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Note

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Brønsted Acid Catalyzed Three-component Reaction of Anilines, α-Oxoaldehydes and α-Angelicalactone for the Synthesis of Complex Pyrrolidones

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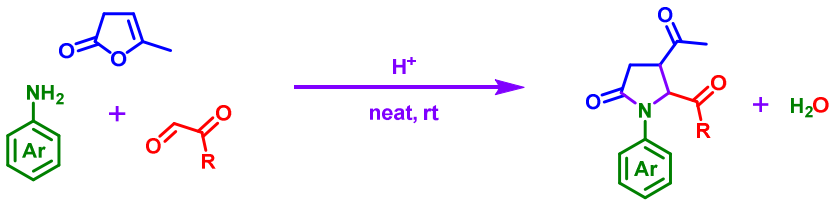


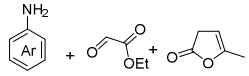
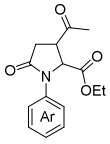
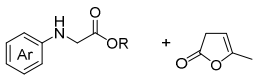
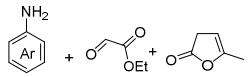
Abstract: A green and efficient three-component reaction of easily available anilines, α-oxoaldehydes and α-angelicalactone was developed for the synthesis of highly functionalized pyrrolidones using dilute sulfuric acid as the catalyst. Products were obtained in good to high yields at room temperature and under solvent-free conditions. The reaction could also be performed on a multi-gram scale with the same efficiency.

Substituted pyrrolidones are valuable Nitrogen-containing heterocycles and ubiquitously present in natural products and pharmaceutical drugs, which are associated with a broad spectrum of biological activities.[1] Therefore, exploring of new synthesis methods of this five-membered heterocycle skeletons from easily accessible starting materials with a simple operation is of great significance. To our surprise, despite the widely recognized importance and utility of these compounds, there is still relative rare general procedure that exists for their synthesis.[2]

Multi-component reactions (MCRs) have already become a useful synthetic tool in modern organic chemistry, and they allow the construction of complex molecular structures from simple and easily available precursors with high efficiency and step-economic feature.[3]

In 2007, Lavilla's group reported a novel three-component reaction of anilines, glyoxylate and α-angelicalactone to construct *N*-arylated pyrrolidones in 3 steps (1, $Sc(OTf)_3$; 2, $SOCl_2$/Py; 3, TFA) (Scheme 1).[2a] Very recently, our group reported a new efficient copper-catalyzed aerobic oxidative dehydrogenative formal [2 + 3] cyclization of glycine derivatives with α-angelicalactone to construct *N*-arylated pyrrolidones (Scheme 1).[2b]

Scheme 1. Methods for the synthesis of 1,4,5-trisubstituted pyrrolidone

	substrates	conditions	products	results
2007		1, $Sc(OTf)_3$ (20 mol %), MeCN, rt, 12 h 2, $SOCl_2$/Py 3, TFA		**5 examples, up to 31% yields**
2015		$CuCl_2$ (5 mol %), H_2SO_4 (10 M, 50 mol %), MeCN, air, rt		**22 examples, up to 80% yields**
This work		H_2SO_4 (5 M, 30 mol %), neat, rt, 1 h		**25 examples, up to 75% yields**

However, there are still some drawbacks in both processes. For the first one, only 5 successful pyrrolidone examples were demonstrated with multiple steps and low yields (11-31%). In the second one, *N*-aryl glycine derivatives need to be prepared before the reactions. And

moreover, in the both preparation methods of the *N*-aryl pyrrolidones, metal catalysts were used. As one of the main interests in heterocycles is their biological activity, which is always sensitive to the residual amount of metal reagent in the final products.[4] Therefore, develop of general, convenient and environmentally benign strategies for the synthesis of these compounds is still of great importance and interest.

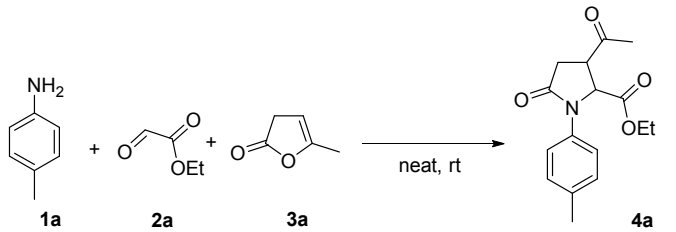
Under above backgrounds and our own research interests on heterocycle synthesis,[2b,5] we report here a practical one-pot three-component procedure for the synthesis of complex pyrrolidones under metal- and solvent- free conditions. Only diluted H_2SO_4 was required as the catalyst here and the reaction could be easily performed on a large scale (Scheme 1).

