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A facile synthesis of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones with Brønsted acid-catalyzed condensation–cyclization reactions of β-enamino esters and ethyl trifluoropyruvate

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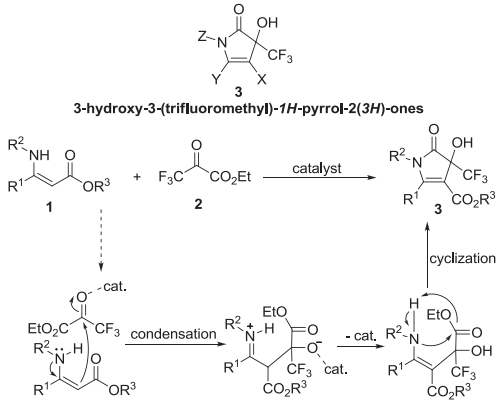
ABSTRACT

A facile synthesis of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones based on trifluoroacetic acid-catalyzed condensation–cyclization reactions of β-enamino esters and ethyl trifluoropyruvate is described. These reactions afford a series of α-trifluoromethylated γ-lactam compounds in good to excellent yields under mild conditions. A preliminary trial of an asymmetric catalytic version with chiral BINOL-derived phosphoric acid as enantioselective catalyst was conducted and showed promising enantioselectivity of the desired product.

1. Introduction

The efficient and facile construction of promising heterocycles is a continuing challenge for synthetic chemistry. Heterocyclic compounds containing a trifluoromethyl group in particular have emerged as attractive synthetic targets due to their applications in various fields like pharmacy, medicine, agriculture, material science, etc.[1] Among them, 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones **3** (Scheme 1) as one type of trifluoromethyl-containing γ-lactams are important *N*-heterocyclic compounds in organic synthesis, due to the potential application of the heterocyclic structure for the synthesis of a series of drug-like molecules bearing a trifluoromethylated quaternary carbon center,[2] and the α-hydroxy-α-trifluoromethyl amide skeleton is frequently encountered in many natural products and pharmaceuticals with significant biologically activities.[3] In this context, the development of novel and efficient methods for the construction of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-one structures is therefore highly important and desirable. However, the synthetic approaches to the 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-one skeletons are very rare.[2,4] In continuation of our program on the synthesis of various *N*-heterocyclic compounds,[5] we have been interested in exploring efficient method for the synthesis of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones. We envisioned that the reaction between β-enamino esters **1** and ethyl trifluoropyruvate **2** with appropriate catalyst could provide rapid access to 3-hydroxy-



Scheme 1. Design strategy for the synthesis of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-one compounds.

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3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-one compounds via a tandem condensation–cyclization pathway (Scheme 1).

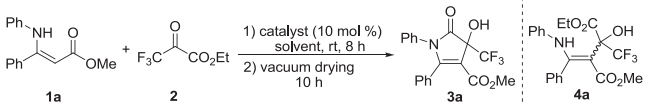
Actually, as a building block for generating trifluoromethylated heterocycles, ethyl trifluoropyruvate is envisioned to be an ideal candidate. There are many examples of nucleophilic addition to ethyl trifluoropyruvate with various nucleophiles have been reported.[2,4,6] Indeed, each of the reported methods results in a different class of CF_3-containing compounds that may play as promising biologically active motifs for pharmaceuticals and agrochemicals. However, there were very few examples found in the literature on the application of β-enamino esters as nucleophiles reacting with ethyl trifluoropyruvate,[2,4] despite that β-enamino esters have been utilized as versatile reagents that participate in a wide range of organic reactions.[7] Herein, we report the trifluoroacetic acid-catalyzed reactions between β-enamino esters and ethyl trifluoropyruvate for the synthesis of functionalized 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones via a tandem condensation–cyclization process.

2. Results and discussion

Our experiments began with the reaction of (*Z*)-methyl-3-phenyl-3-(phenylamino)acrylate (**1a**) and ethyl trifluoropyruvate (**2**). Reaction optimization involved variation of catalyst, solvent, and catalyst loading and the results from these experiments were shown in Table 1. We examined the model reaction in CH_2Cl_2 in the presence of 10 mol % *p*-toluenesulfonic acid (TsOH) at room temperature. After 8 h, a mixture of the desired condensation–cyclization product **3a** and condensation product **4a** in 89:11 ratio was provided in 41% yield (Table 1, entry 1). However, when the mixture of **3a** and **4a** was dried under vacuum at 80 °C for 10 h, **4a** could be completely converted to **3a**, giving the final product 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-one **3a** in 41% yield for two steps (Table 1, entry 2). Among the Brønsted acids that were screened, trifluoroacetic acid (TFA) gave the best result (Table 1, entries 2–6). In the case of TFA, it was observed that the expected condensation–cyclization product **3a** could be smoothly obtained in 95% yield (Table 1, entry 4). We then evaluated the effect of solvents, the survey of reaction media, such as DCE, toluene, CH_3CN, and THF, revealed that the results could not be further improved (Table 1, entries 7–10). Afterward, some polar solvents (DMF, DMSO, and H_2O) were investigated, unfortunately, almost no product was obtained with DMF or DMSO as the reaction medium, and the reaction did not occur in water (Table 1, entries 11–13). Thus, the best result was achieved in CH_2Cl_2 (Table 1, entry 4). Lowering the catalyst loading from 10 mol % to 5 mol % and 1 mol % led to significant decrease in chemical yield (Table 1, entries 14 and 15). Accordingly, these studies provided the optimal reaction conditions described in Table 1, entry 4.

