 134.0 (H$C$=CCHO), 143.4 (HC=$C$N), 164.9 (HC=$C$CHO), 170.1 (CHO), 172.7 (CO$_2$H). MS (ESI+, MeOH) m/z (rel int): 178.0 (20), 224.0 (100, M + H$^+$), 246.0 (100, M + Na$^+$), 262.0 (20), 469.1 (20, 2M + Na$^+$). MS (ESI-, MeOH) m/z (rel int): 222.0 (100, M − H$^-$), 445.1 (15, 2M − H$^-$). HRMS (ESI+, MeOH) m/z: calcd for (M + H$^+$) C$_{11}$H$_{14}$NO$_4$ 224.0923; found 224.0889.

(*S*)-(1-(5-Formylfuran-2-yl)pyrrolidin-2-yl)methylmethanesulfonate (1g)

To a solution of **1c** (217.5 mg, 1.114 mmol, 1 eq) in CH$_2$Cl$_2$ (5 mL) was added triethylamine (185 µL, 1.321 mmol, 1.2 eq). The reaction was cooled to 0 °C and MsCl (100 µL, 1.266 mmol, 1.1 eq) was added dropwise. The mixture was allowed to reach rt and stirred during 2 h. The reaction was stopped by the addition of a NaHCO$_3$ saturated solution (10 mL) and organic materials were extracted with CH$_2$Cl$_2$ (4 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel flash chromatography to afford 292.9 mg of **1g** with 96% as a blue oil (petroleum ether : EtOAc 3 : 7 to 2 : 8). R$_f$: 0.28 (petroleum ether : EtOAc 2 : 8). $[\alpha]_D^{20\,°C}$ = −143 ± 10 (c = 0.029; CHCl$_3$); $[\alpha]_{546Hg}^{20\,°C}$ = −225 ± 11 (c = 0.029; CHCl$_3$). IR (neat, v, cm^{-1}): 3128, 3011, 2975, 2959, 2936, 2879, 2084, 1650, 1567, 1545, 1479, 1462, 1409, 1354, 1281, 1174, 1030, 960, 927, 914, 850, 826, 765. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.99–2.17 (m, 4H, NCH$_2$C$_2$$H_4$), 2.99 (s, 3H, CH$_3$), 3.33–3.41 (m, 1H, NC$H_2$), 3.52–3.59 (m, 1H, NC$H_2$), 4.15–4.22 (m, 1H, NC$HCH_2$OMs), 4.26–4.32 (m, 2H, NCHCH_2OMs), 5.28 (d, ^3J = 4.1 Hz, 1H, HC≡CN), 7.19 (brs, 1H, HC=CCHO), 8.97 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.5 (NCH$_2$$CH_2CH_2$), 28.3 (NCH$_2CH_2$$CH_2$), 37.2 (SCH$_3$), 48.6 (N$CH_2CH_2CH_2$), 57.8 (N$CHCH_2$OMs), 69.1 (NCH$CH_2$OMs), 86.9 (H$C$≡CN), 131.3 (H$C$=CCHO), 144.7 (HC=$C$N), 161.3 (HC=$C$CHO), 171.2 (CHO). MS (ESI+, CH$_3$CN) m/z (rel int): 250.5 (25), 273.1 (70), 274.1 (50, M + H$^+$), 501.1 (50), 569.1 (100, 2M + Na$^+$). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{11}$H$_{16}$NO$_5$S 274.0749; found 274.0764.

(*S*)-*tert*-Butyl (1-(5-formylfuran-2-yl)pyrrolidin-2-yl)methyl carbonate (1h)

To a solution of **1c** (196.3 mg, 1.005 mmol, 1 eq) in CH$_2$Cl$_2$ (10 mL) were added triethylamine (190 µL, 1.356 mmol, 1.3 eq), then Boc$_2$O (837.0 µL, 3.720 mmol, 3.5 eq). The solution was stirred at reflux for 18 h, then cooled to rt. The reaction was stopped by addition of a NaHCO$_3$ saturated solution (5 mL) and the organic layer was extracted with CHCl$_3$ (2 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 1 : 1) to afford 245.5 mg of **1h** with 83% as a brown oil. R$_f$: 0.31 (petroleum ether : EtOAc 5 : 5); 0.51 (petroleum ether : EtOAc 2 : 8). $[\alpha]_D^{20\,°C}$ = −137 ± 12 (c = 0.045; CHCl$_3$). IR (KBr, v, cm^{-1}): 3127, 2977,

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Org. Biomol. Chem., 2011, **9**, 6055–6065 | 6059

2875, 2796, 1741, 1657, 1651, 1580, 1538, 1409, 1277, 1254, 1158, 1100, 1027, 859, 768. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.42 (s, 9H, CH_3), 1.95–2.07 (m, 4H, NCH$_2$C$_2$H$_4$), 3.35–3.45 (m, 1H, NCH_2), 3.55–3.65 (m, 1H, NCH_2), 3.95–4.01 (m, 1H, NCHCH_2OBoc), 4.04–4.07 (m, 1H, NCHCH$_2$OBoc), 4.17 (dd, ^{2}J = 10.2, ^{3}J = 3.7 Hz, 1H, NCHCH_2OBoc), 5.30 (d, ^{3}J = 3.9 Hz, 1H, HC≡CN), 7.10–7.20 (m, 1H, HC≡CCHO), 8.94 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.4 (NCH$_2$$CH_2CH_2$), 27.6 (CO$CH_3$), 28.5 (NCH$_2CH_2$$CH_2$), 48.3 (N$CH_2CH_2CH_2$), 57.8 (N$CHCH_2$OBoc), 66.2 (NCH$CH_2$OBoc), 82.4 (C), 86.7 (H$C$≡CN), 131.5 (H$C$≡CCHO), 144.6 (C), 153.1 (C), 161.7 (CO$_2$Boc), 170.8 (CHO). MS (ESI+, CH$_3$CN) m/z (rel int): 218.1 (15), 262.1 (35), 318.1 (100, M + Na$^+$), 613.2 (40, 2M + Na$^+$). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + Na$^+$) C$_{15}$H$_{21}$NO$_5$Na 318.1317; found 318.1303.

(S)-5-(2-(Hydroxymethyl)pyrrolidin-1-yl)thiophene-2-carboxaldehyde (2c)

Following the general procedure for amination,[11d] 5-bromo-2-thiophenecarboxaldehyde led to 127.8 mg of **2c** as an yellow solid (23%) after silica gel flash chromatography (petroleum ether : EtOAc 2 : 8). R$_f$: 0.40 (petroleum ether : EtOAc 1 : 9); 0.11 (petroleum ether : EtOAc 1 : 1). Mp: 94.2–94.8 °C. $[\alpha]_D^{20\,°C}$ = −119 ± 8 (c = 0.102; CHCl$_3$). IR (KBr, v, cm^{-1}): 3361, 2979, 2918, 2855, 1607, 1534, 1493, 1455, 1367, 1272, 1052, 1036, 768, 744. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.01–2.25 (m, 4H, NCH$_2$C$_2$H$_4$), 2.69 (brs, 1H, OH), 3.25–3.34 (m, 1H, NCH_2), 3.48–3.55 (m, 1H, NCH_2), 3.73 (dd, ^{3}J = 5.1, ^{2}J = 1.3 Hz, 2H, NCHCH_2OH), 3.78–3.86 (m, 1H, NCHCH$_2$OH), 5.98 (d, ^{3}J = 4.4 Hz, 1H, HC≡CN), 7.44 (d, ^{3}J = 4.4 Hz, 1H, HC≡CCHO), 9.40 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.0 (NCH$_2$$CH_2CH_2$), 28.8 (NCH$_2CH_2$$CH_2$), 52.1 (N$CH_2CH_2CH_2$), 62.2 (NCH$CH_2$OH), 64.2 (N$CHCH_2$OH), 103.9 (H$C$≡CN), 126.1 (HC≡$C$N), 140.6 (H$C$≡CCHO), 164.9 (HC≡$C$CHO), 179.9 (CHO). MS (ESI-, CH$_3$CN) m/z (rel int): 297.1 (20), 311.1 (45), 325.2 (100), 339.2 (25). MS (ESI+, CH$_3$CN) m/z (rel int): 177.1 (70), 212.1 (100, M + H$^+$), 234.1 (50, M + Na$^+$), 245.1 (70), 248.2 (20), 445.1 (20, 2M + Na$^+$), 467 (20). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + Na$^+$) C$_{10}$H$_{13}$NO$_2$SNa 234.0565; found 234.0562.