During our studies of copper-catalyzed aerobic oxidative dehydrogenative formal [2+3] cyclization of glycine derivatives with α-angelicalactone, careful control experiments were carried out to investigate the details of the mechanism.[2b] The results indicate that copper salt is the catalyst for the oxidation of glycine derivatives to generate imine intermediates under aerobic conditions.[2b,6] Brønsted acid was utilized as a proton donor to improve the electrophilicity of the imines and facilitate the following nucleophilic procedures between imines and α-angelicalactone. This inspired us to develop a Brønsted acid catalyzed three-component reaction of anilines, α-oxoaldehydes and α-angelicalactone to construct highly functionalized pyrrolidones.

Initially, we examined the reaction of *p*-toluidine **1a**, ethyl 2-oxoacetate **2a** and 5-methylfuran-2(3H)-one **3a**, conducted under room temperature in neat condition using stoichiometric amounts of concentrated sulfuric acid as the catalyst. Solvent-free protocol leads to a clean and economical technology not only with the increment of safety and the reduction of cost, but also increased amounts of reactants can be achieved in the same equipment without huge modifications.[7] We were delighted to find that the designed three-component condensation product **4a** could be isolated from the reaction mixture in 46% yield within 5 minutes (Table 1, entry 1). The concentration of the sulfuric acid was then investigated (Table 1, entries 1-4). The best yield was obtained when 5 M sulfuric acid was

used. Further evaluation using a higher or lower catalyst loading indicated that the optimum yield of **4a** was obtained in the presence of 30 mol % 5 M sulfuric acid (Table 1, entry 7). In the absence of a catalyst, the reaction did not occur. Following these results, other Brønsted acids (HCl, HBr, p-TSA, TFA, AcOH, TfOH) were then screened for the three-component *N*-aryl pyrrolidones synthesis. However, no further increase of the yields was observed (Table 1, entries 10-15). Furthermore, the reaction completes within 1 hour. The prolonged reaction time did not affect the product yield much. it needs to mention that **4a** was always obtained as a pair of unseparable diastereoisomers (5:1). The diastereomeric ratio was determined by 1H NMR spectroscopic analysis of the crude reaction mixtures, and the *trans*-isomer was identified as the major stereoisomer in accordance with the literature.[2a, 2b]

Table 1. Screening of Reaction Conditions[a]

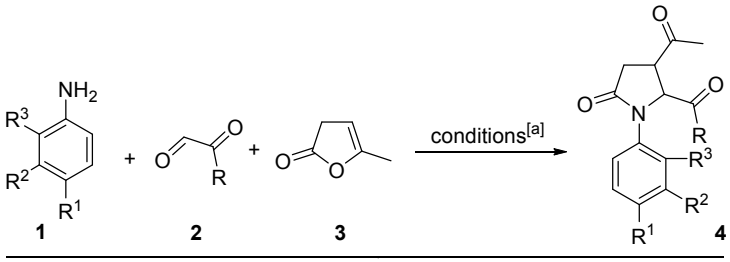


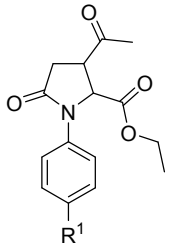
1a **2a** **3a** **4a**

Entry	Catalyst	t (h)	**4a** (yield %)[b]
1	H_2SO_4 (18 M, 50 mol %)	0.1	46
2	H_2SO_4 (10 M, 50 mol %)	0.2	54
3	H_2SO_4 (5 M, 50 mo l%)	1	61
4	H_2SO_4 (1 M, 50 mol %)	2	29
5	H_2SO_4 (5 M, 60 mol %)	1	51
6	H_2SO_4 (5 M, 40 mol %)	1	61
7	H_2SO_4 (5 M, 30 mol %)	1	63
8	H_2SO_4 (5 M, 25 mol %)	1	59
9	H_2SO_4 (5 M, 20 mol %)	1	56
10	HCl (conc, 60 mol %)	1	49
11	HBr (conc, 60 mol %)	1	47
12 [c]	TsOH (60 mol %)	1	52
13 [c]	TFA (60 mol %)	1	57
14 [c]	AcOH (60 mol %)	1	trace
15 [c]	TfOH (60 mol %)	1	55

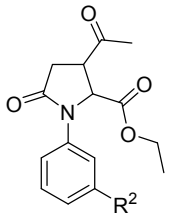
[a] Reaction Conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), **3a** (2.0 mmol). [b] Isolated Yields of the isolated products. [c] The organic acids were used as pure compound.