Having a reasonable set of reaction conditions in hand, we evaluated the scope of the *N*-protected β-enamino esters and the results were shown in Table 2. Firstly, for the β-aryl-*N*-PMP β-enamino esters **1b**–**k**, it was observed that these substrates tolerated substitution at any position of the aromatic ring, and both electron-withdrawing (**1b**–**f**) and electron-donating (**1g**–**h**) functionalities were compatible. The expected 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones **3b**–**h** could be smoothly obtained in high yields (Table 2, entries 1–7). In the case of the 2-

Table 1
Optimization of the reaction conditions[a]



1a 2 3a 4a

Entry	Solvent	Catalyst	Yield[b] (%)
1	CH_2Cl_2	TsOH	41[c]
2	CH_2Cl_2	TsOH	41
3	CH_2Cl_2	AcOH	41
4	CH_2Cl_2	TFA	95
5	CH_2Cl_2	$MeSO_3H$	77
6	CH_2Cl_2	$PhCO_2H$	56
7	DCE	TFA	73
8	Toluene	TFA	90
9	CH_3CN	TFA	82
10	THF	TFA	Trace
11	DMF	TFA	Trace
12	DMSO	TFA	Trace
13	H_2O	TFA	nr
14	CH_2Cl_2	TFA	83[d]
15	CH_2Cl_2	TFA	67[e]

[a] Unless otherwise noted, the reaction was firstly carried out with **1a** (0.2 mmol), **2** (0.5 mmol), and catalyst (0.02 mmol) in solvent (2.0 mL) at room temperature for 8 h. The product was purified as a mixture of **3a** and **4a** via column chromatography on silica gel, and then the mixture was dried under vacuum at 80 °C for 10 h to furnish the end product **3a**.

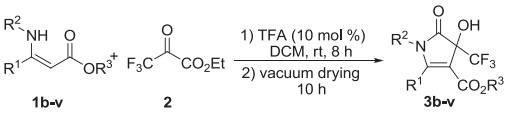
[b] Isolated yield of **3a** for two steps.

[c] Isolated yield of the mixture of **3a** and **4a** and the ratio 89:11 was determined by ^{1}H NMR analysis.

[d] TFA (5 mol %) was used.

[e] TFA (1 mol %) was used. TFA=trifluoroacetic acid, DCE=1,2-dichloroethane, nr=no reaction.

Table 2
Substrate scope for the tandem condensation–cyclization reaction of *N*-protected β-enamino esters and ethyl trifluoropyruvate[a]



1b-v 2 3b-v

Entry	1	3	Yield[b] (%)
1	R^1=4-FC_6H_4 (**1b**)	**3b**	94
2	R^1=4-BrC_6H_4 (**1c**)	**3c**	96
3	R^1=2-ClC_6H_4 (**1d**)	**3d**	96
4	R^1=3-ClC_6H_4 (**1e**)	**3e**	94
5	R^1=4-ClC_6H_4 (**1f**)	**3f**	95
6	R^1=4-MeC_6H_4 (**1g**)	**3g**	88
7	R^1=4-$MeOC_6H_4$ (**1h**)	**3h**	88
8	R^1=2-Naphthyl (**1i**)	**3i**	91
9	R^1=2-Thienyl (**1j**)	**3j**	86
10	R^1=Cyclohexyl (**1k**)	**3k**	90
11	R^2=4-FC_6H_4 (**1l**)	**3l**	92
12	R^2=4-BrC_6H_4 (**1m**)	**3m**	91
13	R^2=4-ClC_6H_4 (**1n**)	**3n**	88
14	R^2=4-MeC_6H_4 (**1o**)	**3o**	96
15	R^2=2-$MeOC_6H_4$ (**1p**)	**3p**	93
16	R^2=3-$MeOC_6H_4$ (**1q**)	**3q**	95
17	R^2=4-$MeOC_6H_4$ (**1r**)	**3r**	95
18	R^2=Bn (**1s**)	**3s**	86
19	R^3=Et (**1t**)	**3t**	96
20	R^3=^{i}Pr (**1u**)	**3u**	95
21	R^3=^{t}Bu (**1v**)	**3v**	98

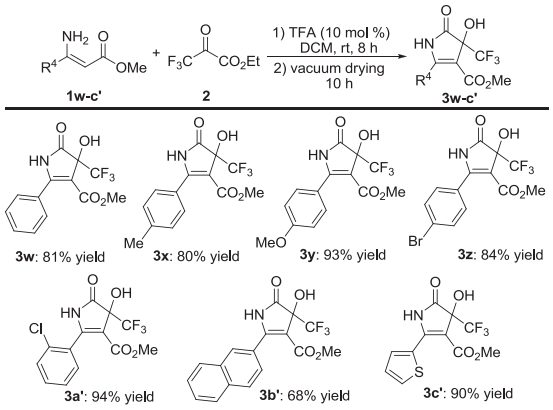
[a] Unless otherwise noted, the reaction was firstly carried out with **1** (0.2 mmol), **2** (0.5 mmol), and TFA (0.02 mmol) in CH_2Cl_2 (2.0 mL) at room temperature for 8 h. The product was purified as a mixture of the desired condensation–cyclization product **3** and the condensation product via column chromatography on silica gel and then the mixture was dried under vacuum at 80 °C for 10 h to furnish the final product **3**.