(S)-1-(5-Formylthiophen-2-yl)pyrrolidine-2-carboxylic acid (2d)

In a 25 mL round-bottom flask were mixed 5-bromo-2-thiophenecarboxaldehyde (246.2 mg, 1.29 mmol, 1 eq), (−)-(L)-proline (156.7 mg, 1.36 mmol, 1.1 eq) and NaHCO$_3$ (347.7 mg, 4.46 mmol, 3 eq) in a mixture of water : ethanol 1 : 1 (15 mL). The mixture was heated at reflux for 18 h. The mixture was allowed to cool to rt and then a HCl solution (2 N) was added until pH ≈ 3 (1.7 mL). The organic materials were extracted with EtOAc (4 × 50 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 50 : 50 to 20 : 80) to afford 116.3 mg of **2d** as a blue powder (40%). R$_f$: 0.10 (CH$_2$Cl$_2$: MeOH 9 : 1). Mp: 176.9–180.0 °C. The solution was too dark therefore the optical rotation could not be measured. IR (KBr, v, cm^{-1}): 3434–2871, 1734, 1629, 1532, 1488, 1473, 1457, 1209, 1063. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.80–2.40 (m, 4H, NCH$_2$C$_2$H$_4$), 3.30–3.70 (m, 2H, NCH_2), 4.10–4.40 (m, 1H, NCHCOOH), 5.90 (d, ^{3}J = 3.2 Hz, 1H, HC≡CN), 7.44 (d, ^{3}J =

3.7 Hz, 1H, HC≡CCHO), 8.50–9.29 (br, 1H, COOH), 9.29 (s, 1H, CHO). ^{13}C NMR (acetone-d_6, 50 MHz) δ 24.7 (NCH$_2$$CH_2CH_2$), 31.6 (NCH$_2CH_2$$CH_2$), 52.0 (N$CH_2CH_2CH_2$), 63.8 (N$C$HCOOH), 104.2 (H$C$≡CN), 127.9 (H$C$≡CCHO), 140.7 (HC≡$C$N), 163.8 (HC≡$C$CHO), 172.9 (COOH), 180.2 (CHO). MS (ESI+, CH$_3$CN) m/z (rel int): 182.1 (50), 217.0 (60), 226.0 (20, M + H$^+$), 229.1 (80), 248.0 (50, M + Na$^+$), 251.1 (100), 301.1 (25), 473.1 (20, 2M + Na$^+$). MS (ESI−, CH$_3$CN) m/z (rel int): 152.0 (100), 162.9 (25), 224.0 (40, M − H$^-$), 471.1 (5, 2M − 2H+Na$^-$). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{10}$H$_{12}$NO$_3$S 226.0538; found 226.0545.

(S)-1-(5-(2-(Hydroxymethyl)pyrrolidin-1-yl)thiophen-2-yl) ethanone (2e)

In a reactor tube 5-bromo-2-acetylthiophene (998.0 mg, 4.818 mmol, 1 eq) was dissolved in a mixture of water : triethylamine 1 : 1 (8 mL), then (S)-prolinol (0.97 mL, 8.979 mmol, 2 eq) was added. The tube was sealed and the mixture was stirred at 145 °C for 66 h. The reaction was allowed to cool to rt, then stopped with a NaHCO$_3$ saturated solution (5 mL) and the organic layer was extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 1 : 1) to afford 460.0 mg of **2e** with 43% as orange crystals. R$_f$: 0.14 (petroleum ether : EtOAc 1 : 1); 0.46 (petroleum ether : EtOAc 2 : 8). Mp: 98.5–99.6 °C. $[\alpha]_D^{20\,°C}$ = −119 ± 8 (c = 0.102; CHCl$_3$). IR (KBr, v, cm^{-1}): 3321, 2965, 2927, 2874, 2849, 1580, 1534, 1518, 1475, 1359, 1325, 1130, 1097, 1072, 1022, 934, 760. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.00–2.20 (m, 4H, NCH$_2$C$_2$H$_4$), 2.38 (s, 3H, CH$_3$), 2.44–2.50 (m, 1H, OH), 3.21–3.30 (m, 1H, NCH_2), 3.46–3.53 (m, 1H, NCH_2), 3.68–3.75 (m, 2H, NCHCH_2OH), 3.75–3.85 (m, 1H, NCHCH$_2$OH), 5.88 (d, ^{3}J = 4.4 Hz, 1H, HC≡CN), 7.42 (d, ^{3}J = 4.4 Hz, 1H, HC≡CCOMe). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.0 (Me), 24.1 (NCH$_2$$CH_2CH_2$), 28.8 (NCH$_2CH_2$$CH_2$), 52.0 (N$CH_2CH_2CH_2$), 62.3 (NCH$CH_2$OH), 64.1 (N$CHCH_2$OH), 103.0 (H$C$≡CN), 126.7 (HC≡$C$N), 135.9 (H$C$≡CCOMe), 163.8 (HC≡$C$COMe), 188.4 ($C$OMe). MS (ESI+, CH$_3$CN) m/z (rel int): 226.1 (5, M + H$^+$), 248.1 (80, M + Na$^+$), 301.1 (100), 473.1 (25), 526.1 (25), 579.1 (100, M + Na$^+$), 580.2 (50). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{11}$H$_{16}$NO$_2$S 226.0902; found 226.0911.

(S)-(1-(5-Acetylthiophen-2-yl)pyrrolidin-2-yl)methylmethane sulfonate (2f)

To a solution of **2e** (309.2 mg, 1.372 mmol, 1 eq) in CH$_2$Cl$_2$ (6 mL) was added triethylamine (230 μL, 1.642 mmol, 1.2 eq). The reaction was cooled to 0 °C and MsCl (120 μL, 1.519 mmol, 1 eq) was added dropwise. The mixture was allowed to reach rt and stirred for 4 h. The reaction was stopped by addition of a NaHCO$_3$ saturated solution (10 mL) and the organic layer was extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 1 : 1) to afford 380.5 mg of **2f** with 92% as a green powder. R$_f$: 0.65 (petroleum ether : EtOAc 2 : 8). Mp: 87.4–87.8 °C. $[\alpha]_D^{20\,°C}$ = −119 ± 6 (c = 0.146; CHCl$_3$). IR (KBr, v, cm^{-1}): 3009, 2932, 2913, 2858, 2836, 1620, 1538, 1477,

1454, 1360, 1310, 1167, 989, 967, 919, 851, 772, 532. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.08–2.19 (m, 4H, NCH$_2$C$_2$H$_4$), 2.40 (s, 3H, COCH$_3$), 2.99 (s, 3H, SCH$_3$), 3.22–3.32 (m, 1H, NCH$_2$), 3.49–3.55 (m, 1H, NCH$_2$), 3.95–4.00 (m, 1H, NCHCH$_2$OMs), 4.19 (dd, ^2J = 10.2, ^3J = 6.8 Hz, 1H, NCHCH$_2$OMs), 4.28 (dd, ^2J = 10.3, ^3J = 4.0 Hz, 1H, NCHCH$_2$OMs), 5.91 (d, ^3J = 4.3 Hz, 1H, HC=CN), 7.44 (d, ^3J = 4.3 Hz, 1H, HC=CCOMe). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.7 (NCH$_2$CH$_2$CH$_2$), 25.1 (COCH$_3$), 28.8 (NCH$_2$CH$_2$CH$_2$), 37.5 (SCH$_3$), 51.7 (NCH$_2$CH$_2$CH$_2$), 60.8 (NCHCH$_2$OMs), 67.6 (NCHCH$_2$OMs), 103.2 (HC=CN), 128.1 (HC=CN), 135.4 (HC=CCOMe), 162.4 (HC=CCOMe), 188.6 (COMe). MS (ESI+, CH$_3$CN) m/z (rel int): 304.1 (30, M + H$^+$), 326.1 (100, M + Na$^+$), 629.1 (30, 2M + Na$^+$), 753.1 (15). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{12}$H$_{18}$NO$_4$S$_2$ 304.0677; found 304.0679 and calcd for (M + Na$^+$) C$_{12}$H$_{17}$NO$_4$S$_2$Na 326.0497; found 326.0511.