Table 2. Brønsted acid catalyzed three-component reaction of anilines, α-oxoaldehydes and *α*-angelicalactone

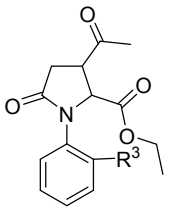




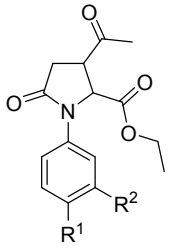
R^1 = Me	**4a** (63%, 4.9:1)
Et	**4b** (66%, 5.0:1)
^{i}Pr	**4c** (64%, 4.8:1)
^{n}Bu	**4d** (62%, 4.9:1)
^{t}Bu	**4e** (60%, 4.5:1)
Ph	**4f** (28%, 5.0:1)
MeO	**4g** (56%, 4.5:1)
EtO	**4h** (62%, 5.0:1)
PhO	**4i** (62%, 4.9:1)
F	**4j** (43%, 4.8:1)
Cl	**4k** (75%, 5.1:1)
Br	**4l** (71%, 5.0:1)
I	**4m** (52%, 4.8:1)
NO_2	**4n** (50%, 5.1:1)
CN	**4o** (44%, 5.1:1)
C(O)OEt	**4p** (57%, 4.7:1)



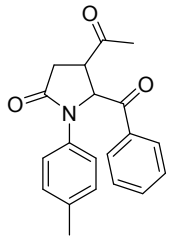
R^2 = Me	**4q** (29%, 5.0:1)
^{i}Pr	**4r** (48%, 5.0:1)
Cl	**4s** (47%, 5.1:1)
NO_2	**4t** (57%, 4.9:1)



R^3 = Me **4u** (0 %)



R^1 = Me; R^2 = Me	**4v** (55%, 4.7:1)
R^1 = Me; R^2 = F	**4w** (58%, 4.8:1)
R^1 = Me; R^2 = Cl	**4x** (55%, 4.7:1)

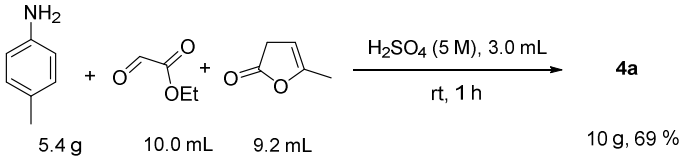


R = Ph **4y** (47 %, 9.3:1)

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (2.0 mmol), H_2SO_4 (5 M, 30 mol %), neat, rt, 1-2 h. [b] Yield of the isolated product. [c] Diastereomeric ratio.

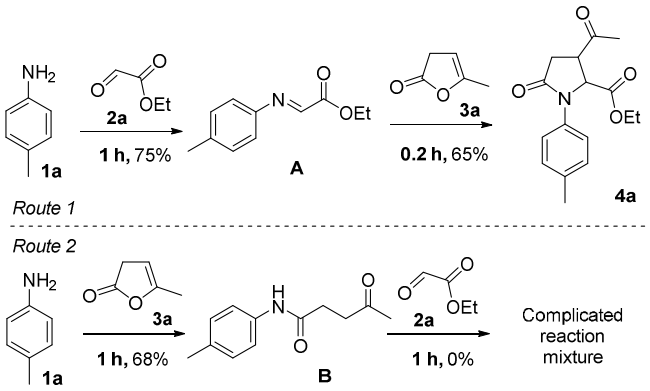
With the optimized reaction conditions in hand, we next examined the reaction scope of this transformation. The typical results on the synthesis of substituted pyrrolidones via this three-component process are shown in Table 2. A variety of substituted anilines were first examined. The optimal conditions were compatible with a variety of substituents, including methoxy, nitro, cyano and ester groups. No remarkable differences in reactivity were observed when electron-withdrawing or electron-donating groups were present in the aromatic ring. It's worth noting that this is complementary to our early developed copper catalyzed approach in which *N*-aryl glycine derivative bearing strong electron-withdrawing group such as nitro group cannot be oxidized to generate corresponding product. In particular, all kinds of halo substituents could survive in the reaction, which provide useful handles for further transformations. Moreover, molecules bearing a fluorine atom could have a significant effect on their pharmacological properties.[8] Anilines bearing groups at the *para*-position all furnished the corresponding three-component products in good yields. Similarly, *meta*-Substituted anilines and *poly*-substituted anilines also delivered the corresponding products in moderate to good yields. In contrast, no product was observed with *ortho*-methyl-substituted anilines as the substrates. We were delighted to find that 2-oxo-2-phenylacetaldehyde was also consistent with the optimal conditions, leading to compound **4y** in 47% yield.