[b] Isolated yield of **3** for two steps. PMP=*p*-methoxyphenyl.

naphthyl derivative **1i**, very high yield for the corresponding product **3i** was achieved as well (Table 2, entry 8). *N*-PMP β-enamino ester bearing heteroaromatic β-substituent was also suitable substrate as exemplified by the preparation of **3j** (Table 2, entry 9). Notably, the less reactive aliphatic compound **1k** also proved to be a competent substrate in the tandem condensation–cyclization reaction affording the product **3k** in 90% yield (Table 2, entry 10). Our subsequent efforts focused on the β-phenyl-*N*-aryl β-enamino esters **1l**–**r**. Introduction of an electron-withdrawing or electron-donating group at the benzene ring of the *N*-aryl group did not significantly affect the yield (Table 2, entries 11–17). Diverse products **3l**–**r** could be smoothly obtained in yields ranging from 88% to 96%. Nevertheless, switching the *N*-aryl group to *N*-benzyl group was no deleterious to the reactivity and furnished **3s** in 86% yield (Table 2, entry 18). Ultimately, it was found that the R^3 group in the ester moiety had no obvious influence on the reactivity of this reaction (Table 2, entries 19–21). Remarkably, high to excellent yields were obtained for all substrates above-evaluated, demonstrating the generality and robustness of the present catalytic system.

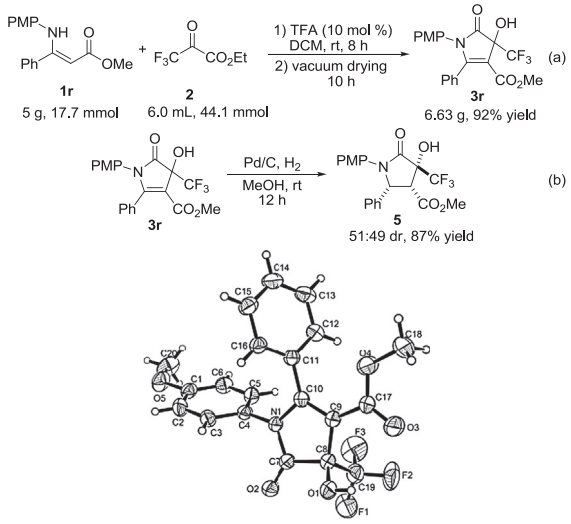
Subsequently, the method was further extended to *N*-unprotected β-enamine ester substrates (Table 3). The electronic property of substituents on the aryl ring of the substrates had no obvious effect on the generation of the product. Substrates bearing electron-donating or electron-withdrawing substituents on the aromatic ring were all able to smoothly react with ethyl trifluoropyruvate, delivering the corresponding products (Table 3, **3x**–**a**′) in very high yields. Furthermore, the 2-naphthyl substrate **1b**′ and 2-thienyl **1c**′ could afford the corresponding products **3b**′ and **3c**′ in 68% and 90% yields, respectively. Overall, the results, illustrated in Tables 2 and 3, not only demonstrate that there is good substrate scope for the reaction of β-enamine esters with ethyl trifluoropyruvate (**2**) using trifluoroacetic acid as catalyst, providing access to a range of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones in high to excellent yields, but also show that the feature of *N*-protected or *N*-unprotected in the substrates has no deleterious to the reactivity.

Table 3
Substrate scope for the tandem condensation–cyclization reaction of *N*-unprotected β-enamino esters and ethyl trifluoropyruvate[a]



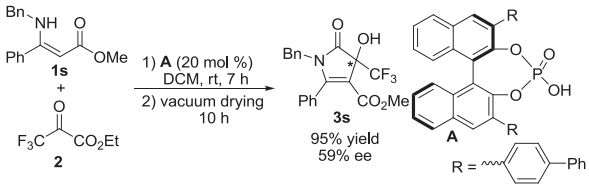
[a] For reaction conditions see the footnote of **Table 2**.

To test the practicality of the current method for the synthesis of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones, reaction of compound **1r** with ethyl trifluoropyruvate (**2**) was performed on a large scale under the standard reaction conditions. The reaction proceeded smoothly to provide **3r** in high to 92% yield (Scheme 2a). The structure of product **3r** has been confirmed by X-ray crystal structure analysis (Scheme 2).[8] Furthermore, the obtained 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-one product **3r** could be transformed into the densely functionalized 3-hydroxy-3-(trifluoromethyl)pyrrolidin-2-one **5** by means of reduction with Pd/C and hydrogen in 87% yield with 51:49 dr under mild conditions (Scheme 2b).[8]



Scheme 2. Large scale experiment for the synthesis of **3r**, the transformation of **3r** to **5**, and the X-ray structure of **3r**.

We also tried to develop a catalytic asymmetric version for the tandem condensation–cyclization process. The reaction of β-enamine ester **1s** and ethyl trifluoropyruvate (**2**) was selected as a model to illustrate the possibility of the catalytic asymmetric process (Scheme 3). Gratifyingly, in the presence of 20 mol % chiral BINOL-derived phosphoric acid **A**,[9] the expected tandem condensation–cyclization process proceeded smoothly under the standard reaction conditions, and afforded product **3s** in 95% yield with 59% ee.[10] The absolute configuration of **3s** was not determined at the moment and the exploration of more effective chiral Brønsted acids is undergoing.



Scheme 3. A preliminary attempt on the catalytic asymmetric reaction of β-enamine ester and ethyl trifluoropyruvate.