(S)-(1-(5-Formylthiophen-2-yl)pyrrolidin-2-yl)methylmethane sulfonate (2g)

To a solution of **2c** (99.8 mg, 0.47 mmol, 1 eq) in CH$_2$Cl$_2$ (6 mL) was added triethylamine (80 μL, 0.57 mmol, 1.2 eq). The reaction was cooled to −10 °C and MsCl (38 μL, 0.48 mmol, 1 eq) was added dropwise. The mixture was allowed to reach rt and stirred during 2 h. The reaction was stopped by addition of a NaHCO$_3$ saturated solution (10 mL), then organic materials were extracted with CH$_2$Cl$_2$ (2 × 10 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 1 : 1) to afford 134.4 mg of **2g** with 99% as an yellow oil. R$_f$: 0.16 (petroleum ether : EtOAc 1 : 1); 0.63 (EtOAc). [α]$_D^{20\,°C}$ = −159 ± 25 (c = 0.0094; CHCl$_3$). IR (neat, v, cm^{-1}): 2960, 2933, 2876, 2795, 1633, 1533, 1470, 1455, 1353, 1253, 1172, 1142, 1058, 960, 826, 746, 660. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.05–2.25 (m, 4H, NCH$_2$C$_2$H$_4$), 2.98 (s, 3H, CH$_3$), 3.20–3.35 (m, 1H, NCH$_2$), 3.40–3.60 (m, 1H, NCH$_2$), 3.95–4.10 (m, 1H, NCHCH$_2$OMs), 4.10–4.35 (m, 1H, NCHCH$_2$OMs), 6.00 (d, ^3J = 4.4 Hz, 1H, HC=CN), 7.47 (d, ^3J = 4.3 Hz, 1H, HC=CCHO), 9.47 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.5 (NCH$_2$CH$_2$CH$_2$), 28.6 (NCH$_2$CH$_2$CH$_2$), 37.3 (SCH$_3$), 51.6 (NCH$_2$CH$_2$CH$_2$), 60.7 (NCHCH$_2$OMs), 67.4 (NCHCH$_2$OMs), 103.9 (HC=CN), 127.0 (HC=CN), 140.1 (HC=CCHO), 163.4 (HC=CCHO), 180.1 (CHO). MS (ESI+, CH$_3$CN) m/z (rel int): 290.0 (80, M + H$^+$), 312.0 (100, M + Na$^+$), 533.1 (40), 601.1 (2M + Na$^+$). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + Na$^+$) C$_{11}$H$_{15}$NO$_4$S$_2$Na 312.0340; found 312.0360.

3-Morpholino-2-thiophenecarboxaldehyde (2h)

Following the general procedure for amination,[11d] 3-bromo-2-thiophenecarboxaldehyde led to 237.2 mg of **2h** as a brown oil (82%) after silica gel flash chromatography (petroleum ether : EtOAc 8 : 2 to 7 : 3). R$_f$: 0.17 (petroleum ether : EtOAc 8 : 2). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.28 (t, ^3J = 4.7 Hz, 4H, NCH$_2$), 3.78 (t, ^3J = 4.8 Hz, 4H, OCH$_2$), 6.76 (d, ^3J = 5.4 Hz, 1H, SCHCH), 7.55 (dd, ^3J = 5.3 Hz, ^4J = 0.7 Hz, 1H, SCHCH), 9.79 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 52.8 (NCH$_2$), 66.3 (OCH$_2$), 120.1 (HC=CN), 123.0 (HC=CN), 135.4 (HC=CCHO), 157.5 (HC=CCHO), 180.4 (CHO) ppm. Full agreement with the literature spectroscopic data.[17]

General procedure for 4-substituted-5-amino-2-carbonylated furan or thiophene derivatives synthesis

In a 10 mL round-bottom flask, 5-amino-2-carbonylated furan or thiophene derivative **1** or **2** (50 mg, 1 eq) and the electrophile **α**, **β**, or **γ** (2 eq) were stirred in toluene (3 mL) at reflux overnight. The crude mixture was allowed to cool to rt and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (petroleum ether : EtOAc).

Methyl 3,3,3-trifluoro-2-(5-formyl-2-morpholinofuran-3-yl)-2-hydroxypropanoate (3aα). Following the general procedure for enamine reactivity, **1a** (50.0 mg, 0.27 mmol, 1 eq) and methyl trifluoropyruvate **α** (42 μL, 0.40 mmol, 1.5 eq) afforded 82.5 mg of **3aα** as brown crystals (90%) after silica gel flash chromatography (petroleum ether : EtOAc 65 : 35 to 6 : 4). R$_f$: 0.28 (petroleum ether : EtOAc 60 : 40). Mp: 126.5–127.2 °C. IR (KBr, v, cm^{-1}): 3172, 2991, 2966, 2894, 2799, 1765, 1731, 1660, 1589, 1542, 1447, 1404, 1372, 1310, 1248, 1224, 1179, 1139, 1068, 1046, 1000, 950, 890, 867, 844, 793, 752, 687, 666. ^{1}H NMR (CDCl$_3$, 300 MHz): δ = 3.11–3.22 (m, 2H, NCH$_2$), 3.28–3.38 (m, 2H, NCH$_2$), 3.71–3.77 (m, 4H, OCH$_2$), 3.91 (s, 3H, CO$_2$CH$_3$), 7.34 (s, 1H, CH=CCHO), 8.73 (s, 1H, OH), 9.36 (s, 1H, CHO) ppm. ^{13}C NMR (CDCl$_3$, 75 MHz): δ = 50.7 (2C, NCH$_2$), 54.6 (CO$_2$CH$_3$), 66.4 (2C, OCH$_2$), 75.0 (q, $^2J_{C\text{-}F}$ = 31 Hz, CCF$_3$), 105.1 (NC=CCCF$_3$OH), 122.9 (q, $^1J_{C\text{-}F}$ = 285 Hz, CF$_3$), 124.1 (CH=CCHO), 146.2 (NC=CCCF$_3$OH), 159.7 (CH=CCHO), 168.5 (CO$_2$CH$_3$), 176.0 (CHO) ppm. ^{19}F NMR (CDCl$_3$, 188 MHz): δ = −76.9 (s, 3F) ppm. ESI-MS CH$_3$CN m/z (rel int): 338.2 (100, M + H$^+$), 360.0 (50, M + Na$^+$). ESI-MS MeOH m/z (rel int): 338.0 (100, M + H$^+$), 360.0 (50, M + Na$^+$), 370.1 (60), 382.1 (40), 697.1 (10, 2M + Na$^+$). ESI-HRMS MeOH m/z: calcd for (M + H$^+$) C$_{13}$H$_{15}$NO$_6$F$_3$ 338.0851; found 338.0841.

4-(Hexafluoro-2-hydroxypropan-2-yl)-5-morpholinofurancarboxaldehyde (3aβ). Following the general procedure for enamine reactivity, **1a** (75 mg, 0.41 mmol, 1 eq) and 1,1,1,3,3,3-hexafluoroacetone sesquihydrate **β** (95 μL, 0.83 mmol, 2 eq) afforded 120.9 mg of **3aβ** as an yellow solid (85%) after silica gel flash chromatography (petroleum ether : EtOAc 9 : 1 to 8 : 2). R$_f$: 0.29 (petroleum ether : EtOAc 8 : 2). Mp: 107.1–108.2 °C. IR (KBr, v, cm^{-1}): 3093, 2918, 2765, 1670, 1627, 1540, 1448, 1391, 1365, 1271, 1259, 1219, 1050, 1172, 1146, 951, 879, 765, 726. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.16–3.21 (m, 4H, NCH$_2$), 3.84–3.88 (m, 4H, OCH$_2$), 7.23 (s, 1H, CH=CCHO), 8.30 (s, 1H, OH), 9.58 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 51.7 (2C, NCH$_2$), 66.4 (2C, OCH$_2$), 74.5 (sep, $^2J_{C\text{-}F}$ = 31 Hz, CCF$_3$), 106.6 (NC=CC(CF$_3$)$_2$), 120.0 (CH=CCHO), 122.1 (q, $^1J_{C\text{-}F}$ = 337 Hz, 2C, CF$_3$), 148.9 (NC=CC(CF$_3$)$_2$), 158.1 (CH=CCHO), 177.1 (CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −77.8 (s, 6F). MS (ESI, CH$_3$CN) m/z (rel int): 348.0 (100, M + H$^+$), 382.1 (30). HRMS (ESI) m/z: calcd for (M + H$^+$) C$_{12}$H$_{12}$NO$_4$F$_6$ 348.0671; found 348.0655.