Scheme 2. Scalability of the reaction to the multi-gram scale



Scalability is an important aspect of chemical industries.[9] To examine the scalability of the present methodology, a reaction of *p*-toluidine **1a**, ethyl 2-oxoacetate **2a** and α-angelicalactone **3a** was performed at the 10 grams scale. The corresponding **4a** was obtained in 69% isolated yield as shown in Scheme 2. That is to say, here we present a practical and scalable synthetic entry to the highly functionalized pyrrolidone derivatives.

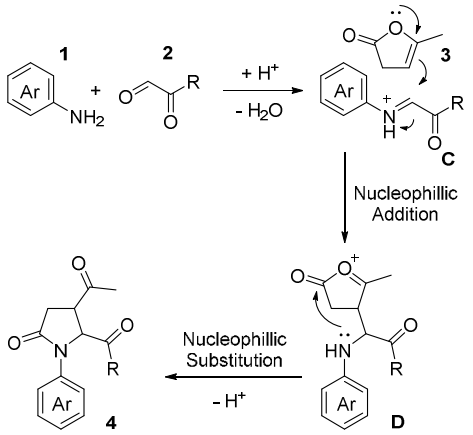
Scheme 3. Control experiments



To gain some insight into the pathway of this catalytic three-component reaction, several control experiments were conducted. This reaction possibly undergoes one of the two pathways either with imine **A** as the intermediate [(**1**+**2**)+**3**] or with amide **B** as the intermediate [(**1**+**3**)+**2**] as shown in **Scheme 3**. The following reactions were carried out. (1) Treatment of **1a** with **2a** gave imine intermediate **A**, isolated with 75% yield after 1 hour reaction time. Subsequently, **A** was treated with **3a** in the presence of sulfuric acid (5 M, 30 mol %), which led smoothly to the expected pyrrolidone **4a** in 65% isolated yield. (2) Treatment of **1a** with **3a** gave amide intermediate **B**, isolated with 68% yield after 1 hour reaction time. However, under identical conditions, the reaction between **B** and **2a** gave **4a** in 0% yield. These results clearly indicated that this three-component reaction proceeded through a stepwise (**1**+**2**)+**3** pathway.

Therefore, a tentative mechanism for the H_2SO_4-catalyzed three-component cyclization reaction is proposed in **Scheme 4**. The iminium ion intermediate **C** was generated under a Brønsted acid catalyzed nucleophilic reaction. Subsequently, nucleophilic addition of activated intermediate **C** with α-angelicalactone occurred to give intermediate **D**. Finally, an intramolecular nucleophilic substitution and the following deprotonation lead to product **4.**

Scheme 4. Proposed mechanism



In conclusion, we have developed a simple, highly efficient and environmentally benign three-component reaction of anilines, α-oxoaldehydes and α-angelicalactone, leading to 1,4,5-trisubstituted pyrrolidone derivatives by using Bronsted acid as the proton source under solvent-free conditions. This protocol is also applicable on a gram-scale synthesis.

Experimental Section

General Information.

The starting materials, reagents and solvents, purchased from commercial suppliers, were used without further purification. Analytical TLC was performed with silica gel GF254 plates, and the products were visualized by UV detection. Flash chromatography was carried out using silica gel 200−300. ^{1}HNMR (600 MHz) and ^{13}CNMR (150 MHz) spectra were measured with $CDCl_3$ as solvent. High-resolution mass spectra (HRMS) were measured on an electrospray ionization (ESI) apparatus using time of flight (TOF) mass spectrometry.

General procedure for the preparation of highly functionalized pyrrolidones 4.

To a stirred mixture of α-angelicalactone (**3**, 2.0 mmol) α-oxoaldehydes (**2**, 1.0 mmol) and anilines (**1**, 1.0 mmol), H_2SO_4 (5 M, 30 mol%) were added. The reactions were performed at room temperature and completed within 1-2 hours as monitored by TLC. The products **4** were isolated by silica gel column chromatography using petroleum ether/acetone (v/v 4:1 to 3:1).

Characterization of the products

Ethyl 3-acetyl-5-oxo-1-(p-tolyl)pyrrolidine-2-carboxylate (4a).[2a, 2b] light Yellow oil, 63% yield (182 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 7.8, 2H), 7.16 (d, *J* = 7.9, 2H), 5.01 (d, *J* = 2.0, 1H), 4.16 (q, *J* = 7.1, 2H), 3.37 – 3.31 (m, 1H), 3.01 (dd, *J* = 17.2, 10.4, 1H), 2.73 (dd, *J* = 17.2, 3.9, 1H), 2.31 (s, 6H), 1.19 (t, *J* = 7.1, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 171.3, 170.9, 136.2, 134.8, 129.6, 123.2, 62.5, 62.0, 47.5, 33.2, 28.0, 20.9, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.33 – 7.28 (m, 2H), 7.19 – 7.13 (m, 2H), 4.83 (d, *J* = 8.4, 1H), 4.14 – 4.09 (m, 2H), 3.76 – 3.69 (m, 1H), 3.19 (dd, *J* = 16.6, 11.9, 1H), 2.61 (dd, *J* = 16.6, 8.6, 1H), 2.31 (s, 6H), 1.21 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 169.5, 136.0, 134.9, 129.7, 122.4, 63.5, 48.4, 32.8, 27.6, 20.9, 13.9. HRMS (ESI) exact mass calcd for $C_{16}H_{20}NO_4$ $[M+H]^+$ m/z 290.1392, found 290.1385.

