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Photoredox-Enabled Synthesis of *β*-Substituted Pyrroles from Pyrrolidines

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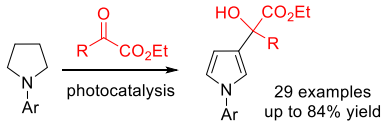
Graphic Abstract



Abstract: The merger of photoredox-initiated enamine-imine tautomerization and nucleophilic addition processes to access *β*-substituted pyrroles from pyrrolidines has been achieved. The significant advantage of this method is suppressing the Friedel-Crafts reaction, which usually occurs between *N*-aryl pyrrolidines and the highly electrophilic ketoesters. The good functional group tolerance, high atom-economy and high regioselectivity as well as easy handling conditions make it appealing alternative to synthesize *β*-substituted pyrroles.

INTRODUCTION

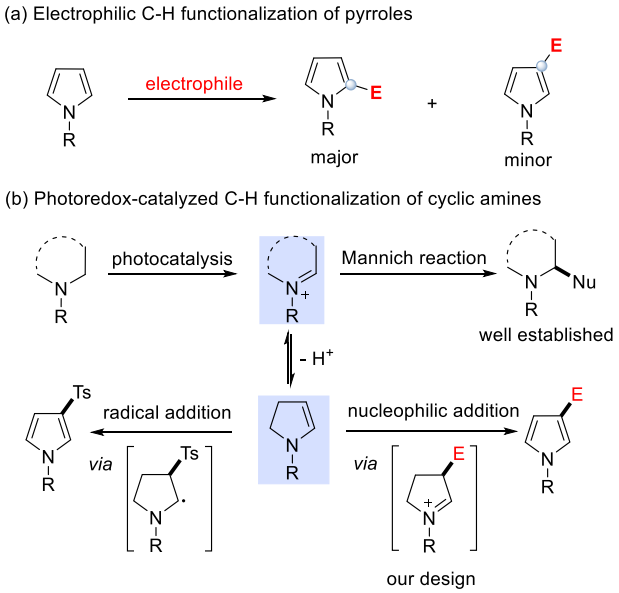
The pyrrole ring represents not only an essential motif of natural products and biologically important molecules,[1] but also one kind of significant precursors for synthesis of pharmaceutical molecules and functional materials.[2] Meanwhile, the introduction of trifluoromethyl group into pharmaceutical molecules would significantly improve their bio-receptor selectivity.[3] As a consequence, the synthesis of pyrrole derivatives containing trifluoromethyl group would open an

access to the new drug discovery.

The electrophilic substitution reaction provides the classic method towards various pyrrole derivatives.[4] However, due to the intrinsic α-reactivity of the five-membered heterocycles, the electrophilic C–H functionalization of pyrroles preferentially occurs at α-position, leading to α-substituted pyrroles (Scheme 1a).[5] On account of this, the development of novel strategies to access β-substituted pyrroles, which usually display special biological activities,[6] has received significant attention.[7]

In recent years, visible-light promoted transformations has attracted special interest from chemists.[8] Among them, visible-light photoredox catalysis has emerged as a powerful tool for functionalization of cyclic amines with high efficiency.[9] Nevertheless, much attention has been focused on the α-functionalization of cyclic amines *via* Mannich-type reaction of iminium, using various nucleophiles as coupling partners (Scheme 1b).[10] In sharp contrast, only one example was reported to construct β-substituted pyrroles via photoredox β-functionalization of cyclic amines (Scheme 1b).[11] Mechanistically, the single electron oxidation rendered the *in situ* generation of enamine intermediate, which was engaged in the subsequent radical addition and dehydrogenative aromatization to furnish β-substituted sulfonyl pyrroles. However, up to till now, there is no work merging the photoredox catalysis with enamine-involved ionic reaction to synthesize β-substituted pyrroles. Theoretically, the β-position of enamine could serve as a competent nucleophilic site in ionic reaction.[12] Inspired by our recent success on the redox-neutral C–H functionalization of cyclic amines,[13] now we report the visible-light-promoted β-C–H functionalization and aromatization of pyrrolidines with fluorinated ketoesters. This protocol provides a rapid access to a variety of β-substituted pyrroles with trifluoromethyl group from readily available pyrrolidine precursors (Scheme 1b).

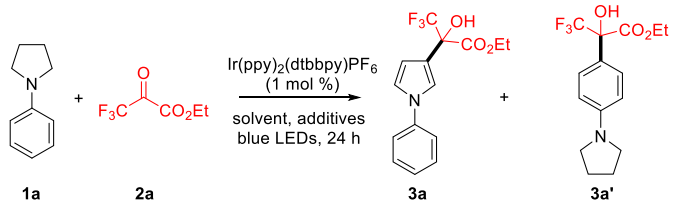
Scheme 1. Approaches towards Substituted Pyrrole Derivatives.



RESULTS AND DISCUSSION

We first explored this protocol using the challenging *N*-aryl pyrrolidine **1a** as the starting material, which might undergo Friedel-Crafts reactions with electrophiles.[14] Ethyl trifluoropyruvate **2a** was employed as an alkylating reagent and a range of photocatalysts (PC) were evaluated at ambient temperature (see the Supporting Information). To our delight, with $Ir(ppy)_2(dtbbpy)PF_6$ as a photocatalyst (PC) and DMSO as a solvent, the desired product **3a** was produced in 53% yield without any Friedel-Crafts product **3a′** detected (Table 1, entry 1). In sharp contrast, only Friedel-Crafts product **3a′** was observed in 66% yield in the absence of photocatalyst, indicating the essential of photoredox initiation in this transformation (Table 1, entry 2). Unfortunately, the other solvents didn't lead to a superior result and CH_3CN afforded **3a′** as the major product (Table 1, entries 3-7). In order to improve the yield, various bases were introduced as additives to facilitate the enamine-imine tautomerization[15] (Table 1, entries 8-12). To our delight, when NaH_2PO_4 was added as an additive, the desired product was furnished in 72% yield (Table 1, entry 10). And the yield could be improved to 78% after screening the dosages of the base and **2a** (Table 1, entries 13-16). Unfortunately, the next decreasing or increasing the amount of **2a** did not improve the yield (Table 1, entries 15-16). Consequently, the optimal reaction condition was indicated as entry 14.