3. Conclusion

In summary, we have developed a facile method for the synthesis of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones with trifluoroacetic acid-catalyzed the reactions of β-enamino esters and ethyl trifluoropyruvate. Using this protocol, a series of functionalized α-trifluoromethylated γ-lactam compounds are able to be smoothly obtained in good to excellent yields via a tandem condensation–cyclization process. The potential utilities of the protocol also had been demonstrated by a large scale experiment and further transformation of the product. Additionally, a preliminary trial of an asymmetric catalytic version with chiral BINOL-derived phosphoric acid as enantioselective catalyst was conducted and afforded the desired product in excellent yield with moderate enantioselectivity.

4. Experimental section

4.1. General

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. ^{1}H NMR and ^{13}C NMR (300 and 75 MHz, respectively) spectra were recorded in $CDCl_3$. ^{1}H NMR chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Melting points were recorded on a Buchi Melting Point B-545.

4.2. General procedure for the synthesis of 3-hydroxy-3-(trifluoromethyl)-1*H*-pyrrol-2(3*H*)-ones

To a test tube equipped with a magnetic stirring bar were sequentially added **1** (0.20 mmol), TFA solution (c=0.01 M, 2 mL CH_2Cl_2), and ethyl trifluoropyruvate (0.5 mmol). Then the mixture was stirred for indicated time at room temperature. After completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure, and the residue was subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate=5:1) to give the mixture of the corresponding product. After that the mixture was dried in vacuum at 100 °C for 10 h to afford the single product **3**.

*4.2.1. Methyl 4-hydroxy-5-oxo-1,2-diphenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3a**).* White solid, 95% yield; mp 126.5–128.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.20 (m, 8H), 6.98–6.96 (m, 2H), 5.18 (br s, 1H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 76.4 (q, J=38.3 Hz, 1C), 103.7, 123.0 (q, J=286.7 Hz, 1C), 127.5, 127.6, 127.9, 128.5, 129.1, 129.2, 130.5, 132.7, 159.9, 163.6, 169.7; HRMS (ESI) calcd for $C_{19}H_{14}F_3NNaO_4$ $[M+Na]^+$: 400.0767, found: 400.0750.

*4.2.2. Methyl 2-(4-fluorophenyl)-4-hydroxy-1-(4-methoxyphenyl)-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3b**).* White solid, 94% yield; mp 155.3–157.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.18 (m, 2H), 7.01–6.95 (m, 2H), 6.86 (d, J=9.0 Hz, 2H), 6.76 (d, J=9.0 Hz, 2H), 5.13 (s, 1H), 3.73 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 55.3, 76.6 (q, J–31.3 Hz, 1C), 103.5, 114.4, 115.3 (d, J=22.0 Hz, 1C), 122.9 (q, J=286.5 Hz, 1C), 123.6 (d, J=3.5 Hz, 1C), 125.0, 128.8, 131.5 (d, J=8.7 Hz, 1C), 159.3, 159.4, 163.4, 163.6 (d, J=250.7 Hz, 1C), 170.0; HRMS (ESI) calcd for $C_{20}H_{15}F_4NNaO_5$ $[M+Na]^+$: 448.0779, found: 448.0770.

*4.2.3. Methyl 2-(4-bromophenyl)-4-hydroxy-1-(4-methoxyphenyl)-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3c**).* White solid, 96% yield; mp 154.1–155.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J=8.1 Hz, 2H), 7.08 (d, J=8.1 Hz, 2H), 6.86 (d, J=8.7 Hz, 2H), 6.76 (d, J=8.7 Hz, 2H), 5.29 (br, 1H), 3.74 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 55.3, 76.6 (q, J=31.2 Hz, 1C), 103.7, 114.5, 122.8 (q, J=286.5 Hz, 1C), 124.8, 125.2, 126.5, 128.7, 130.7, 131.2, 159.1, 159.4, 163.3, 169.9; HRMS (ESI) calcd for $C_{20}H_{15}BrF_3NNaO_5$ $[M+Na]^+$: 507.9978, found: 507.9964.

*4.2.4. Methyl 2-(2-chlorophenyl)-4-hydroxy-1-(4-methoxyphenyl)-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3d**).* White solid, 96% yield; mp 127.9–128.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.11 (m, 4H), 7.01–6.97 (m, 2H), 6.75 (d, J=8.4 Hz, 2H), 5.00–4.89 (br, 1H), 3.73 (s, 3H), 3.62 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 51.9, 55.3, 76.5 (q, J=31.5 Hz, 1C), 105.3, 105.4, 114.3, 122.8 (q, J=286.9 Hz, 0.5C), 122.9 (q, J=286.3 Hz, 0.5C), 124.6, 124.7, 126.5, 126.6, 127.9, 128.2, 128.7, 129.4, 129.5, 130.5, 131.3, 131.4, 132.1, 133.1, 157.5, 157.9, 159.6, 162.8, 163.1, 170.0, 170.2; HRMS (ESI) calcd for $C_{20}H_{15}ClF_3NNaO_5$ $[M+Na]^+$: 464.0483, found: 464.0489.

*4.2.5. Methyl 2-(3-chlorophenyl)-4-hydroxy-1-(4-methoxyphenyl)-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3e**).* Yellow solid, 94% yield; mp 126.8–127.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J=7.8 Hz, 1H), 7.26–7.19 (m, 2H), 7.04 (d, J=7.8 Hz, 1H), 6.88 (d, J=9.0 Hz, 2H), 6.77 (d, J=9.0 Hz, 2H), 5.09 (br s, 1H), 3.74 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 55.4, 76.6 (q, J=31.3 Hz, 1C), 104.0, 114.5, 122.8 (q, J=286.6 Hz, 1C), 124.8, 127.2, 128.8, 129.3, 129.4, 130.6, 133.9, 158.5, 159.5, 163.2, 169.9; HRMS (ESI) calcd for $C_{20}H_{15}ClF_3NNaO_5$ $[M+Na]^+$: 464.0483, found: 464.0479.