Ethyl 3-acetyl-1-(4-ethylphenyl)-5-oxopyrrolidine-2-carboxylate (4b).[2b] light Yellow oil, 66% yield (200 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.32 (d, *J* = 7.9, 2H), 7.19 (d, *J* = 8.0, 2H), 5.01 (d, *J* = 1.9, 1H), 4.17 (q, *J* = 7.1, 2H), 3.37 – 3.31 (m, 1H), 3.01 (dd, *J* = 17.2, 10.4, 1H), 2.73 (dd, *J* = 17.2, 3.8, 1H), 2.62 (q, *J* = 7.6, 2H), 2.31 (s, 3H), 1.23 – 1.15 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 171.2, 170.9, 142.4, 135.0, 128.4, 123.1, 62.5, 62.0, 47.5, 33.1, 28.3, 28.0, 15.4, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.35 – 7.30 (m, 2H), 7.21 – 7.15 (m, 2H), 4.83 (d, *J* = 8.4, 1H), 4.14 – 4.09 (m, 2H), 3.77 – 3.69 (m, 1H), 3.19 (dd, *J* = 16.5, 12.0, 1H), 2.65 – 2.58 (m, 3H), 2.31 (s, 3H), 1.24 – 1.15 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 169.5, 142.2, 135.1, 128.5, 122.4, 63.4, 61.9, 48.4, 32.8, 29.9, 28.3, 13.9. HRMS (ESI) exact mass calcd for $C_{17}H_{22}NO_4$ $[M+H]^+$ m/z 304.1549, found 304.1545.

Ethyl 3-acetyl-1-(4-isopropylphenyl)-5-oxopyrrolidine-2-carboxylate (4c).[2b] light Yellow oil, 64% yield (203 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.33 (d, *J* = 8.0, 2H), 7.21 (d, *J* = 7.9, 2H), 5.01 (d, *J* = 3.1, 1H), 4.17 (q, *J* = 7.1, 2H), 3.37 – 3.30 (m, 1H), 3.01 (dd, *J* = 17.2, 10.4, 1H), 2.92 – 2.83 (m, 1H), 2.74 (dd, *J* = 17.2, 3.9, 1H), 2.31 (s, 3H), 1.22 (d, *J* = 6.9, 6H), 1.18 (t, *J* = 7.1, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 171.2, 170.9, 147.0, 135.0, 127.0, 123.1, 62.5, 62.0, 47.5, 33.7, 33.2, 28.0, 23.9, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.35 – 7.30 (m, 2H), 7.23 – 7.19 (m, 2H), 4.83 (d, *J* = 8.4, 1H), 4.15 – 4.08 (m, 2H), 3.76 – 3.69 (m, 1H), 3.19 (dd, *J* = 16.5,

12.1, 1H), 2.91 – 2.84 (m, 1H), 2.62 (dd, *J* = 16.7, 8.5, 1H), 2.31 (s, 3H), 1.24 – 1.16 (m, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 169.6, 146.8, 135.2, 127.1, 122.4, 63.5, 48.5, 33.6, 32.8, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{18}H_{24}NO_4$ $[M+H]^+$ m/z 318.1705, found 318.1699.