Table 1. Optimization of the Reaction Conditions[a]



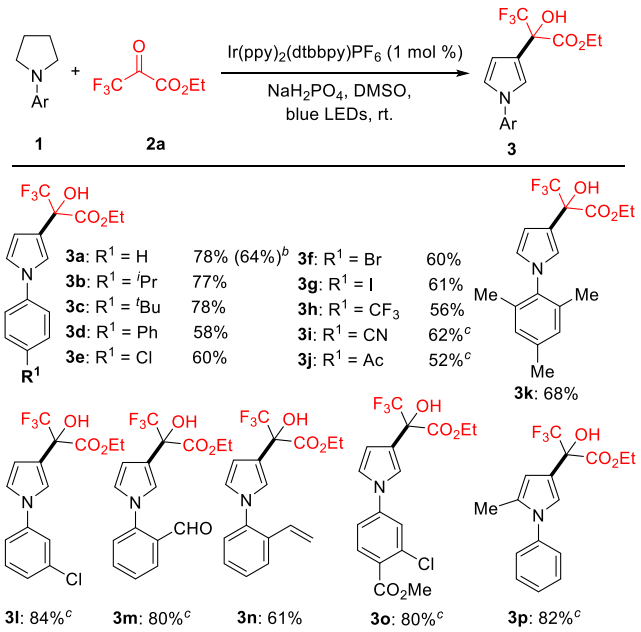
entry	base	solvent	yield of **3a** (%)[b]	yield of **3a′** (%)[b]
1	-	DMSO	53	trace
2[c]	-	DMSO	trace	66
3	-	DMF	48	trace
4	-	1,4-dioxane	44	trace
5	-	THF	38	trace
6	-	DME	27	trace
7	-	CH_3CN	<10	37
8	KH_2PO_4	DMSO	59	12
9	K_2HPO_4	DMSO	31	21
10	NaH_2PO_4	DMSO	72	<10
11	Na_2HPO_4	DMSO	63	<10
12	$NaHCO_3$	DMSO	38	19
13[d]	NaH_2PO_4	DMSO	75	<10
14[e]	NaH_2PO_4	DMSO	78	12
15[e, f]	NaH_2PO_4	DMSO	58	12
16[e, g]	NaH_2PO_4	DMSO	78	12

[a]Reaction conditions: a solution of **1a** (0.1 mmol), **2a** (0.25 mmol), base (0.1 mmol) and $Ir(ppy)_2(dtbbpy)PF_6$ (0.001 mmol) was irradiated by blue LED strips in the solvent (1.0 mL) for 24 h under an air atmosphere. [b]The yield was determined by crude ^1H NMR using dibromomethane as the internal standard. [c]Without $Ir(ppy)_2(dtbbpy)PF_6$. [d]1.5 equiv (0.15 mmol) NaH_2PO_4. [e]2.0 equiv (0.20 mmol) NaH_2PO_4. [f]2.0 equiv (0.20 mmol) **2a**. [g]3.5 equiv (0.35 mmol) **2a**.

With the optimized reaction conditions in hand, the synthetic potential with respect to the *N*-aryl pyrrolidines was firstly evaluated (Table 2). Gratifyingly, either electron-donating or -withdrawing substituents on the aryl ring were fully tolerable in this transformation, furnishing the desired products in good yields. For instance, the alkyl (**3b**, **3c**), phenyl (**3d**), halides (**3e-g**), trifluoromethyl (**3h**), cyano (**3i**) and acetyl (**3j**) substituted substrates were all good reaction partners to afford the corresponding products in 52-78% yields. Besides, the success of bulky 2,4,6-trimethylphenyl group (**3k**) indicated that the steric hindrance of the substituent did not influence the productivity. Remarkably, this reaction exhibited excellent functional group tolerance and a variety of functional groups survived, such as cyano (**3i**), acetyl (**3j**), formyl (**3m**)

and double bond (**3n**) moieties, yielding the products in good yields. Particularly, both the acetyl (**3j**) and formyl (**3m**) groups containing electrophilic sites were tolerable in this nucleophilic addition process. These appealing results demonstrate the great practicability of this new protocol and hold great potential for further application. Changing the chlorine from 4-position (**3e**) to 3-position (**3l**) showed positive influence on the reaction productivity, leading to product **3l** in 84% yield. Notably, when 2-methylpyrrolidine was subjected to the reaction, 2,4-disubstituted pyrrole **3p** could also be obtained in 82% yield. A lower yield (64%) of **3a** was obtained under the catalysis of 2 mol % Ir-catalyst in 1.0 mmol scale.