*4.2.6. Methyl 2-(4-chlorophenyl)-4-hydroxy-1-(4-methoxyphenyl)-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3f**).* Yellow solid, 95% yield; mp 134.1–135.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J=8.4 Hz, 2H), 7.16 (d, J=8.4 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 6.79 (d, J=9.0 Hz, 2H), 5.09 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 55.4, 76.6 (q, J=31.5 Hz, 1C), 103.7, 114.5, 122.9 (q, J=286.6 Hz, 1C), 124.9, 126.0, 128.3, 128.8, 130.6, 136.8, 159.0, 159.4, 163.3, 169.9; HRMS (ESI) calcd for $C_{20}H_{15}ClF_3NaO_5$ $[M+Na]^+$: 464.0483, found: 464.0485.

*4.2.7. Methyl 4-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-(p-tolyl)-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3g**).* Colorless oil, 88% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 4H), 6.86 (d, J=9.0 Hz, 2H), 6.75 (d, J=9.0 Hz, 2H), 5.16 (br s, 1H), 3.73 (s, 3H), 3.64 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 51.7, 55.3, 76.6 (q, J=31.3 Hz, 1C), 103.0, 114.3, 123.0 (q, J=286.5 Hz, 1C), 124.5, 125.3, 128.5, 128.8, 129.1, 140.9, 159.2, 160.5, 163.7, 170.2; HRMS (ESI) calcd for $C_{21}H_{18}F_3NNaO_5$ $[M+Na]^+$: 444.1029, found: 444.1024.

*4.2.8. Methyl 4-hydroxy-1,2-bis(4-methoxyphenyl)-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3h**).* Colorless oil, 88% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, J=8.7 Hz, 2H), 6.87 (d, J=9.0 Hz, 2H), 6.77 (d, J=8.7 Hz, 2H), 6.76 (d, J=9.0 Hz, 2H), 5.19 (s, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 55.2, 55.3, 76.7 (q, J=31.2 Hz, 1C), 102.5, 113.2, 114.3, 119.3, 123.0 (q, J=286.6 Hz, 1C), 125.4, 128.7, 131.2, 159.2, 160.2, 161.1, 163.7, 170.2; HRMS (ESI) calcd for $C_{21}H_{18}F_3NNaO_6$ $[M+Na]^+$: 460.0978, found: 460.0957.

*4.2.9. Methyl 4-hydroxy-1-(4-methoxyphenyl)-2-(naphthalen-2-yl)-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3i**).* Red solid, 91% yield; mp 138.7–140.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82–7.79 (m, 3H), 7.74–7.71 (m, 1H), 7.57–7.49 (m, 2H), 7.20 (d, J=8.4 Hz, 1H), 6.92 (d, J=8.7 Hz, 2H), 6.69 (d, J=8.7 Hz, 2H), 5.25 (br s, 1H), 3.66 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 55.2, 76.7 (q, J=31.3 Hz, 1C), 103.5, 114.3, 123.0 (q, J=286.3 Hz, 1C), 124.9, 125.2, 125.3, 126.8, 127.6, 127.7, 128.5, 128.7, 130.1, 131.9, 133.6, 159.2, 160.2, 163.7, 170.2; HRMS (ESI) calcd for $C_{24}H_{18}F_3NNaO_5$ $[M+Na]^+$: 480.1029, found: 480.1032.

*4.2.10. Methyl 4-hydroxy-5-oxo-1-phenyl-2-(thiophen-2-yl)-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3j**).* White solid, 86% yield; mp 138.3–138.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.47 (m, 1H), 7.26–7.25 (m, 1H), 6.99–6.94 (m, 3H), 6.82 (d, J=9.0 Hz, 2H), 5.24 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 55.4, 76.6 (q, J=31.2 Hz, 1C), 103.5, 114.5,

122.9 (q, J=286.7 Hz, 1C), 125.3, 126.5, 126.6, 129.1, 131.2, 133.8, 153.1, 159.7, 163.5, 169.7; HRMS (ESI) calcd for $C_{18}H_{14}F_3NO_5S$ $[M+Na]^+$: 436.0437, found: 436.0425.

*4.2.11. Methyl 2-cyclohexyl-4-hydroxy-1-(4-methoxyphenyl)-5-oxo-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3k**).* Colorless oil, 90% yield; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (br s, 2H), 6.98 (d, J=9.0 Hz, 2H), 4.90 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 2.90 (br, 1H), 1.69–1.59 (m, 8H), 1.07–1.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2, 26.1, 28.1, 28.9, 38.3, 51.7, 55.5, 76.1 (q, J=30.9 Hz, 1C), 101.6, 114.9, 123.0 (q, J=286.8 Hz, 1C), 125.8, 129.7, 160.4, 163.7, 168.1, 171.0; HRMS (ESI) calcd for $C_{20}H_{22}F_3NNaO_5$ $[M+Na]^+$: 436.1342, found: 436.1348.

*4.2.12. Methyl 1-(4-fluorophenyl)-4-hydroxy-5-oxo-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3l**).* White solid, 92% yield; mp 122.5–123.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 3H), 7.20–7.17 (m, 2H), 6.95–6.92 (m, 4H), 5.19 (s, 1H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 76.7 (q, J=31.3 Hz, 1C), 103.8, 116.2 (d, J=22.9 Hz, 1C), 122.9 (q, J=286.7 Hz, 1C), 127.4, 128.0, 128.6 (d, J=3.4 Hz, 1C), 129.1, 129.4 (d, J=13.5 Hz, 1C), 130.7, 159.5, 161.9 (d, J=248.0 Hz, 1C), 163.5, 169.8; HRMS (ESI) calcd for $C_{19}H_{13}F_4NNaO_4$ $[M+Na]^+$: 418.0673, found: 418.0667.