Ethyl 3-acetyl-1-(4-butylphenyl)-5-oxopyrrolidine-2-carboxylate (4d).[2b] light brown oil, 62% yield (205 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.31 (d, *J* = 8.2, 2H), 7.16 (d, *J* = 8.1, 2H), 5.01 (d, *J* = 2.7, 1H), 4.17 (q, *J* = 7.1, 2H), 3.36 – 3.31 (m, 1H), 3.01 (dd, *J* = 17.2, 10.4, 1H), 2.74 (dd, *J* = 17.2, 3.9, 1H), 2.57 (t, *J* = 7.7, 2H), 2.31 (s, 3H), 1.60 – 1.52 (m, 2H), 1.37 – 1.29 (m, 2H), 1.18 (t, *J* = 7.1, 3H), 0.90 (t, *J* = 7.3, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 171.2, 170.9, 141.1, 134.9, 129.0, 123.0, 62.5, 62.0, 47.5, 35.1, 33.4, 33.2, 28.0, 22.2, 14.0, 13.9. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.34 – 7.29 (m, 2H), 7.20 – 7.13 (m, 2H), 4.83 (d, *J* = 8.4, 1H), 4.15 – 4.09 (m, 2H), 3.75 – 3.69 (m, 1H), 3.19 (dd, *J* = 16.6, 12.0, 1H), 2.62 (dd, *J* = 16.7, 8.6, 1H), 2.59 – 2.55 (m, 2H), 2.31 (s, 3H), 1.59 – 1.52 (m, 2H), 1.37 – 1.29 (m, 2H), 1.20 – 1.15 (m, 3H), 0.93 – 0.88 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 169.5, 140.9, 135.1, 129.0, 122.3, 63.5, 48.4, 35.0, 32.8, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{19}H_{26}NO_4$ $[M+H]^+$ m/z 332.1862, found 332.1864.

Ethyl 3-acetyl-1-(4-(tert-butyl)phenyl)-5-oxopyrrolidine-2-carboxylate (4e).[2b] light Yellow oil, 60% yield (199 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37 (d, *J* = 8.6, 2H), 7.33 (d, *J* = 8.2, 2H), 5.01 (d, *J* = 1.6, 1H), 4.18 (q, *J* = 7.1, 2H), 3.36 – 3.30 (m, 1H), 3.01 (dd, *J* = 17.2, 10.4, 1H), 2.74 (dd, *J* = 17.2, 3.6, 1H), 2.31 (s, 3H), 1.29 (s, 9H), 1.19 (t, *J* = 7.0, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 171.2, 170.9, 149.2, 134.7, 125.9, 122.6, 62.4, 62.0, 47.5, 34.5, 33.2, 31.2, 28.0, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.39 – 7.36 (m, 2H), 7.35 – 7.32 (m, 2H), 4.83 (d, *J* = 8.3, 1H), 4.15 – 4.10 (m, 2H), 3.75 – 3.69 (m, 1H), 3.19 (dd, *J* = 16.6, 12.0, 1H), 2.62 (dd, *J* = 16.6, 8.5, 1H), 2.31 (s, 3H), 1.29 (s, 9H), 1.21 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.4, 169.6, 149.0, 134.9, 126.0, 121.9, 63.4, 48.5, 34.4, 32.8, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{19}H_{26}NO_4$ $[M+H]^+$ m/z 332.1862, found 332.1858.

Ethyl 1-([1,1'-biphenyl]-4-yl)-3-acetyl-5-oxopyrrolidine-2-carboxylate (4f). light Yellow oil and white solid, 28% yield (98 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.61 – 7.51 (m, 6H), 7.43 (t, *J* = 7.4, 2H), 7.34 (t, *J* = 7.3, 1H), 5.12 – 5.09 (m, 1H), 4.20 (q, *J* = 7.0, 2H), 3.41 – 3.34 (m,

1H), 3.05 (dd, *J* = 17.2, 10.4, 1H), 2.78 (dd, *J* = 17.2, 1.9, 1H), 2.34 (s, 3H), 1.21 (t, *J* = 7.1, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 171.3, 170.8, 140.3, 139.0, 136.7, 128.8, 127.7, 127.4, 127.0, 122.9, 62.2, 62.2, 47.5, 33.3, 28.0, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.62 – 7.50 (m, 6H), 7.45 – 7.40 (m, 2H), 7.36 – 7.31 (m, 1H), 4.92 (d, *J* = 8.3, 1H), 4.18 – 4.13 (m, 2H), 3.79 – 3.72 (m, 1H), 3.23 (dd, *J* = 16.5, 12.2, 1H), 2.65 (dd, *J* = 16.7, 8.5, 1H), 2.34 (s, 3H), 1.24 – 1.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 169.5, 140.2, 136.8, 128.8, 127.7, 127.4, 126.9, 122.1, 63.2, 48.3, 32.9, 29.9, 14.0. HRMS (ESI) exact mass calcd for $C_{21}H_{22}NO_4$ $[M+H]^+$ m/z 352.1549, found 352.1541.