4-(1,3-Dichloro-1,1,3,3-tetrafluoro-2-hydroxypropan-2-yl)-5-morpholinofuran-2-carboxaldehyde (3aγ). Following the general procedure for enamine reactivity, **1a** (75.0 mg, 0.41 mmol, 1 eq) and 1,3-dichloro-1,1,3,3-tetrafluoroacetone **γ** (135 μL, 1.03 mmol, 2.5 eq) afforded 120.2 mg of **3aγ** as a white solid (78%) after silica gel flash chromatography (petroleum ether : EtOAc 8 : 2). R$_f$: 0.34 (petroleum ether : EtOAc 8 : 2). Mp: 138.8–139.2 °C. IR (KBr, v, cm^{-1}): 3144, 2923, 2860, 2774, 1766, 1658, 1592,

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Org. Biomol. Chem., 2011, **9**, 6055–6065 | 6061

1557, 1446, 1397, 1362, 1337, 1311, 1292, 1269, 1235, 1210, 1175, 1143, 1112, 1068, 1005, 942, 922, 874, 840, 785, 757, 705, 687, 654. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.19–3.23 (m, 4H, NCH_2), 3.85–3.89 (m, 4H, OCH_2), 7.23 (s, 1H, CH=CCHO), 8.73 (s, 1H, OH), 9.56 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 51.5 (2C, NCH$_2$), 66.4 (2C, OCH$_2$), 80.7 (pent, $^2J_{C\text{-}F}$ = 27 Hz, CCF$_2$Cl), 109.4 (NC=CC(CF$_2$Cl)$_2$), 120.4 (CH=CCHO), 128.4 (t, $^1J_{C\text{-}F}$ = 301 Hz, 2C, CF$_2$Cl), 148.6 (NC=CC(CF$_2$Cl)$_2$), 157.9 (CH=CCHO), 177.3 (CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −64.2–(−64.1) (m, 1F)), −63.5–(−63.3) (m, 1F), −61.3–(−61.1) (m, 1F)), −60.4–(−60.3) (m, 1F). MS (ESI, CH$_3$CN) m/z (rel int): 380.0 (100, M + H$^+$). MS (ESI, MeOH) m/z (rel int): 380.0 (100, M + H$^+$), 382.0 (75), 412.0 (50, M + MeOH + H$^+$), 414.0 (40). HRMS (ESI, MeOH) m/z: calcd for (M + H$^+$) C$_{12}$H$_{12}$NO$_4$F$_4$Cl$_2$ 380.0080; found 380.0071.

4-(Hexafluoro-2-hydroxypropan-2-yl)-5-piperidinofuran-2-car-boxaldehyde (3bβ). Following the general procedure for enamine reactivity **1b** (40 mg, 0.22 mmol, 1 eq) and 1,1,1,3,3,3-hexafluoroacetone sesquihydrate **β** (50 μL, 0.44 mmol, 2 eq) afforded 32.1 mg of **3bβ** as an yellow oil (42%) after silica gel flash chromatography (petroleum ether : EtOAc 70 : 30 to 55 : 45). R$_f$: 0.30 (petroleum ether : EtOAc 8 : 2). ^{1}H NMR (acetone-d_6, 300 MHz) δ 3.16–3.21 (m, 4H, NCH_2), 3.84–3.88 (m, 4H, OCH_2), 7.23 (s, 1H, CH=CCHO), 8.30 (s, 1H, OH), 9.58 (s, 1H, CHO). ^{13}C NMR (acetone-d_6, 75 MHz) δ 23.8 (NCH$_2$CH$_2$CH$_2$), 26.2 (2C, NCH$_2$CH$_2$), 53.5 (2C, NCH$_2$), 75.7 (q, $^2J_{C\text{-}F}$ = 31 Hz, CCF$_3$), 104.7 (NC=CC(CF$_3$)$_2$), 121.7 (CH=CCHO), 124.2 (q, $^1J_{C\text{-}F}$ = 327 Hz, 2C, CF$_3$), 149.7 (NC=CC(CF$_3$)$_2$), 160.8 (CH=CCHO), 178.1 (CHO). MS (ESI, CH$_3$CN) m/z (rel int): 368.2 (95, M + Na$^+$), 400.3 (100), 593.3 (40). HRMS (EI) m/z: calcd for (M$^{+\bullet}$) C$_{13}$H$_{13}$NO$_3$F$_6$ 345.0800; found 345.0800.

(2S)-1-(3-(1-(Methoxycarbonyl)-2,2,2-trifluoro-1-hydroxyethyl)-5-formylfuran-2-yl)pyrrolidine-2-carboxylic acid (3dα). To a solution of **1d** (70 mg, 0.320 mmol, 1 eq) in CH$_2$Cl$_2$ (4 mL) was added methyl trifluoropyruvate **α** (42 μL, 0.415 mmol, 1.3 eq) at rt. After 18 h, the solvent was evaporated and the residue was purified by silica gel flash chromatography (CH$_2$Cl$_2$: MeOH 97 : 3 to 92 : 8) to afford 56.6 mg of **3dα** as a red brown oil (50%, 2 diastereomers in the ratio 6 : 1). R$_f$: 0.09 (CH$_2$Cl$_2$: MeOH 95 : 5). IR (KBr, ν, cm^{-1}): 3154, 2880, 2360, 2325, 1743, 1626, 1538, 1436, 1235, 1149, 1100, 956, 896, 783, 734. ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.94–2.42 (m, 4H, NCH$_2$C$_2H_4$), 3.58–3.85 (m, 2H, NCH_2), 3.88 (s, 0.4H, CH$_3$), 3.93 (s, 2.5H, CH$_3$), 4.90 (dd, ^3J = 8.2 and 5.2 Hz, 1H, NCHCOOH), 7.40–7.42 (m, 1H, HC=CCHO), 8.84 (s, 0.85H, CHO), 8.91 (s, 0.15H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.9 (0.2C, NCH$_2$$CH_2CH_2$), 24.8 (1C, NCH$_2$$CH_2CH_2$), 29.6 (1C, NCH$_2CH_2$$CH_2$), 30.2 (0.2C, NCH$_2CH_2$$CH_2$), 50.9 (1C, N$CH_2CH_2CH_2$), 54.0 (0.2C, N$C$HCOOH), 55.0 (1C, N$C$HCOOH), 62.0 (1C, CO$_2$$CH_3$), 74.9 (1C, CCF$_3$), 97.3 (1C), 132.3 (HC=CCHO), 141.7 (1C), 159.9 (1C), 167.5 (1C, CO$_2$CH$_3$), 169.8 (1C), 172.2 (1C, CHO), 174.3 (1C, COOH). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −76.6 (s, 0.6F), −76.2 (s, 3F). MS (ESI, CH$_3$CN) m/z (rel int): 366.0 (20, M + H$^+$), 388.0 (100, M + Na$^+$), 753.1 (30, 2M + Na$^+$). HRMS (ESI, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{14}$H$_{15}$NO$_7$F$_3$ 366.0801; found 366.0800.

1-(3-(1-Methoxycarbonyl)-(2,2,2-trifluoro-1-hydroxyethyl)-5-formylfuran-2-yl)piperidine-2-carboxylic acid (3eα). Following the general synthesis procedure of **1c**, **1e** (70 mg, 0.31 mmol, 1 eq) and methyl trifluoropyruvate **α** (42 μL, 0.40 mmol, 1.3 eq) afforded 41.8 mg of **3eα** as a brown oil (79%, 2 diastereomers in the ratio 1 : 1) after silica gel flash chromatography (CH$_2$Cl$_2$: MeOH 97.5 : 2.5 to 95 : 5). R$_f$: 0.11 (CH$_2$Cl$_2$: MeOH 95 : 5). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.65–1.68 (m, 3H, NCH$_2$CH_2), 1.75–1.86 (m, 3H, NC$_2$H$_4$CH_2CHH), 2.38–2.45 (m, 1H, NC$_2$H$_4$CH$_2$CHH), 3.30–3.47 (m, 2H, NCH_2), 3.89 (s, 3H, CO$_2$CH_3), 4.38 (t, ^3J = 4.8 Hz, 0.5H, NCHCOOH), 4.44 (t, ^3J = 4.8 Hz, 0.5H, NCHCOOH), 7.35 (s, 0.5H, HC=CCHO), 7.36 (s, 0.5H, HC=CCHO), 9.28 (s, 0.5H, CHO), 9.29 (s, 0.5H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 21.2 (NCH$_2$CH$_2$$CH_2$), 24.7 (NCH$_2$$CH_2CH_2$), 27.8 (NC$_2H_4CH_2$$CH_2$), 49.2 (N$CH_2CH_2CH_2$), 54.5 and 54.6 (N$C$HCOOH), 60.1 and 60.4 (CO$_2$$CH_3$), 75.1–75.6 (m, CCF$_3$), 103.7 and 104.0 (HC=CN), 125.6 and 125.8 (HC=CCHO), 145.1 and 145.2 (HC=CN), 160.1 and 160.5 (C), 168.3 and 168.7 (CO$_2$CH$_3$), 175.5 and 175.6 (CHO), 175.7 and 175.8 (COOH). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −76.7 (s, 3F), −76.6 (s, 3F). MS (ESI, CH$_3$CN) m/z (rel int): 380.0 (20, M + H$^+$), 402.0 (100, M + Na$^+$), 781.1 (20, 2M + Na$^+$). HRMS (ESI, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{15}$H$_{17}$NO$_7$F$_3$ 380.0957; found 380.0950.