*4.2.13. Methyl 1-(4-bromophenyl)-4-hydroxy-5-oxo-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3m**).* Light yellow solid, 91% yield; mp 186.1–187.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5H), 7.20–7.18 (m, 2H), 6.83 (d, J=8.7 Hz, 2H), 5.17 (s, 1H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 77.0 (q, J=37.8 Hz, 1C), 104.1, 122.5, 122.9 (q, J=286.6 Hz, 1C), 127.3, 128.1, 128.9, 129.2, 130.8, 131.7, 132.3, 159.2, 163.5, 169.5; HRMS (ESI) calcd for $C_{19}H_{13}BrF_3NNaO_4$ $[M+Na]^+$: 477.9872, found: 477.9858.

*4.2.14. Methyl 1-(4-chlorophenyl)-4-hydroxy-5-oxo-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3n**).* Yellow solid, 88% yield; mp 161.6–163.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.39 (m, 1H), 7.35–7.31 (m, 2H), 7.28–7.20 (m, 4H), 6.91 (d, J=8.7 Hz, 2H), 5.19 (s, 1H), 3.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.9, 76.8 (q, J=31.0 Hz, 1C), 103.9, 122.8 (q, J=286.7 Hz, 1C), 127.3, 128.1, 128.7, 129.1, 129.3, 130.8, 131.1, 134.4, 159.3, 163.5, 169.6; HRMS (ESI) calcd for $C_{19}H_{13}ClF_3NNaO_4$ $[M+Na]^+$: 434.0377, found: 434.0380.

*4.2.15. Methyl 4-hydroxy-5-oxo-2-phenyl-1-(p-tolyl)-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3o**).* White solid, 96% yield; mp 160.8–161.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.25 (m, 3H), 7.21–7.18 (m, 2H), 7.03 (d, J=8.1 Hz, 2H), 6.83 (d, J=8.1 Hz, 2H), 5.16 (br s, 1H), 3.62 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 51.7, 76.7 (q, J=31.1 Hz, 1C), 103.5, 123.0 (q, J=286.5 Hz, 1C), 127.3, 127.7, 127.8, 129.1, 129.7, 130.0, 130.4, 138.6, 160.1, 163.6, 169.9; HRMS (ESI) calcd for $C_{20}H_{16}F_3NNaO_4$ $[M+Na]^+$: 414.0924, found: 414.0924.

*4.2.16. Methyl 4-hydroxy-1-(2-methoxyphenyl)-5-oxo-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3p**).* Yellow solid, 93% yield; mp 160.1–161.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 (s, 0.4H), 7.60 (s, 0.6H), 7.30–7.23 (m, 4H), 7.18–7.16 (m, 2H), 7.11–7.08 (m, 1H), 6.94–6.85 (m, 2H), 3.60 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.9, 55.6, 55.7, 76.6 (q, J=30.8 Hz, 1C), 105.0, 105.3, 112.1, 112.2, 120.3, 120.5, 121.6, 121.7, 123.0 (q, J=285.1 Hz, 0.5C), 123.2 (q, J=286.1 Hz, 0.5C), 127.4, 127.5, 128.2, 128.3, 128.7, 128.8, 129.7, 129.8, 130.1, 130.2, 130.7, 130.9, 154.9, 155.0, 160.2, 160.4, 161.8, 161.9, 171.3, 171.9; HRMS (ESI) calcd for $C_{20}H_{16}F_3NNaO_5$ $[M+Na]^+$: 430.0873, found: 430.0870.

*4.2.17. Methyl 4-hydroxy-1-(3-methoxyphenyl)-5-oxo-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3q**).* White solid, 95% yield; mp 141.6–142.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.20 (m, 5H), 7.13–7.10 (m, 1H), 6.78–6.77 (m, 1H), 6.54–6.47 (m, 2H), 5.18 (s, 1H), 3.64 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 55.3, 76.8 (q, J=31.5 Hz, 1C), 103.6, 113.1, 114.5, 119.7, 122.9 (q, J=286.5 Hz, 1C), 127.6, 127.9, 129.1, 129.7, 130.6, 133.6, 159.8, 163.5, 169.6; HRMS (ESI) calcd for $C_{20}H_{16}F_3NNaO_5$ $[M+Na]^+$: 430.0873, found: 430.0872.

*4.2.18. Methyl 4-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3r**).* White solid, 95% yield; mp 148.8–149.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (m, 3H), 7.20–7.17 (m, 2H), 6.88–6.84 (m, 2H), 6.75–6.72 (m, 2H), 5.11 (s, 1H), 3.72 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.6, 55.3, 76.7 (q, J=31.3 Hz, 1C), 103.4, 114.3, 123.0 (q, J=286.6 Hz, 1C), 125.2, 127.7, 127.8, 128.8, 129.1, 130.4, 159.3, 160.2, 163.6, 170.1; HRMS (ESI) calcd for $C_{20}H_{16}F_3NNaO_5$ $[M+Na]^+$: 430.0873, found: 430.0879.