Table 2. Substrate Scope for the Synthesis of 3 [a]

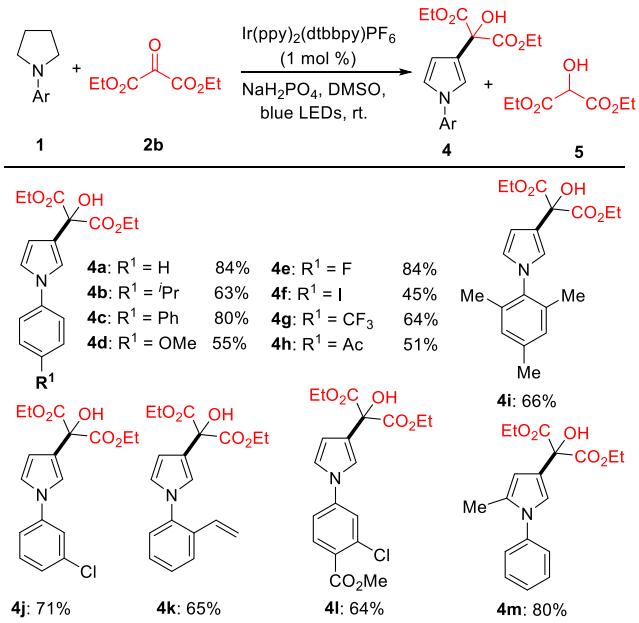


[a]Reaction conditions: a solution of **1** (0.2 mmol), **2a** (0.5 mmol), NaH_2PO_4 (0.4 mmol) and $Ir(ppy)_2(dtbbpy)PF_6$ (0.002 mmol) in DMSO (2.0 mL) was irradiated by blue LED strips under an air atmosphere. The yields are isolated yields after purification. [b]The reaction was performed on a 1.0 mmol scale. [c]The amount of **2a** was 3.5 equiv (0.7 mmol).

To further explore the substrate scope, diethyl 2-oxomalonate **2b** was also tested under the standard reaction conditions (Table 3). Generally, an array of *N*-aryl pyrrolidines could engage in this cascade *β*-functionalization/aromatization with **2b** as an alkylating agent. As expected, either electron-donating or -withdrawing substituents, such as alkyl (**4b**), phenyl (**4c**), methoxy (**4d**), halides (**4e**, **4f**), trifluoromethyl (**4g**) groups on *para*-position of the *N*-phenyl moiety, could tolerate in this reaction with good efficiencies (45-84% yield). The sterically hindered pyrrolidine

with two methyl groups at the *ortho*-position delivered the corresponding product **4i** in 66% yield. Same as the above observations, substrate modified with ketone (**4h**), double bond (**4k**), ester (**4l**) fragment still exhibited appealing efficiency in this transformation. Identically, 2-methylpyrrolidine afforded the pyrrole **4m** in 80% yield. Interestingly, for reactions with diethyl 2-oxomalonate **2b**, alcohol **5** was observed as a by-product, implying that the reduction of ketoester occurred in this reaction. As a comparison, the failure of detecting alcohol of ethyl trifluoropyruvate **2a** might be ascribed to the lower boiling point of ethyl 3,3,3-trifluoro-2-hydroxypropanoate.[16]

Table 3. Substrate Scope for the Synthesis of 4 [a]



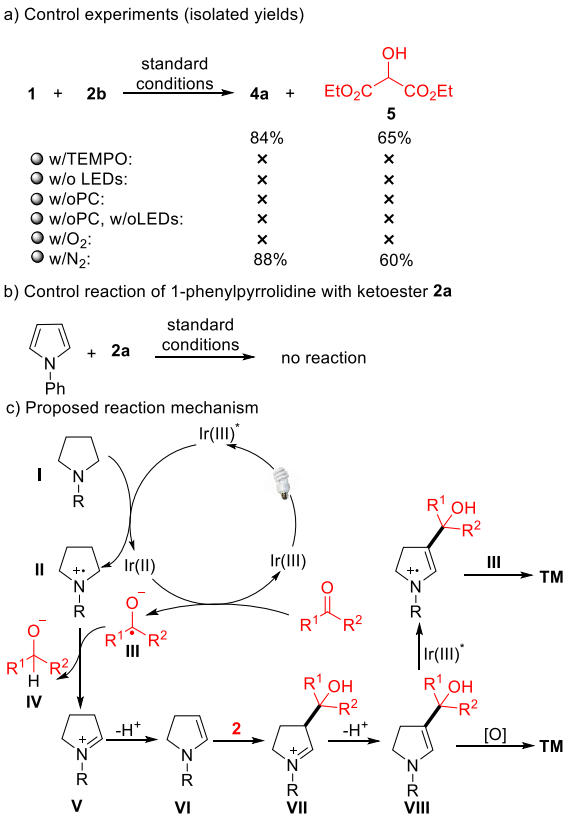
[a]Reaction conditions: a solution of **1** (0.2 mmol), **2b** (0.7 mmol), NaH_2PO_4 (0.4 mmol) and $Ir(ppy)_2(dtbbpy)PF_6$ (0.002 mmol) in the DMSO (2.0 mL) was irradiated by blue LED strips under an air atmosphere. The yields are isolated yields after purification.

To get a deep insight into this transformation, the mechanistic study was conducted using diethyl 2-oxomalonate **2b** as a reaction partner (Scheme 2a). When TEMPO was added to the reaction system, this reaction failed to produce the desired product, pointing toward a radical mechanism. In addition, the control experiments indicated that the iridium (III) complex photocatalyst was essential for the initiation of this radical reaction (Table 1, entry 2). Therefore, our previously reported hydride transfer pathway was excluded in this transformation.[13b] The detection of by-product **5** suggested that ketoester **2b** served as an oxidant in the dehydrogenation of pyrrolidine,[17] which also gave an explanation on the necessity of excess amount (2.5 - 3.5 eq)

of ketoesters. This assumption was further supported by the production of **4a** in 88% yield under N_2 atmosphere. However, this reaction could be quenched under a pure oxygen atmosphere. Besides, treatment of 1-phenylpyrrolidine with **2a** under the standard conditions failed to give the Friedel-Crafts product (Scheme 2b). Therefore, the direct Friedel-Crafts alkylation of pyrrole was excluded in the mechanism.