5-(N-Allyl-N-methylamino)-4-(hexafluoro-2-hydroxypropan-2-yl)furan-2-carboxaldehyde (3fβ). Following the general procedure for enamine reactivity, **1f** (50.0 mg, 0.30 mmol, 1 eq) and 1,1,1,3,3,3-hexafluoroacetone sesquihydrate **β** (68 μL, 0.60 mmol, 2 eq) afforded 61.0 mg of **3fβ** as an yellow oil (57%) after silica gel flash chromatography (petroleum ether : EtOAc 9 : 1). R$_f$: 0.45 (petroleum ether : EtOAc 1 : 1). ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.82 (s, 3H, NCH$_3$), 3.65 (d, ^3J = 6.9 Hz, 2H, NCH_2CHCH$_2$), 5.23–5.30 (m, 2H, NCH$_2$CHCH_2), 5.75–5.86 (m, 1H, NCH$_2$CHCH$_2$), 7.22 (s, 1H, HC=CCHO), 9.55 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 40.5 (NCH$_3$), 58.1 (NCH$_2$CH=CH$_2$), 73.7 (q, $^2J_{C\text{-}F}$ = 31 Hz, CCF$_3$), 106.0 (NC=CC(CF$_3$)$_2$), 119.3 (CH=CCHO), 120.2 (NCH$_2$CH=CH$_2$), 122.9 (q, $^1J_{C\text{-}F}$ = 288 Hz, 2C, CF$_3$), 130.2 (NCH$_2$$C$H=CH$_2$), 147.7 (N$C$=CC(CF$_3$)$_2$) 158.3 (CH=$C$CHO), 176.7 (CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −78.3 (s, 6F). MS (CI, CH$_4$) m/z (rel int): 332.0 (100, M + H$^+$), 360.0 (20, M + C$_2$H$_5$$^+$), 372.0 (10, M + C$_3H_5$$^+$). MS (ESI, CH$_3$CN) m/z (rel int): 332.0 (100, M + H$^+$). HRMS (EI) m/z: calcd for (MH$^{+\bullet}$) C$_{12}$H$_{11}$NO$_3$F$_6$ 331.0643; found 331.0643.

Methyl 3,3,3-trifluoro-2-(5-formyl-2-((S)-2-((methylsulfony-loxy)methyl)pyrrolidin-1-yl)furan-3-yl)-2-hydroxypropanoate (3gα). To a solution of **1g** (18.5 mg, 0.068 mmol, 1 eq) in toluene (0.50 mL) was added methyl trifluoropyruvate **α** (20 μL, 0.189 mmol, 2.5 eq) at rt. The solution was stirred at reflux for 16 h, then cooled to rt. The solvent was evaporated and the residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 5 : 5) to afford 20.9 mg of **3gα** as an brown oil (72%, 2 diastereomers in the ratio 2 : 1). R$_f$: 0.34 and 0.40 (petroleum ether : EtOAc 1 : 1); 0.66 (petroleum ether : EtOAc 2 : 8). IR (KBr, ν, cm^{-1}): 3434, 3030, 2959, 2853, 1754, 1668, 1595, 1537, 1441, 1354, 1285, 1258, 1174, 949, 904, 847, 798, 784. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.60–1.70 (m, 2H, NCH$_2$C$_2H_4$), 1.93–2.04 (m, 4H, NCH$_2$C$_2H_4$), 3.10 (s, 4.5H, SCH$_3$), 3.13–3.36 (m, 3.5H, NCH_2 + NCHCH_2OMs), 3.45 (dd, ^2J = 12.4,

^3J = 3.0 Hz, 0.5H, NCHCH_2OMs), 3.56 (dd, ^2J = 12.6, ^3J = 2.8 Hz, 1H, NCHCH_2OMs), 3.58–3.90 (m, 0.5H, NCHCH_2OMs), 3.92 (s, 3H, OCH_3), 3.93 (s, 1.5H, OCH_3), 3.95–3.99 (m, 0.5H, NCHCH_2OMs), 4.85–4.92 (m, 1.5H, NCHCH_2OMs), 5.55 (brs, 1H, OH), 5.83 (brs, 0.5H, OH), 7.34–7.36 (m, 1.5H, HC=CCHO), 9.41 (s, 1H, CHO), 9.43 (s, 0.5H, CHO). ^{13}C NMR (CDCl$_3$, 50 MHz) δ 21.4 (0.5C, NCH$_2$CH_2CH$_2$), 21.5 (1C, NCH$_2$CH_2CH$_2$), 29.4 (1C, NCH$_2$CH$_2$CH_2), 30.9 (0.5C, NCH$_2$CH$_2$CH_2), 38.5 (1C, SCH$_3$), 38.6 (0.5C, SCH$_3$), 50.5 (1C, NCH_2CH$_2$CH$_2$), 50.9 (0.5C, NCH_2CH$_2$CH$_2$), 53.4 (0.5C, OCH$_3$), 54.5 (1C, OCH$_3$), 54.6 (0.5C, NCHCH$_2$OMs), 54.9 (1C, NCHCH$_2$OMs), 73.7 (0.5C, NCHCH$_2$OMs), 74.2 (1C, NCHCH$_2$OMs), 74.9 (q, $^2J_{C\text{-}F}$ = 31 Hz, 1C, CCF$_3$), 75.0 (q, $^2J_{C\text{-}F}$ = 31 Hz, 0.5C, CCF$_3$), 105.6 (1C, C=CN), 106.6 (0.5C, C=CN), 122.9 (q, $^1J_{C\text{-}F}$ = 285 Hz, 1.5C, CF$_3$), 123.5 (0.5C, HC=CCHO), 123.8 (1C, HC=CCHO), 146.3 (1C, C=CN), 146.7 (0.5C, C=CN), 159.0 (0.5C, HC=CCHO), 159.4 (1C, HC=CCHO), 168.0 (0.5C, CO$_2$CH$_3$), 168.3 (1C, CO$_2$CH$_3$), 176.1 (1C, CHO), 176.3 (0.5C, CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −76.8 (s, 3F), −76.9 (s, 1.5F). MS (ESI+, CH$_3$CN) m/z (rel int): 242.3 (30), 452.1 (100, M + Na$^+$), 881.1 (100, 2M + Na$^+$). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + Na$^+$) C$_{15}$H$_{18}$NO$_8$SF$_3$Na 452.0603; found 452.0603.