*4.2.19. Methyl 1-benzyl-4-hydroxy-5-oxo-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3s**).* White solid, 86% yield; mp 122.8–123.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.45 (m, 1H), 7.40–7.35 (m, 2H), 7.20–7.15 (m, 3H), 7.11–7.09 (m, 2H), 6.80–6.77 (m, 2H), 4.97 (s, 1H), 4.71 (d, J=15.3 Hz, 1H), 4.40 (d, J=15.3 Hz, 1H), 3.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.6, 51.5, 76.5 (q, J=31.4 Hz, 1C), 104.2, 122.9 (q, J=286.2 Hz, 1C), 127.2, 127.8, 127.9, 128.2, 128.5, 130.5, 135.3, 160.4, 163.3, 171.0; HRMS (ESI) calcd for $C_{20}H_{16}F_3NNaO_4$ $[M+Na]^+$: 414.0924, found: 414.0903.

*4.2.20. Ethyl 4-hydroxy-5-oxo-1,2-diphenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3t**).* White solid, 96% yield; mp 104.0–105.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.19 (m, 8H), 6.98–6.95 (m, 2H), 5.31 (br s, 1H), 4.16–4.05 (m, 2H), 1.01 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 61.0, 76.9 (q, J=39.9 Hz, 1C), 103.9, 123.0 (q, J=286.5 Hz, 1C), 127.5, 127.7, 127.8, 128.5, 129.1, 129.2, 130.4, 132.6, 159.6, 163.3, 169.8; HRMS (ESI) calcd for $C_{20}H_{16}F_3NNaO_4$ $[M+Na]^+$: 414.0924, found: 414.0916.

*4.2.21. iso-Propyl 4-hydroxy-5-oxo-1,2-diphenyl-4-(trifluoromethyl)-4, 5-dihydro-1H-pyrrole-3-carboxylate (**3u**).* White solid, 95% yield; mp 110.2–111.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.18 (m, 8H), 6.98–6.95 (m, 2H), 5.34 (s, 1H), 5.03–4.95 (m, 1H), 1.12 (d, J=6.3 Hz, 3H), 0.94 (d, J=6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 21.6, 69.0, 76.9 (q, J=31.7 Hz, 1C), 104.5, 123.1 (q, J=286.4 Hz, 1C), 127.6, 127.7, 128.0, 128.4, 129.0, 129.3, 130.3, 132.9, 159.2, 162.9, 169.7; HRMS (ESI) calcd for $C_{21}H_{18}F_3NNaO_4$ $[M+Na]^+$: 428.1080, found: 428.1088.

*4.2.22. tert-Butyl 4-hydroxy-5-oxo-1,2-diphenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3v**).* White foam, 98% yield; mp 126.4–127.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (m, 8H), 6.96–6.94 (m, 2H), 5.48 (br s, 1H),1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 76.9 (q, J=31.2 Hz, 1C), 82.8, 105.3, 123.1 (q, J=286.4 Hz, 1C), 127.6, 127.8, 128.2, 128.4, 129.0, 129.2, 130.1, 132.9, 158.3, 163.0, 169.8; HRMS (ESI) calcd for $C_{22}H_{20}F_3NNaO_4$ $[M+Na]^+$: 442.1237, found: 442.1231.

*4.2.23. Methyl 4-hydroxy-5-oxo-2-phenyl-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3w**).* White solid, 81% yield; mp 124.8–125.1 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.61–7.47 (m, 5H), 5.03 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 77.5 (q, J=31.8 Hz, 1C), 102.3, 122.8 (q, J=286.4 Hz, 1C), 125.0, 127.9, 128.6, 132.0, 156.4, 163.5, 171.1; HRMS (ESI) calcd for $C_{13}H_{10}F_3NNaO_4$ $[M+Na]^+$: 324.0454, found: 324.0442.

*4.2.24. Methyl 4-hydroxy-5-oxo-2-(p-tolyl)-4-(trifluoromethyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3x**).* White solid, 80% yield; mp

168.0–169.1 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09 (br s, 1H), 7.41 (d, J=8.1 Hz, 2H), 7.34 (s, 1H), 7.29 (d, J=8.1 Hz, 2H), 3.52 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.1, 50.9, 77.3 (q, J=30.4 Hz, 1C), 102.6, 123.2 (q, J=285.0 Hz, 1C), 126.0, 128.7, 141.2, 157.5, 162.6, 173.3; HRMS (ESI) calcd for $C_{14}H_{12}F_3NNaO_4$ [M+Na]$^+$: 338.0611, found: 338.0601.

*4.2.25. Methyl 4-hydroxy-2-(4-methoxyphenyl)-5-oxo-4-(trifluoro methyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3y**).* White solid, 93% yield; mp 165.5–167.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.04 (br s, 1H), 7.51 (d, J=8.7 Hz, 2H), 7.27 (s, 1H), 7.03 (d, J=8.7 Hz, 2H), 3.82 (s, 3H), 3.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.8, 55.5, 77.4 (q, J=30.4 Hz, 1C), 101.8, 113.6, 120.8, 123.3 (q, J=285.0 Hz, 1C), 130.7, 157.2, 161.5, 162.8, 173.3; HRMS (ESI) calcd for $C_{14}H_{12}F_3NNaO_5$ [M+Na]$^+$: 354.0560, found: 354.0559.

*4.2.26. Methyl 2-(4-bromophenyl)-4-hydroxy-5-oxo-4-(trifluoro methyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3z**).* White solid, 84% yield; mp 180.1–181.2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.21 (br s, 1H), 7.71 (d, J=8.4 Hz, 2H), 7.46 (d, J=8.4 Hz, 2H), 7.41 (s, 1H), 3.53 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.0, 77.3 (q, J=30.5 Hz, 1C), 103.7, 123.1 (q, J=284.9 Hz, 1C), 124.6, 128.2, 130.8, 131.3, 156.7, 162.3, 173.2; HRMS (ESI) calcd for $C_{13}H_9BrF_3NNaO_4$ [M+Na]$^+$: 401.9559, found: 401.9549.