Based on the above control experiments and our precedent work,[13a] a plausible mechanism is proposed as shown in Scheme 2c. Visible-light excitation of the Ir(III) leads to an excited-state species Ir(III)*, which oxidizes the redox-active amine **I** *via* single-electron transfer. The resultant Ir(II) complex would subsequently reduce the ketoester to an anion radical intermediate **III**,[18] which would trap a hydrogen atom from amine cation radical **II** to produce an iminium intermediate **V**. Followed by the enamine-imine tautomerization/nucleophilic addition/enamine-imine tautomerization sequence, the *β*-substituted *α,β*-unsaturated amine **VIII** was furnished. Eventually, the atmospheric oxidation delivers the *β*-substituted pyrroles, which was supported by the mechanistic study (see the Supporting Information). Alternatively, the aromatization could also be achieved by the photoredox dehydrogenation.

Scheme 2. Mechanistic Study



CONCLUSION

In conclusion, we have developed an efficient method for the synthesis of *β*-substituted pyrroles from pyrrolidines in one step through single electron oxidation/hydrogen atom transfer/enamine-imine tautomerization/nucleophilic addition sequence. This work merges photoredox catalysis-initated enamine-imine tautomerization and nucleophilic addition, and it does not require strong oxidants and high temperature. Remarkably, the Friedel-Crafts reaction is suppressed, which usually occurs between *N*-aryl pyrrolidines and highly electrophilic ketoesters. Moreover, the good functional group tolerance, high regioselectivity and atom-economy as well as easy handling conditions make it a more appealing alternative to construct *β*-substituted pyrroles. The resultant *β*-substituted pyrroles containing trifluoromethyl group will find wide application in medicinal chemistry community.

EXPERIMENTAL SECTION

All commercially available reagents, unless otherwise indicated, were used without further purification. All solvents were purified and dried according to standard methods prior to use. Molecular sieves were activated at 550 °C for 6 h before use. Reactions were monitored by thin layer chromatography (TLC) with 0.2 mm silica gel-coated HSGF 254 plates, visualized by UV light at 254 or 365 nm. Products were isolated and purified by column chromatography on 200-300 mesh silica gel. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker AMX 500 (500 MHz for ^{1}H, 126 MHz for ^{13}C and 471 MHz for ^{19}F NMR) spectrometer at room temperature. The chemical shifts (δ) were reported in ppm with respect to an internal standard, tetramethylsilane (0 ppm), and the solvent ($CDCl_3$, ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.16 ppm). Coupling constants (*J*) are given in Hertz. Splitting patterns of apparent multiplets associated with an averaged coupling constants were designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets) and br (broadened). All ^{13}C spectra were recorded with broadband proton decoupling. HRMS were performed on a Waters XEVO QTOF mass spectrometer. Starting

material pyrrolidines **1** were synthesized according to the literature.[12b]

General Procedure: Synthesis of β-Substituted Pyrroles.

A 20-mL reaction tube was equipped with a rubber stopper and magnetic stir bar and was charged with **1** (0.2 mmol), NaH_2PO_4 (0.4 mmol), and $Ir(ppy)_2(dtbbpy)PF_6$ (0.002 mmol). DMSO (2.0 mL) and ketoesters **2** were then added with syringe. The mixture was then irradiated by blue LED strips under an air atmosphere. After the reaction was completed (as judged by TLC analysis), the mixture was poured into a separatory funnel containing 20 mL of saturated NaCl and 20 mL of EtOAc. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The crude product was purified by flash chromatography on silica gel to afford the desired product.

Scale-up Experiment.

An 50-mL sealed tube equipped with and magnetic stir bar was charged with **1a** (1 mmol), NaH_2PO_4 (2.0 mmol), and $Ir(ppy)_2(dtbbpy)PF_6$ (0.02 mmol). DMSO (10.0 mL) and ketoester **2a** (2.5 mmol) were then added with syringe. The mixture was then irradiated by blue LED strips under an air atmosphere. After the reaction was completed (as judged by TLC analysis), the mixture was poured into a separatory funnel containing 50 mL of saturated NaCl and 50 mL of EtOAc. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The residue was directly purified by flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether = 1:30) to afford **3a** with 64% yield (198.9 mg).

ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-phenyl-1H-pyrrol-3-yl)propanoate (3a): yellow oil, 48.7 mg, 78% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 8.5, 7.2 Hz, 2H), 7.32 – 7.29 (m, 2H), 7.24 (t, *J* = 2.1 Hz, 1H), 7.22 – 7.19 (m, 1H), 6.97

(t, *J* = 2.7 Hz, 1H), 6.45 (dt, *J* = 2.1, 1.0 Hz, 1H), 4.41 – 4.28 (m, 3H), 4.19 (s, 1H), 1.32 (t, *J* = 7.2 Hz, 4H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -78.05. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.4, 140.2, 129.6, 126.2, 123.1 (q, *J* = 285.6 Hz), 120.7, 119.9, 119.0, 118.7, 109.7, 75.8 (q, *J* = 31.7 Hz), 64.0, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{15}F_3NO_3$: 314.0999; found: 314.0997.

ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-(4-isopropylphenyl)-1H-pyrrol-3-yl)propanoate (3b): yellow oil, 54.6 mg, 77% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.25 (m, 1H), 7.00 (t, *J* = 2.7 Hz, 1H), 6.50 (t, *J* = 2.2 Hz, 1H), 4.49 – 4.33 (m, 2H), 4.27 (s, 1H), 2.97-2.89 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 6H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.03. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.5, 147.0, 138.2, 127.5, 124.3 (q, *J* = 285.5 Hz), 120.8, 119.9, 119.1, 118.3, 109.3, 75.8 (q, *J* = 31.3 Hz), 64.0, 33.6, 24.0, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{21}F_3NO_3$: 356.1468; found: 356.1467.

ethyl 2-(1-(4-(tert-butyl)phenyl)-1H-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3c): yellow oil, 57.5 mg, 78%, purification on silica gel (EtOAc : hexane = 1:30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.6 Hz, 2H), 7.25 – 7.18 (m, 3H), 6.92 (t, *J* = 2.7 Hz, 1H), 6.42 (t, *J* = 2.1 Hz, 1H), 4.42 – 4.26 (m, 2H), 4.19 (s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.26 (s, 9H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.01. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.5, 149.4, 137.8, 126.5, 123.2 (q, *J* = 285.5 Hz), 120.4, 119.9, 119.1, 118.4, 109.4, 75.8 (q, *J* = 31.2 Hz), 64.0, 34.5, 31.4, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{23}F_3NO_3$: 370.1625; found: 370.1624.

ethyl 2-(1-([1,1'-biphenyl]-4-yl)-1H-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3d): yellow oil, 45.2 mg, 58% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.49 – 7.42 (m, 4H), 7.40 – 7.32 (m, 2H), 7.08 (t, *J* = 2.8 Hz, 1H), 6.55 (t, *J* = 2.2 Hz, 1H), 4.49 – 4.36 (m, 2H), 4.28 (s, 1H),

1.40 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.03. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.4, 140.0, 139.4, 139.2, 128.9, 128.3, 127.5, 126.7, 123.2 (q, *J* = 285.5 Hz), 120.9, 119.8, 119.0, 118.8, 109.8, 75.8 (q, *J* = 31.1 Hz), 64.1, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{21}H_{19}F_3NO_3$: 390.1312; found: 390.1310.

ethyl 2-(1-(4-chlorophenyl)-1H-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3e): yellow oil, 41.3 mg, 60% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 3.3 Hz, 1H), 6.99 (t, *J* = 2.8 Hz, 1H), 6.53 (t, *J* = 2.2 Hz, 1H), 4.53 – 4.33 (m, 2H), 4.27 (s, 1H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.09. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.3, 138.8, 131.8, 129.7, 123.1 (q, *J* = 285.3 Hz), 121.8, 119.8, 119.1, 119.0, 110.1, 75.7 (q, *J* = 31.4 Hz), 64.1, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{14}ClF_3NO_3$: 348.0609; found: 348.0610.

ethyl 2-(1-(4-bromophenyl)-1H-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3f): yellow oil, 47.3 mg, 60% yield, purification on silica gel (EtOAc : hexane = 1:25). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.8 Hz, 2H), 7.28-7.25 (m, 3H), 6.99 (t, *J* = 2.7 Hz, 1H), 6.53 (t, *J* = 2.2 Hz, 1H), 4.53 – 4.33 (m, 2H), 4.29 (s, 1H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.07. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.3, 139.2, 132.7, 123.1 (q, *J* = 285.3 Hz), 122.1, 119.8, 119.4, 119.2, 118.9, 110.1, 75.7 (q, *J* = 31.2 Hz), 64.2, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{14}BrF_3NO_3$: 392.0104; found: 392.0109.

ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-(4-iodophenyl)-1H-pyrrol-3-yl)propanoate (3g): yellow oil, 53.2 mg, 61% yield, purification on silica gel (EtOAc : hexane = 1:30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.7 Hz, 2H), 7.27 (t, *J* = 2.1 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.99 (t, *J* = 2.7 Hz, 1H), 6.53 (t, *J* = 2.2 Hz, 1H), 4.50 – 4.33 (m, 2H), 4.29 (s, 1H), 1.38 (t, *J* = 7.1 Hz, 3H).

^{19}F NMR (471 MHz, $CDCl_3$) δ -78.05. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.3, 139.9, 138.6, 123.1 (q, *J* = 285.3 Hz), 122.3, 119.7, 119.2, 118.8, 110.2, 90.2, 75.7 (q, *J* = 31.3 Hz), 64.2, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{14}F_3INO_3$: 439.9965; found: 439.9967.

ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)propanoate (3h): yellow oil, 42.8 mg, 56% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.36 (t, *J* = 2.1 Hz, 1H), 7.09 (t, *J* = 2.8 Hz, 1H), 6.58 (t, *J* = 2.2 Hz, 1H), 4.48 – 4.37 (m, 2H), 4.32 (d, *J* = 6.6 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -62.32, -78.07. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.2, 142.7, 128.2 (q, *J* = 33.0 Hz), 127.0 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 277.2 Hz), 123.1 (q, *J* = 285.3 Hz), 120.3, 119.8, 119.7, 118.9, 110.7, 75.7 (q, *J* = 31.3 Hz), 64.2, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{14}F_6NO_3$: 382.0872; found: 382.0876.

ethyl 2-(1-(4-cyanophenyl)-1H-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3i): yellow oil, 41.7 mg, 62% yield, purification on silica gel (EtOAc : hexane = 1:15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.5 Hz, 2H), 7.38 (s, 1H), 7.10 (t, *J* = 2.8 Hz, 1H), 6.59 (s, 1H), 4.50 – 4.36 (m, 2H), 4.32 (s, 1H), 1.39 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.10. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.0, 143.1, 133.9, 123.0 (q, *J* = 285.6 Hz), 120.4, 120.3, 119.5, 118.7, 118.3, 111.3, 109.5, 75.6 (q, *J* = 31.4 Hz), 64.3, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{14}F_3N_2O_3$: 339.0951; found: 339.0954.

ethyl 2-(1-(4-acetylphenyl)-1H-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3j): yellow oil, 36.7 mg, 52% yield, purification on silica gel (EtOAc : hexane = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.40 (s, 1H), 7.13 (s, 1H), 6.59 (s, 1H), 4.51 – 4.36 (m, 2H), 4.33 (s, 1H), 2.62 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz,

$CDCl_3$) δ -78.07. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 196.7, 169.2, 143.5, 134.6, 130.2, 123.1 (q, *J* = 285.7 Hz), 119.9, 119.6, 118.8, 110.8, 75.7 (q, *J* = 31.1 Hz), 64.2, 26.6, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{17}F_3NO_4$: 356.1104; found: 356.1109.

ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-mesityl-1H-pyrrol-3-yl)propanoate (3k): yellow oil, 48.9 mg, 68% yield, purification on silica gel (EtOAc : hexane = 1:30). ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 2H), 6.81 (t, *J* = 2.0 Hz, 1H), 6.54 (t, *J* = 2.6 Hz, 1H), 6.48 (t, *J* = 2.2 Hz, 1H), 4.48 – 4.35 (m, 2H), 4.22 (s, 1H), 2.32 (s, 3H), 1.97 (d, *J* = 3.7 Hz, 6H), 1.35 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.29. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.7, 138.1, 136.9, 135.7, 135.7, 128.7, 123.3 (q, *J* = 285.6 Hz), 122.0, 121.2, 116.9, 107.9, 75.9 (q, *J* = 31.1 Hz), 63.8, 21.0, 17.2, 17.2, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{21}F_3NO_3$: 356.1468; found: 356.1465.

ethyl 2-(1-(3-chlorophenyl)-1H-pyrrol-3-yl)-3,3,3-trifluoro-2-hydroxypropanoate (3l): yellow oil, 58.0 mg, 84% yield, purification on silica gel (EtOAc : hexane = 1:15). ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.30 – 7.24 (m, 3H), 7.02 (t, *J* = 2.8 Hz, 1H), 6.54 (t, *J* = 2.2 Hz, 1H), 4.48 – 4.36 (m, 2H), 4.29 (s, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.08. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.3, 141.2, 135.3, 130.7, 126.3, 123.1 (d, *J* = 285.5 Hz), 120.8, 119.8, 119.3, 118.9, 118.6, 110.2, 75.7 (q, *J* = 31.5 Hz), 64.2, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{15}H_{14}ClF_3NO_3$: 348.0609; found: 348.0613.

ethyl 3,3,3-trifluoro-2-(1-(2-formylphenyl)-1H-pyrrol-3-yl)-2-hydroxypropanoate (3m): yellow oil, 64.8 mg, 80% yield, purification on silica gel (EtOAc : hexane = 1:25). ^1H NMR (500 MHz, $CDCl_3$) δ 9.80 (d, *J* = 0.8 Hz, 1H), 8.01 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.55 – 7.49 (m, 1H), 7.45 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.17 (t, *J* = 2.0 Hz, 1H), 6.89 (t, *J* = 2.7 Hz, 1H), 6.59 (t, *J*

= 2.2 Hz, 1H), 4.53 – 4.34 (m, 2H), 4.29 (s, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.19. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 189.5, 169.3, 143.2, 134.8, 130.8, 128.4, 128.2, 126.6, 124.1, 123.1 (q, *J* = 285.3 Hz), 123.1, 119.1, 109.9, 75.6 (q, *J* = 31.3 Hz), 64.2, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{15}F_3NO_4$: 342.0948; found: 342.0949.

ethyl 3,3,3-trifluoro-2-hydroxy-2-(1-(2-vinylphenyl)-1H-pyrrol-3-yl)propanoate (3n): yellow oil, 41.4 mg, 61% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.35 (dtd, *J* = 17.9, 7.4, 1.6 Hz, 2H), 7.28-7.25 (m, 1H), 7.03 (t, *J* = 2.1 Hz, 1H), 6.77 (t, *J* = 2.6 Hz, 1H), 6.54 – 6.43 (m, 2H), 5.71 (dd, *J* = 17.5, 1.1 Hz, 1H), 5.28 (dd, *J* = 11.0, 1.1 Hz, 1H), 4.50 – 4.34 (m, 2H), 4.23 (s, 1H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.11. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.5, 138.5, 133.5, 132.2, 128.4, 127.9, 126.5, 126.4, 123.2 (q, *J* = 285.3 Hz), 123.1, 122.2, 117.5, 116.5, 108.4, 75.6 (q, *J* = 31.3 Hz), 64.0, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{17}F_3NO_3$: 340.1155; found: 340.1158.

ethyl

2-chloro-4-(3-(3-ethoxy-1,1,1-trifluoro-2-hydroxy-3-oxopropan-2-yl)-1H-pyrrol-1-yl)benzoate

(3o): yellow oil, 59.0 mg, 80% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 1H), 7.42 (d, *J* = 2.3 Hz, 1H), 7.28 (t, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.01 (t, *J* = 2.8 Hz, 1H), 6.51 (t, *J* = 2.3 Hz, 1H), 4.41 – 4.33 (m, 2H), 4.23 (s, 1H), 3.88 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -78.10. $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 169.1, 165.2, 143.0, 135.7, 133.3, 126.7, 123.1 (q, *J* = 285.3 Hz), 122.2, 120.3, 119.6, 118.7, 117.6, 111.1, 75.6 (q, *J* = 31.1 Hz), 64.3, 52.5, 14.0. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{18}H_{17}ClF_3NNaO_5$: 442.0640; found: 442.0634.

ethyl 3,3,3-trifluoro-2-hydroxy-2-(5-methyl-1-phenyl-1H-pyrrol-3-yl)propanoate (3p): yellow oil, 53.8 mg, 82% yield, purification on silica gel (EtOAc : hexane = 1:25). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46-7.41 (m, 2H), 7.38 – 7.33 (m, 1H), 7.30 – 7.26 (m, 2H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.21 (s, 1H), 4.48-4.32 (m, 2H), 4.20 (s, 1H), 2.17 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -77.87. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.6, 139.8, 129.7, 129.1, 127.3, 125.8, 123.3 (q, *J* = 285.4 Hz), 120.8, 116.3, 107.3, 75.8 (q, *J* = 31.2 Hz), 63.9, 14.0, 12.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{16}H_{17}F_3NO_3$: 328.1155; found: 328.1161.