Methyl 2-(2-((S)-2-((tert-butoxycarbonyloxy)methyl) pyrrolidin-1-yl)-5-formylfuran-3-yl)-3,3,3-trifluoro-2-hydroxy propanoate (3hα). To a solution of **1h** (245.0 mg, 0.829 mmol, 1 eq) in CH$_2$Cl$_2$ (10 mL) was added methyl trifluoropyruvate α (270 µL, 2.551 mmol, 3.0 eq) at rt. The solution was stirred at rt for 16 h, then the solvent was evaporated and the residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 1 : 1) to afford 229.4 mg of **3hα** as an yellow oil (62%, 2 diastereomers in the ratio 5 : 1). R$_f$: 0.69 (petroleum ether : EtOAc 1 : 1). IR (in CCl$_4$, v, cm^{-1}): 3411–3233, 2980, 2896, 1747, 1660, 1651, 1645, 1583, 1548, 1538, 1455, 1395, 1370, 1281, 1255, 1155, 1103, 1026, 998, 957, 911, 861, 796, 786, 733, 679, 648. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.39 (s, 3H, OBoc), 1.40 (s, 9H, OBoc), 1.76–1.97 (m, 3.8H, NCH$_2$C$_2$H$_4$), 1.99–2.11 (m, 1.3H, NCH$_2$C$_2$H$_4$), 3.41–3.47 (m, 1H, NCH_2), 3.49–3.57 (m, 1.2H, NCH_2), 3.86 (s, 0.8H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 4.05 (d, ^3J = 4.6 Hz, 2.5H, NCHCH_2OBoc), 4.33–4.42 (m, 1.3H, NCHCH$_2$OBoc), 4.80–5.06 (br, 1H, OH), 5.05–5.20 (br, 0.2H, OH), 7.30–7.32 (m, 1.2H, HC=CCHO), 9.15 (s, 1H, CHO), 9.16 (s, 0.2H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.2 (0.2C, NCH$_2$CH_2CH$_2$), 24.9 (1C, NCH$_2$CH_2CH$_2$), 27.5 (OCO$_2$CH$_3$), 27.6 (3C, NCH$_2$CH$_2$CH_2), 51.7 (0.2C, NCH_2CH$_2$CH$_2$), 52.9 (1C, NCH_2CH$_2$CH$_2$), 54.3 (0.2C, OCH$_3$), 54.6 (1C, OCH$_3$), 59.0 (1C, NCH), 59.2 (0.2C, NCH), 66.8 (1C, OCH_2), 75.1 (q, $^2J_{C\text{-}F}$ = 30 Hz, 1C, CCF$_3$), 75.4 (q, $^2J_{C\text{-}F}$ = 30 Hz, 0.2C, CCF$_3$), 82.2 (1C, C), 82.3 (0.2C, C), 99.2 (1C, C), 99.7 (0.2C, C), 122.9 (q, $^1J_{C\text{-}F}$ = 286 Hz, 1C, CF$_3$), 126.9 (0.2C, HC=CCHO), 127.3 (1C, HC=CCHO), 143.5 (1C, C), 143.9 (0.2C, C), 153.2 (0.2C, C), 153.3 (1C, C), 158.1 (0.2C, OCO$_2$), 159.0 (1C, OCO$_2$), 168.8 (0.2C, CO$_2$), 169.5 (1C, CO$_2$), 173.8 (1C, CHO), 173.9 (0.2C, CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −76.8 (s, 3F), −77.4 (s, 0.6F). MS (ESI+, CH$_3$CN) m/z (rel int): 474.1 (20, M + Na$^+$), 635.2 (10), 925.2 (100, 2M + Na$^+$), 926.2 (40). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + Na$^+$) C$_{19}$H$_{24}$NO$_8$F$_3$Na 474.1352; found 474.1351.

Methyl 3,3,3-trifluoro-2-(5-formyl-2-morpholinothiophen-3-yl)-2-hydroxypropanoate (4a). Following the general procedure for

enamine reactivity, **2a** (195.3 mg, 0.990 mmol, 1 eq) and methyl trifluoropyruvate (320 µL, 3.023 mmol, 3.0 eq) afforded 292.0 mg of **4a** as white crystals (84%) after silica gel flash chromatography (petroleum ether : EtOAc 80 : 20). R$_f$: 0.19 (petroleum ether : EtOAc 80 : 20). Mp: 138.1–139.4 °C. IR (KBr, v, cm^{-1}): 3433, 3112, 2963, 2894, 2858, 1737, 1681, 1464, 1435, 1372, 1283, 1251, 1208, 1161, 1121, 997, 920, 892, 650. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 2.87–2.94 (m, 2H, NCH_2), 3.07–3.14 (m, 2H, NCH_2), 3.75–3.88 (m, 4H, OCH_2), 3.88 (s, 3H, CO$_2$CH_3), 7.17 (brs, 1H, OH), 7.79 (d, ^4J = 1.1 Hz, 1H, CH=CCHO), 9.78 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 54.0 (CO$_2$$CH_3$), 55.8 (2C, NCH$_2$), 66.34 (2C, OCH$_2$), 77.2 (q, $^2J_{C\text{-}F}$ = 30 Hz, CCF$_3$), 123.0 (q, $^1J_{C\text{-}F}$ = 285 Hz, CF$_3$), 126.1 (NC=CCF$_3$OH), 135.3 (CH=CCHO), 137.8 (NC=CCCF$_3$OH), 164.9 (CH=CCHO), 168.2 (CO$_2$CH$_3$), 182.7 (CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −76.7 (s, 3F). MS (ESI+, CH$_3$CN) m/z (rel int): 217.1 (65), 262.1 (20), 318.1 (30), 376.0 (50, M + Na$^+$), 418.1 (30), 474.1 (100), 729.1 (20, 2M + Na$^+$). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + Na$^+$) C$_{13}$H$_{14}$NO$_5$F$_3$SNa 376.0442; found 376.0434.

Methyl 3,3,3-trifluoro-2-(5-formyl-2-(piperidin-1-yl)thiophen-3-yl)-2-hydroxypropanoate (4b). Following the general procedure for enamine reactivity, **2b** (51.5 mg, 0.264 mmol, 1 eq) and methyl trifluoropyruvate (32 µL, 0.312 mmol, 1.2 eq) afforded 61.1 mg of **4b** as white solid (66%) after silica gel flash chromatography (petroleum ether : EtOAc 85 : 15). R$_f$: 0.41 (petroleum ether : EtOAc 80 : 20); 0.81 (petroleum ether : EtOAc 60 : 40). Mp: 112.4–113.2 °C. IR (KBr, v, cm^{-1}): 3244, 2943, 2854, 2815, 1758, 1659, 1443, 1416, 1374, 1315, 1279, 1245, 1214, 1179, 1152, 1124, 1042, 1028, 1008, 996, 860, 786, 724, 664, 648. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.58–1.64 (m, 2H, NCH$_2$CH$_2$CH_2), 1.72–1.79 (m, 4H, NCH$_2$CH_2), 2.86–2.93 (m, 2H, NCH_2), 2.96–3.04 (m, 2H, NCH_2), 3.88 (s, 3H, CO$_2$CH_3), 7.79 (d, ^4J = 1.4 Hz, 1H, CH=CCHO), 8.60 (brs, 1H, OH), 9.80 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.0 (1C, NCH$_2$CH$_2$CH_2), 25.6 (2C, NCH$_2$CH_2CH$_2$), 53.8 (CO$_2$$CH_3$), 57.7 (2C, NCH$_2$), 77.7 (q, $^2J_{C\text{-}F}$ = 30 Hz, CCF$_3$), 123.2 (q, $^1J_{C\text{-}F}$ = 283 Hz, CF$_3$), 125.6 (NC=CCCF$_3$OH), 135.2 (CH=CCHO), 138.0 (NC=CCCF$_3$OH), 165.9 (CH=CCHO), 168.0 (CO$_2$CH$_3$), 182.7 (CHO). MS (ESI+, CH$_3$CN) m/z (rel int): 352.1 (15, M + H$^+$), 374.1 (100, M + Na$^+$), 725.1 (70, 2M + Na$^+$). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{14}$H$_{17}$NO$_4$F$_3$S 352.0830; found 352.0816.

(2S)-1-(3-(1-Methoxycarbonyl)-2,2,2-trifluoro-1-hydroxyethyl-5-formylthiophen-2-yl)pyrrolidine-2-carboxylic acid (4d). To a solution of **2d** (185.6 mg, 0.824 mmol, 1 eq) in CH$_2$Cl$_2$ (6 mL) was added methyl trifluoropyruvate (135 µL, 1.275 mmol, 1.5 eq) at rt. After 42 h, the solvent was evaporated and the residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 1 : 1 to 0 : 1) to afford 312.5 mg of **4d** as an yellow oil (99%, 2 diastereomers in the ratio 2 : 1). R$_f$: 0.15 (petroleum ether : EtOAc 1 : 1); 0.04–0.25 (CH$_2$Cl$_2$: MeOH 95 : 5). IR (KBr, v, cm^{-1}): 3450–2400, 1755, 1747, 1651, 1633, 1470, 1462, 1454, 1416, 1281, 1241, 1159, 1122, 1094, 1027, 996, 937, 730, 675. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.93–2.20 (m, 4.5H, NCH$_2$C$_2$H$_4$), 2.35–2.47 (m, 1.5H, NCH$_2$C$_2$H$_4$), 3.02–3.10 (m, 0.5H, NCH_2), 3.18–3.25 (m, 1H, NCH_2), 3.58–3.71 (m, 1.5H, NCH_2), 3.81 (s, 3H, CH$_3$), 3.84 (s, 1.5H, CH$_3$), 3.88 (s, 1.5H, OH), 4.22 (dd, ^3J = 8.6 and 5.0 Hz, 0.5H, NCHCOOH), 4.29 (dd, ^3J = 8.4 and 5.3 Hz, 1H, NCHCOOH), 6.77–7.60 (brs, COOH), 7.73 (d, ^4J = 1.5 Hz, 1H, HC=CCHO), 7.76 (d,