Ethyl 3-acetyl-1-(4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylate (4g).[2a, 2b] brown oil, 56% yield (171 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 – 7.29 (m, 2H), 6.92 – 6.87 (m, 2H), 4.98 (d, *J* = 3.0, 1H), 4.17 (q, *J* = 7.1, 2H), 3.79 (s, 3H), 3.39 – 3.32 (m, 1H), 3.01 (dd, *J* = 17.2, 10.4, 1H), 2.73 (dd, *J* = 17.2, 4.1, 1H), 2.32 (s, 3H), 1.23 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 171.3, 170.9, 158.0, 130.2, 125.4, 114.3, 62.8, 62.0, 55.4, 47.5, 33.0, 28.0, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 – 7.29 (m, 2H), 6.93 – 6.85 (m, 2H), 4.80 (d, *J* = 8.4, 1H), 4.15 – 4.10 (m, 2H), 3.79 (s, 3H), 3.77 – 3.70 (m, 1H), 3.18 (dd, *J* = 16.6, 11.8, 1H), 2.62 (dd, *J* = 16.6, 8.6, 1H), 2.32 (s, 3H), 1.20 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 172.5, 169.6, 157.8, 130.3, 124.7, 114.4, 63.9, 61.9, 48.4, 32.6, 29.8, 13.9. HRMS (ESI) exact mass calcd for $C_{16}H_{20}NO_5$ $[M+H]^+$ m/z 306.1342, found 306.1344.

Ethyl 3-acetyl-1-(4-ethoxyphenyl)-5-oxopyrrolidine-2-carboxylate (4h).[2b] brown oil, 62% yield (198 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 8.9, 2H), 6.88 – 6.84 (m, 2H), 4.96 (d, *J* = 3.1, 1H), 4.18 – 4.13 (m, 2H), 4.00 (q, *J* = 7.0, 2H), 3.36 – 3.31 (m, 1H), 2.99 (dd, *J* = 17.2, 10.4, 1H), 2.71 (dd, *J* = 17.2, 4.1, 1H), 2.30 (s, 3H), 1.38 (t, *J* = 7.0, 3H), 1.20 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 171.3, 170.9, 157.4, 130.0, 125.3, 114.9, 63.6, 62.8, 612.0, 47.5, 33.0, 28.0, 14.7, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.32 – 7.27 (m, 2H), 6.90 – 6.83 (m, 2H), 4.78 (d, *J* = 8.4, 1H), 4.13 – 4.09 (m, 2H), 4.03 – 3.92 (m, 2H), 3.76 – 3.68 (m, 1H), 3.17 (dd, *J* = 16.6, 11.9, 1H), 2.60 (dd, *J* = 16.6, 8.6, 1H), 2.30 (s, 3H), 1.41 – 1.36 (m, 3H), 1.20 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 172.5, 169.6, 157.2, 130.1, 124.7, 114.9, 63.9, 61.9, 48.4, 32.6,

29.8, 13.9. HRMS (ESI) exact mass calcd for $C_{17}H_{22}NO_5$ $[M+H]^+$ m/z 320.1498, found 320.1503.

Ethyl 3-acetyl-5-oxo-1-(4-phenoxyphenyl)pyrrolidine-2-carboxylate (4i).[2b] light Yellow oil, 62% yield (228 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42 – 7.30 (m, 4H), 7.15 – 7.08 (m, 1H), 7.04 – 6.95 (m, 4H), 5.01 (d, *J* = 3.0, 1H), 4.24 – 4.16 (m, 2H), 3.40 – 3.33 (m, 1H), 3.03 (dd, *J* = 17.3, 10.4, 1H), 2.74 (dd, *J* = 17.3, 4.0, 1H), 2.33 (s, 3H), 1.24 – 1.17 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 171.3, 170.8, 156.8, 155.5, 132.5, 129.8, 125.0, 123.5, 119.1, 119.0, 62.6, 62.1, 47.5, 33.1, 28.0, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 – 7.28 (m, 4H), 7.15 – 7.07 (m, 1H), 7.05 – 6.95 (m, 4H), 4.83 (d, *J* = 8.4, 1H), 4.16 – 4.12 (m, 2H), 3.80 – 3.69 (m, 1H), 3.20 (dd, *J* = 16.7, 11.9, 1H), 2.64 (dd, *J* = 16.7, 8.6, 1H), 2.32 (s, 3H), 1.25 – 1.17 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.6, 172.5, 169.5, 156.8, 155.3, 132.6, 129.8, 124.3, 123.6, 119.1, 63.6, 62.1, 48.4, 32.7, 29.9, 14.0. HRMS (ESI) exact mass calcd for $C_{21}H_{22}NO_5$ $[M+H]^+$ m/z 368.1498, found 368.1497.