*4.2.27. Methyl 2-(2-chlorophenyl)-4-hydroxy-5-oxo-4-(trifluoro methyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3a′**).* White solid, 94% yield; mp 133.7–135.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.13 (br s, 1H), 7.60–7.57 (m, 1H), 7.51–7.47 (m, 1H), 7.45–7.36 (m, 3H), 3.43 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.9, 76.8 (q, J=30.8 Hz, 1C), 106.0, 123.1 (q, J=285.1 Hz, 1C), 127.3, 129.5, 129.8, 131.4, 131.7, 156.0, 161.5, 173.2; HRMS (ESI) calcd for $C_{13}H_9ClF_3NNaO_4$ [M+Na]$^+$: 358.0064, found: 358.0061.

*4.2.28. Methyl 4-hydroxy-2-(naphthalen-2-yl)-5-oxo-4-(trifluoro methyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3b′**).* White solid, 68% yield; mp 109.1–110.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.25 (br s, 1H), 8.16 (s, 1H), 8.07–7.99 (m, 3H), 7.67–7.55 (m, 3H), 7.41 (br s, 1H), 3.53 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 50.9, 77.4 (q, J=30.4 Hz, 1C), 103.5, 123.2 (q, J=284.9 Hz, 1C), 125.6, 126.6, 126.9, 127.5, 127.7, 127.9, 128.7, 132.0, 133.8, 157.8, 162.5, 173.3; HRMS (ESI) calcd for $C_{17}H_{12}F_3NNaO_4$ [M+Na]$^+$: 374.0611, found: 374.0600.

*4.2.29. Methyl 4-hydroxy-5-oxo-2-(thiophen-2-yl)-4-(trifluoro methyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**3c′**).* White solid, 90% yield; mp 163.4–164.9 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.26 (br s, 1H), 8.03 (d, J=5.1 Hz, 1H), 7.91–7.89 (m, 1H), 7.31 (s, 1H), 7.24 (t, J=5.1 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 51.2, 77.2 (q, J=30.4 Hz, 1C), 100.7, 123.2 (q, J=285.2 Hz, 1C), 127.3, 128.6, 133.9, 134.9, 149.3, 163.1, 172.7; HRMS (ESI) calcd for $C_{11}H_8F_3NNaO_4S$ [M+Na]$^+$: 330.0018, found: 330.0009.

4.3. The procedure for the transformation of 3r to 5

A solution of **3r** (1 mmol) in anhydrous methanol (30 mL) was treated with palladium (20 wt % on charcoal) under a hydrogen atmosphere. The reaction mixture was stirred for 12 h at room temperature. After completion of the reaction, as determined by TLC, the mixture was filtered through Celite, concentrated, and the residue was purified by column chromatography (EtOAc/hexane=5:1) to obtain **5**.

*4.3.1. Methyl 4-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-phenyl-4-(trifluoromethyl)pyrrolidine-3-carboxylate (**5**).* White foam, 87% yield; mp 71.5–72.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 6H), 7.10–7.08 (m, 1H), 6.78–6.73 (m, 2H), 5.75 (d, J=6.6 Hz, 0.4H), 5.69 (d, J=6.6 Hz, 0.6H), 5.08 (br s, 0.4H), 4.94 (br s, 0.6H), 3.78 (s, 1.7H), 3.72–3.70 (m, 3.4H), 3.45 (d, J=6.6 Hz, 0.6H), 3.27 (s, 1.3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.7, 51.8. 53.0, 54.5, 55.2, 55.3, 61.9, 62.5, 76.6 (q, J=31.3 Hz, 0.4C), 78.5 (q, J=31.5 Hz, 0.6C), 113.9, 114.1, 122.6 (q, J=282.6 Hz, 0.4C), 123.3 (q, J=283.4 Hz, 0.6C), 124.6, 125.3, 126.8, 128.0, 128.1, 128.3, 128.5, 128.7, 129.1, 133.2, 137.5, 157.4, 157.9, 166.2, 166.4, 167.8, 168.3; HRMS (ESI) calcd for $C_{20}H_{18}F_3NNaO_5$ [M+Na]$^+$: 432.1029, found: 432.1015.

4.4. Procedure for the catalytic asymmetric reaction of β-enamine ester and ethyl trifluoropyruvate

To a test tube equipped with a magnetic stirring bar were sequentially added **1s** (0.20 mmol), **A** (20 mol %), CH_2Cl_2 (2 mL), and **2** (0.5 mmol). The mixture was stirred at room temperature for 7 h, concentrated, and the residue was subjected to flash chromatography on silica gel (petroleum ether/ethyl acetate=5:1) to give the mixture of the corresponding product. Then the mixture was dried in vacuum at 100 °C for 10 h to afford the chiral product **3s** as a white solid in 95% yield, 59% ee. $[\alpha]_D^{20}$ −2.6 (*c* 0.72, EtOH); chiral HPLC condition: Daicel Chiralpak AD-H, hexanes/*i*-PrOH=70:30, flow rate=1.0 mL/min, UV=254 nm, t_R=5.77 min (minor) and t_R=6.35 min (major).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.05.052.

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10. For the enantiomeric excess analysis of chiral **3s**, see Supplementary data.