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Org. Biomol. Chem., 2011, **9**, 6055–6065 | 6063

$^4J = 1.3$ Hz, 0.5H, HC=CCHO), 9.62 (s, 1H, CHO), 9.65 (s, 0.5H, CHO). ^{13}C NMR (CDCl$_3$, 50 MHz) δ 24.2 (1C, NCH$_2$$CH_2CH_2$), 24.4 (0.5C, NCH$_2$$CH_2CH_2$), 30.5 (1C, NCH$_2CH_2$$CH_2$), 30.7 (0.5C, NCH$_2CH_2$$CH_2$), 54.0 (0.5C, OCH$_3$), 54.3 (1C, OCH$_3$), 57.6 (1C, N$CH_2CH_2CH_2$), 58.1 (0.5C, N$CH_2CH_2CH_2$), 67.1 (1C, N$CH$COOH), 67.6 (0.5C, N$CH$COOH), 77.2–78.1 (m, CCF$_3$), 90.6 (q, $^2J_{C-F}$ = 34 Hz, CCF$_3$), 122.8 (1C, C=CN), 123.0 (q, $^1J_{C-F}$ = 285 Hz, CF$_3$), 123.8 (0.5C, C=CN), 133.7 (1C, C=CN), 134.4 (0.5C, C=CN), 137.4 (0.5C, HC=CCHO), 137.7 (1C, HC=CCHO), 162.9 (0.5C, HC=CCHO), 163.5 (1C, HC=CCHO), 167.5 (1C, CO$_2$CH$_3$), 167.9 (0.5C, CO$_2$CH$_3$), 176.8 (1C, CO$_2$CH$_3$), 176.9 (0.5C, CO$_2$CH$_3$), 182.9 (1.5C, CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −76.2 (s, 3F), −76.6 (s, 1.5F). MS (ESI−, CH$_3$CN) m/z (rel int): 234.0 (20), 304.0 (15), 380.0 (100, M − H$^-$), 783.1 (5, 2M − 2H + Na$^-$). MS (ESI+, CH$_3$CN) m/z (rel int): 226.0 (30), 279.1 (15), 336.0 (30), 382.0 (100, M + H$^+$), 404.0 (60, M + Na$^+$), 785.1 (15, 2M + Na$^+$). HRMS (ESI−, CH$_3$CN) m/z: calcd for (M − H$^-$) C$_{14}$H$_{13}$NO$_6$SF$_3$ 380.0416; found 380.0435. HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{14}$H$_{15}$NO$_6$SF$_3$ 382.0572; found 382.0556.

Methyl 2-(5-acetyl-2-((S)-2-((methylsulfonyloxy)methyl)pyrrolidin-1-yl)thiophen-3-yl)-3,3,3-trifluoro-2-hydroxy propanoate (4f). In a 10 mL round bottom flask was introduced **2f** (101.5 mg, 0.335 mmol, 1 eq) dissolved in toluene (5 mL). Then methyl trifluoropyruvate (110 μL, 1.039 mmol, 3 eq) was added and the solution was stirred at reflux for 18 h, then cooled to rt. The solvent was evaporated and the residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 7 : 3 to 6 : 4) to afford 137.3 mg of **4f** as an yellow powder (89%, 2 diastereomers in the ratio 1 : 1). R$_f$: 0.47 (petroleum ether : EtOAc 6 : 4); 0.67 (petroleum ether : EtOAc 2 : 8). Mp: 54.1–59.3 °C. IR (KBr, v, cm^{-1}): 3441, 3030, 2959, 2847, 1752, 1669, 1445, 1359, 1279, 1250, 1173, 1120, 953, 932, 905, 844. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.69–2.12 (m, 8H, NCH$_2$C$_2$$H_4$), 2.53 (s, 3H, COCH$_3$), 2.54 (s, 3H, COCH$_3$), 2.83–3.12 (m, 6H, 4H NCH_2 + 1H OH + 2H NCHCH_2OMs), 3.12 (s, 3H, SCH$_3$), 3.15 (s, 3H, SCH$_3$), 3.22–3.29 (m, 2H, NCHCH_2OMs), 3.87 (s, 3H, OCH$_3$), 3.90 (s, 3H, OCH$_3$), 3.91–3.92 (m, 1H, OH), 4.94–5.01 (m, 2H, NCHCH$_2$OMs), 7.64–7.67 (m, 2H, HC=CCOMe). ^{13}C NMR (CDCl$_3$, 50 MHz) δ 21.0 (NCH$_2$$CH_2CH_2$), 21.5 (NCH$_2$$CH_2CH_2$), 25.9 (2C, CO$CH_3$), 28.6 (NCH$_2CH_2$$CH_2$), 28.8 (NCH$_2CH_2$$CH_2$), 38.5 (2C, SCH$_3$), 53.8 (OCH$_3$), 53.9 (OCH$_3$), 55.4 (N$CH_2CH_2CH_2$), 56.1 (N$CH_2CH_2CH_2$), 59.5 (NCH$CH_2$OMs), 59.8 (NCH$CH_2$OMs), 73.3 (N$CHCH_2$OMs), 73.6 (N$CHCH_2$OMs), 76.6–78.6 (m, 2C, CCF$_3$), 123.0 (2q, $^1J_{C-F}$ = 288 Hz, 2C, CF$_3$), 125.9 (C=CN), 126.5 (C=CN), 130.5 (2q, $^3J_{C-F}$ = 2 Hz, 2C, HC=CCOMe), 138.9 (C=CN), 139.4 (C=CN), 162.5 (HC=CCOMe), 162.6 (HC=CCOMe), 167.9 (CO$_2$CH$_3$), 168.1 (CO$_2$CH$_3$), 190.1 (2C, COMe). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −76.9 (s, 3F), −76.3 (s, 3F). MS (ESI+, CH$_3$CN) m/z (rel int): 460.1 (5, M + H$^+$), 482.0 (100, M + Na$^+$), 638.1 (15), 941.1 (15, 2M + Na$^+$), 1097.1 (10). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{16}$H$_{21}$NO$_7$F$_3$S$_2$ 460.0712; found 460.0733 and calcd for (M + Na$^+$) C$_{16}$H$_{20}$NO$_7$F$_3$S$_2$Na 482.0531; found 482.0533.

Methyl 3,3,3-trifluoro-2-(5-formyl-2-((S)-2-((methylsulfonyloxy)methyl)pyrrolidin-1-yl)thiophen-3-yl)-2-hydroxypropanoate (4g). To a solution of **2g** (119.9 mg, 0.414 mmol, 1 eq) in toluene (5 mL) was added methyl trifluoropyruvate (88 μL,

0.831 mmol, 2.0 eq) at rt. The solution was stirred at reflux for 24 h, then cooled to rt. The solvent was evaporated and the residue was purified by silica gel flash chromatography (petroleum ether : EtOAc 7 : 3) to afford 126.9 mg of **4g** as an yellow oil (69%, 2 diastereomers in the ratio 2 : 1). R$_f$: 0.42 (petroleum ether : EtOAc 1 : 1). IR (in CCl$_4$, v, cm^{-1}): 2956, 2925, 2854, 1749, 1682, 1581, 1572, 1537, 1461, 1347, 1261, 1178, 1166, 1157, 1099, 1014. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.67–1.82 (m, 1.5H, NCH$_2$C$_2$$H_4$), 1.89–2.08 (m, 4.5H, NCH$_2$C$_2$$H_4$), 2.84–3.09 (m, 4.5H, NCH_2 + NCHCH_2OMs), 3.10 (s, 1.5H, SCH$_3$), 3.12 (s, 3H, SCH$_3$), 3.22–3.27 (m, 0.5H, NCHCH$_2$OMs), 3.32–3.37 (m, 1H, NCHCH$_2$OMs), 3.85 (s, 3H, OCH$_3$), 3.88 (s, 1.5H, OCH$_3$), 4.89–4.97 (m, 1.5H, NCHCH$_2$OMs), 7.76–7.79 (m, 1.5H, HC=CCHO), 9.77 (s, 1H, CHO), 9.78 (s, 0.5H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 21.1 (0.5C, NCH$_2$$CH_2CH_2$), 21.6 (1C, NCH$_2$$CH_2CH_2$), 28.7 (0.5C, NCH$_2CH_2$$CH_2$), 28.9 (1C, NCH$_2CH_2$$CH_2$), 38.4 (1C, SCH$_3$), 38.5 (0.5C, SCH$_3$), 54.0 (1.5C, OCH$_3$), 55.2 (1C, N$CH_2CH_2CH_2$), 54.0 (0.5C, N$CH_2CH_2CH_2$), 59.4 (0.5C, NCH$CH_2$OMs), 59.8 (1C, NCH$CH_2$OMs), 73.3 (0.5C, N$CHCH_2$OMs), 73.6 (1C, N$CHCH_2$OMs), 77.2–77.6 (m, 1.5C, CCF$_3$), 123.0 (q, $^1J_{C-F}$ = 285 Hz, 1.5C, CF$_3$), 126.1 (1C, C=CN), 126.8 (0.5C, C=CN), 135.1 (0.5C, HC=CCHO), 135.3 (1C, HC=CCHO), 137.8 (1C, C=CN), 138.3 (0.5C, C=CN), 164.1 (0.5C, HC=CCHO), 164.3 (1C, HC=CCHO), 167.9 (0.5C, CO$_2$CH$_3$), 168.1 (1C, CO$_2$CH$_3$), 182.6 (1C, CHO), 182.7 (0.5C, CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −76.9 (s, 1.5F), −76.8 (s, 3F). MS (ESI-, CH$_3$CN) m/z (rel int): 416.1 (30), 430.0 (100), 460.0 (50), 480.0 (35). MS (ESI+, CH$_3$CN) m/z (rel int): 446.0 (100, M + H$^+$), 468.0 (75, M + Na$^+$), 913.1 (55, 2M + Na$^+$). HRMS (ESI+, CH$_3$CN) m/z: calcd for (M + H$^+$) C$_{15}$H$_{19}$NO$_7$S$_2$F$_3$ 446.0555; found 446.0554 and calcd for (M + Na$^+$) C$_{15}$H$_{18}$NO$_7$S$_2$F$_3$Na 468.0375; found 468.0376.