diethyl 2-hydroxy-2-(1-phenyl-1H-pyrrol-3-yl)malonate (4a): yellow oil, 53.3 mg, 84% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.35 (m, 5H), 7.31 (t, *J* = 2.1 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.04 (t, *J* = 2.7 Hz, 1H), 6.49 (t, *J* = 2.3 Hz, 1H), 4.39 – 4.26 (m, 5H), 4.18 (s, 1H), 1.32 (t, *J* = 7.1 Hz, 7H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.1, 140.5, 129.5, 125.9, 121.8, 120.5, 119.5, 118.4, 110.0, 90.0, 62.8, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{20}NO_5$: 318.1336; found: 318.1339.

diethyl 2-hydroxy-2-(1-(4-isopropylphenyl)-1H-pyrrol-3-yl)malonate (4b): yellow oil, 45.2 mg, 63% yield, purification on silica gel (EtOAc : hexane = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 7.28 – 7.23 (m, 3H), 7.00 (t, *J* = 2.7 Hz, 1H), 6.47 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.36 – 4.27 (m, 4H), 4.18 (s, 1H), 2.93 (p, *J* = 6.9 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 6H), 1.26 (d, *J* = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.2, 146.6, 138.4, 127.4, 121.4, 120.6, 119.5, 118.5, 109.7, 90.0, 62.8, 33.6, 24.0, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{26}NO_5$: 360.1805; found: 360.1809.

diethyl 2-(1-([1,1'-biphenyl]-4-yl)-1H-pyrrol-3-yl)-2-hydroxymalonate (4c): yellow oil, 63.2 mg, 80% yield, purification on silica gel (DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.61 (m, 2H),

7.61 – 7.57 (m, 2H), 7.48 – 7.42 (m, 4H), 7.38 – 7.33 (m, 2H), 7.08 (t, *J* = 2.7 Hz, 1H), 6.52 (dd, *J* = 3.0, 1.7 Hz, 1H), 4.39 – 4.26 (m, 4H), 4.21 (s, 1H), 1.33 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 170.1, 140.1, 139.6, 138.8, 128.9, 128.2, 127.4, 126.9, 121.9, 120.7, 119.4, 118.3, 110.2, 62.8, 14.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{23}H_{24}NO_5$: 394.1649; found: 394.1653.

diethyl 2-hydroxy-2-(1-(4-methoxyphenyl)-1H-pyrrol-3-yl)malonate (4d): yellow oil, 37.4 mg, 55% yield, purification on silica gel (DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.21 (dd, *J* = 2.4, 1.7 Hz, 1H), 6.96 – 6.90 (m, 3H), 6.46 (dd, *J* = 2.9, 1.7 Hz, 1H), 4.41 – 4.21 (m, 4H), 4.16 (s, 1H), 3.83 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 170.2, 157.8, 134.2, 122.2, 121.2, 119.8, 118.7, 114.6, 109.5, 62.8, 55.6, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{22}NO_6$: 348.1442; found: 348.1442.

diethyl 2-(1-(4-fluorophenyl)-1H-pyrrol-3-yl)-2-hydroxymalonate (4e): yellow oil, 57.0 mg, 84% yield, purification on silica gel (EtOAc : hexane = 1:15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.24 (t, *J* = 2.1 Hz, 1H), 7.10 (t, *J* = 8.5 Hz, 2H), 6.96 (t, *J* = 2.7 Hz, 1H), 6.52 – 6.46 (m, 1H), 4.39 – 4.27 (m, 4H), 4.20 (s, 1H), 1.32 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 170.1, 160.7 (d, *J* = 245.1 Hz), 136.8 (d, *J* = 2.9 Hz), 122.3 (d, *J* = 8.2 Hz), 121.9, 119.7, 118.6, 116.3 (d, *J* = 23.0 Hz), 110.1, 62.8, 14.0. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd. for $C_{17}H_{18}FNNaO_5$: 358.1061; found: 358.1061.

diethyl 2-hydroxy-2-(1-(4-iodophenyl)-1H-pyrrol-3-yl)malonate (4f): yellow oil, 40.0 mg, 45% yield, purification on silica gel (DCM : hexane = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 2.0 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 7.00 (t, *J* = 2.7 Hz, 1H), 6.50 (s, 2H), 4.45 – 4.25 (m, 4H), 4.19 (s, 1H), 1.32 (t, *J* = 7.1 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$)

δ 170.0, 140.1, 138.5, 122.3, 122.1, 119.2, 118.1, 110.6, 89.7, 62.9, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{19}INO_5$: 444.0302; found: 444.0308.

diethyl 2-hydroxy-2-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-yl)malonate (4g): yellow oil, 49.6 mg, 64% yield, purification on silica gel (DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 2.4 Hz, 1H), 7.09 (t, *J* = 3.0, 1H), 6.55 (dd, *J* = 3.1, 1.7 Hz, 1H), 4.41 – 4.26 (m, 4H), 4.21 (s, 1H), 1.33 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.9, 142.9, 127.7 (q, *J* = 32.8 Hz), 126.9 (q, *J* = 3.9 Hz), 123.9 (q, *J* = 270.8 Hz), 122.9, 120.0, 119.3, 118.1, 111.1, 62.9, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{19}F_3NO_5$: 386.1210; found: 386.1216.