Synthesis of the 1,4-oxazepine (5). The furan derivative **3gα** (423.8 mg, 0.987 mmol, 1 eq) was dissolved in THF (10 mL). The reaction was stirred and cooled to 0 °C. Sodium hydride (43 mg 60% in oil, 1.075 mmol, 1.1 eq) was added portionwise. The mixture was allowed to reach rt and stirred during 2 h. The reaction was stopped by the addition of a NaHCO$_3$ saturated solution (10 mL) and organic materials were extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over MgSO$_4$, filtered, and concentrated under vacuum. The residue was purified by silica gel flash chromatography to afford 171.0 mg of **5** with 52% as an yellow oil (petroleum ether : EtOAc 75 : 25). R$_f$: 0.68 (petroleum ether : EtOAc 75 : 25). IR (KBr, v, cm^{-1}): 2957, 2883, 2158, 2030, 1748, 1655, 1553, 1444, 1263, 1101, 987, 888, 776, 683. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.51–1.55 (m, 1H, NCH$_2$C$_2$$H_4$), 1.92–2.10 (m, 3H, NCH$_2C_2$$H_4$), 3.68–3.75 (m, 2H, NC$H_2C_2H_4$), 3.75 (s, 1H, CO$_2CH_3$), 3.81 (s, 3H, CO$_2CH'_3$), 4.05–4.12 (m, 1H, NC$HCH_2$O), 4.18–4.28 (m, 2H, NCHCH_2O), 7.34 (s, 1H, HC=CCHO), 9.04 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 21.0 (NCH$_2$C$_2$$H_4$), 28.7 (NCH$_2C_2$$H_4$), 48.6 (N$CH_2C_2H_4$), 53.5 (N$CHCH_2$O), 62.1 (CO$_2CH_3$), 69.8 + 70.1 (NCH$CH_2$O), 80.2 (q, $^2J_{C-F}$ = 29 Hz, CCF$_3$CO$_2$Me), 90.0 (NC=C), 123.6 (q, $^1J_{C-F}$ = 288 Hz, CCF_3CO$_2$Me), 130.5 (HC=CCHO), 143.7 (C), 156.8 (C), 166.5 + 167.2 (CO$_2$), 171.1 + 172.1 (CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −77.6 (s, 1F, CF$_3$), −77.4 (s, 3F, CF$'_3$). MS (ESI, CH$_3$CN) m/z (rel int): 334.3 (25, M + H$^+$), 356.2 (100, M + Na$^+$).

HRMS (ESI, CH$_3$CN) m/z (rel int): calcd for (MH$^+$) C$_{14}$H$_{15}$NO$_5$F$_3$ 334.0902; found 334.0898.

Rapid synthesis of the 1,4-oxazepine (5). To a solution of **1c** (75 mg, 0.385 mmol, 1 eq) in CH$_2$Cl$_2$ (5 mL) was added triethylamine (65 µL, 0.460 mmol, 1.2 eq). The reaction was cooled to −10 °C and MsCl (30 µL, 0.385 mmol, 1 eq) was added dropwise. After completion to give **1g**, the mixture was allowed to reach rt and methyl trifluoropyruvate **α** (59 µL, 0.577 mmol, 1.5 eq) was added. After 20 h the reaction was stopped by addition of NaHCO$_3$ saturated solution (3 mL) followed by 7 mL of H$_2$O and extracted by CH$_2$Cl$_2$ (2 × 10 mL). The combined organic layers were dried over MgSO$_4$ and evaporated under reduced pressure to afford the crude **3gα** which was engaged without purification. The latter was dissolved in THF (4 mL) and cooled to 0 °C prior to addition of NaH (16.9 mg, 0.423 mmol, 1.1 eq). After 2 h the reaction was quenched with 5 mL of NaHCO$_3$ saturated solution and the organic phase extracted by EtOAc and concentrated under vacuum. The residue was purified by silica gel flash chromatography to afford **5** as a yellow oil, with 36% global yield (mixture 1 : 3 of diastereomers) starting from **1c**.

1,4-Oxazepinone (6). To a 0 °C cooled solution of **3dα** (35 mg, 0.11 mmol, 1 eq) in CH$_2$Cl$_2$ (2 mL) was added triethylamine (23.5 µL, 0.16 mmol, 1.5 eq) followed by EDC (21.5 mg, 0.11 mmol, 1 eq). Then the solution was warmed at rt and stirred overnight. The reaction was stopped by adding water (10 mL) and a saturated solution of NaHCO$_3$ (1 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The combined organic layers were dried over MgSO$_4$ and concentrated under vacuum. The residue was purified by silica gel flash chromatography to afford 19.9 mg of **6** with 60% as a green oil (petroleum ether : EtOAc 6 : 4). R_f: 0.25 (Petroleum ether : EtOAc 6 : 4). IR (KBr, v, cm^{-1}): 2976, 2897, 2158, 2023, 1753, 1652, 1602, 1459, 1300, 1049, 931, 790, 677. ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.98–2.30 (m, 3H, NCH$_2$C$_2$H$_4$), 2.65–2.75 (m, 1H, NCH$_2$C$_2$H$_4$′), 3.67–3.72 (m, 2H, NCH$_2$C$_2$H$_4$), 3.93 (s, 1.3 H, CO$_2$CH$_3$), 4.29–4.34 (m, 1H, NCHCH$_2$O), 4.18–4.28 (m, 2H, NCHCH$_2$O), 7.36 (s, 1H, HC=CCHO), 9.21 (s, 1H, CHO). ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.9 (NCH$_2$C$_2$H$_4$), 28.5 (NCH$_2$C$_2$H$_4$), 48.6 (NCH$_2$C$_2$H$_4$), 55.0 (NCHCO$_2$), 60.8 (CO$_2$CH$_3$), 63.1 (CO$_2$C′H$_3$), 80.7 (q, $^2J_{C-F}$ = 31 Hz, CCF$_3$CO$_2$Me), 90.0 (NC=C), 121.4 (q, $^1J_{C-F}$ = 285 Hz, CCF$_3$CO$_2$Me), 127.1 (HC=CCHO), 144.4 (C), 157.7 (C), 165.4 (CO$_2$Me) + 167.2 (NCCO$_2$), 173.2 (CHO). ^{19}F NMR (CDCl$_3$, 188 MHz) δ −77.1 (s, 1F), −75.2 (s, 9F). MS (ESI, CH$_3$CN) m/z (rel int): 348.0 (20, M + H$^+$), 380.0 (30, M + Na$^+$), 402.0 (50), 491.1 (100), 713.1 (10). HRMS (ESI, CH$_3$CN) m/z (rel int): calcd for (M + H$^+$) C$_{14}$H$_{13}$NO$_6$F$_3$ 348.0695; found 348.0688.

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