diethyl 2-(1-(4-acetylphenyl)-1H-pyrrol-3-yl)-2-hydroxymalonate (4h): yellow oil, 36.3 mg, 51% yield, purification on silica gel (EtOAc : hexane = 1:5). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.8 Hz, 2H), 7.40 (t, *J* = 2.4, 1H), 7.12 (t, *J* = 3.1 Hz, 1H), 6.55 (dd, *J* = 3.1, 1.7 Hz, 1H), 4.39 – 4.27 (m, 4H), 4.21 (s, 1H), 2.61 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 196.8, 169.9, 143.7, 134.2, 130.2, 123.0, 119.4, 119.2, 118.0, 111.2, 62.9, 26.6, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{22}NO_6$: 360.1442; found: 360.1447.

diethyl 2-hydroxy-2-(1-mesityl-1H-pyrrol-3-yl)malonate (4i): yellow oil, 47.8 mg, 66% yield, purification on silica gel (DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 2H), 6.72 (t, *J* = 2.0 Hz, 1H), 6.45 (t, *J* = 2.5 Hz, 1H), 6.37 (dd, *J* = 2.8, 1.7 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 4H), 4.05 (s, 1H), 2.25 (s, 3H), 1.92 (s, 6H), 1.22 (t, *J* = 7.1 Hz, 7H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.4, 137.9, 137.1, 135.8, 128.6, 121.6, 120.8, 120.0, 107.9, 62.5, 21.0, 17.3, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{26}NO_5$: 360.1805; found: 360.1808.

diethyl 2-(1-(3-chlorophenyl)-1H-pyrrol-3-yl)-2-hydroxymalonate (4j): yellow oil, 49.7 mg, 71% yield, purification on silica gel (DCM) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, *J* = 2.1 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 2.0 Hz, 1H), 7.28 – 7.26 (m, 1H), 7.24 – 7.19 (m, 1H), 7.02 (t, *J* = 2.8 Hz, 1H), 6.51 (s, 1H), 4.40 – 4.25 (m, 4H), 4.19 (s, 1H), 1.32 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.9, 141.4, 135.2, 130.6, 125.8, 122.4, 120.6, 119.3, 118.4, 118.2, 110.6, 62.9, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{17}H_{19}ClNO_5$: 352.0946; found: 352.0946.

diethyl 2-hydroxy-2-(1-(2-vinylphenyl)-1H-pyrrol-3-yl)malonate (4k): yellow oil, 44.0 mg, 65% yield, purification on silica gel (DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.3, 1.9 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.29 – 7.27 (m, 1H), 7.03 (t, *J* = 2.3, 1H), 6.76 (t, *J* = 2.9, 1H), 6.55 (dd, *J* = 17.5, 11.0 Hz, 1H), 6.46 (dd, *J* = 2.9, 1.7 Hz, 1H), 5.70 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.27 (dd, *J* = 11.0, 1.2 Hz, 1H), 4.41 – 4.25 (m, 4H), 4.15 (s, 1H), 1.32 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.2, 138.8, 133.4, 132.5, 128.3, 127.6, 126.5, 126.4, 122.8, 121.7, 120.6, 116.2, 108.6, 62.7, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{19}H_{22}NO_5$: 344.1492; found: 344.1497.

diethyl 2-(1-(3-chloro-4-(ethoxycarbonyl)phenyl)-1H-pyrrol-3-yl)-2-hydroxymalonate (4l): yellow oil, 52.0 mg, 64% yield, purification on silica gel (DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.36 (dd, *J* = 2.4, 1.7 Hz, 1H), 7.32 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.08 (t, *J* = 3.1, 1H), 6.55 (dd, *J* = 3.1, 1.7 Hz, 1H), 4.40 – 4.24 (m, 4H), 4.21 (s, 1H), 3.94 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8, 165.2, 143.2, 135.7, 133.2, 126.2, 123.3, 121.9, 119.1, 118.0, 117.4, 111.6, 63.0, 52.5, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{20}H_{22}ClNNaO_7$: 446.0977; found: 446.0981.

diethyl 2-hydroxy-2-(5-methyl-1-phenyl-1H-pyrrol-3-yl)malonate (4m): yellow oil, 52.8 mg, 80% yield, purification on silica gel (DCM). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.44-7.40 (m, 2H), 7.35 – 7.31 (m, 1H), 7.31 – 7.28 (m, 2H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.18 (dd, *J* = 2.0, 1.0 Hz, 1H), 4.40 – 4.25 (m, 4H), 4.10 (s, 1H), 2.18 (d, *J* = 1.0 Hz, 3H), 1.37 – 1.25 (m, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.2, 140.0, 129.0, 127.0, 125.7, 120.3, 119.4, 107.7, 62.7, 14.1, 13.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd. for $C_{18}H_{22}NO_5$: 332.1492; found: 332.1494.

ethyl 3,3,3-trifluoro-2-hydroxy-2-(4-(pyrrolidin-1-yl)phenyl)propanoate (3a'): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.3 Hz, 2H), 6.59 – 6.52 (m, 2H), 4.46 – 4.32 (m, 2H), 4.19 (d, *J* = 2.0 Hz, 1H), 3.28 (q, *J* = 4.2 Hz, 4H), 2.06 – 1.90 (m, 4H), 1.40 – 1.33 (m, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.5, 148.4, 123.4 (q, *J* = 285.5 Hz), 118.9, 111.2, 77.7 (d, *J* = 30.1 Hz), 64.0, 47.6, 25.5, 13.9.

diethyl 2-hydroxymalonate (5):[19] ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.62 (d, *J* = 8.3 Hz, 1H), 4.27-4.19 (m, 4H), 3.33 (d, *J* = 8.3 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.5, 71.5, 62.6, 14.0.

Supporting Information

Structural proofs and NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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