Ethyl 3-acetyl-1-(4-fluorophenyl)-5-oxopyrrolidine-2-carboxylate (4j).[2b] light Yellow oil, 43% yield (126 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.37 (m, 2H), 7.10 – 7.03 (m, 2H), 5.02 (d, *J* = 3.0, 1H), 4.18 (q, *J* = 7.1, 2H), 3.42 – 3.33 (m, 1H), 3.03 (dd, *J* = 17.3, 10.4, 1H), 2.73 (dd, *J* = 17.3, 4.0, 1H), 2.33 (s, 3H), 1.23 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 171.3, 170.6, 161.5, 159.8, 133.4, 133.4, 125.3, 125.3, 115.9, 115.8, 62.4, 62.1, 47.4, 33.0, 28.0, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.36 (m, 2H), 7.12 – 7.00 (m, 2H), 4.83 (d, *J* = 8.4, 1H), 4.15 – 4.10 (m, 2H), 3.80 – 3.70 (m, 1H), 3.19 (dd, *J* = 16.7, 11.9, 1H), 2.64 (dd, *J* = 16.7, 8.6, 1H), 2.33 (s, 3H), 1.24 – 1.14 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.6, 172.5, 169.3, 161.2, 159.6, 133.5, 133.5, 124.5, 124.5, 116.0, 115.8, 63.5, 62.1, 48.2, 32.6, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{15}H_{17}FNO_4$ $[M+H]^+$ m/z 294.1142, found 294.1147.

Ethyl 3-acetyl-1-(4-chlorophenyl)-5-oxopyrrolidine-2-carboxylate (4k).[2a, 2b] light Yellow oil, 75% yield (232 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.40 (d, *J* = 8.4, 2H), 7.32 (d, *J* = 8.5, 2H), 5.03 (d, *J* = 2.5, 1H), 4.17 (q, *J* = 7.1, 2H), 3.37 – 3.32 (m, 1H), 3.02 (dd, *J* = 17.3, 10.4, 1H), 2.73 (dd, *J* = 17.3, 3.8, 1H), 2.31 (s, 3H), 1.20 (t, *J* = 7.0, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.5, 171.2, 170.6, 136.1, 131.5, 129.1, 123.9, 62.2, 62.0, 47.3, 33.2, 28.0, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.43 (d, *J* = 8.6, 2H), 7.35 – 7.30 (m, 2H), 4.84 (d, *J* = 8.4, 1H), 4.15 – 4.10 (m,

2H), 3.76 – 3.68 (m, 1H), 3.18 (dd, *J* = 16.7, 12.0, 1H), 2.62 (dd, *J* = 16.8, 8.5, 1H), 2.31 (s, 3H), 1.23 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.4, 172.4, 169.2, 136.2, 131.1, 129.2, 123.0, 63.0, 48.1, 32.8, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{15}H_{17}ClNO_4$ $[M+H]^+$ m/z 310.0846, found 310.0850.

Ethyl 3-acetyl-1-(4-bromophenyl)-5-oxopyrrolidine-2-carboxylate (4l).[2a, 2b] light Yellow oil, 71% yield (251 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 – 7.45 (m, 2H), 7.39 – 7.32 (m, 2H), 5.05 (d, *J* = 3.0, 1H), 4.23 – 4.14 (m, 2H), 3.41 – 3.31 (m, 1H), 3.02 (dd, *J* = 17.4, 10.4, 1H), 2.73 (dd, *J* = 17.4, 4.0, 1H), 2.32 (s, 3H), 1.23 – 1.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.5, 171.1, 170.5, 136.6, 132.1, 124.1, 119.3, 62.2, 61.9, 47.3, 33.2, 28.0, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 – 7.45 (m, 2H), 7.41 – 7.32 (m, 2H), 4.85 (d, *J* = 8.4, 1H), 4.15 – 4.11 (m, 2H), 3.78 – 3.69 (m, 1H), 3.19 (dd, *J* = 16.8, 11.9, 1H), 2.63 (dd, *J* = 16.8, 8.5, 1H), 2.32 (s, 3H), 1.24 – 1.17 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.5, 169.5, 136.0, 134.9, 129.7, 122.4, 63.5, 48.4, 37.8, 32.8, 27.6, 20.9, 13.9. HRMS (ESI) exact mass calcd for $C_{15}H_{17}BrNO_4$ $[M+H]^+$ m/z 354.0341, found 354.0337.

Ethyl 3-acetyl-1-(4-iodophenyl)-5-oxopyrrolidine-2-carboxylate (4m).[2b] light Yellow oil, 52% yield (209 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 8.4, 2H), 7.26 (d, *J* = 6.1, 2H), 5.05 (d, *J* = 2.8, 1H), 4.19 (q, *J* = 7.2, 2H), 3.39 – 3.32 (m, 1H), 3.02 (dd, *J* = 17.3, 10.4, 1H), 2.73 (dd, *J* = 17.4, 3.9, 1H), 2.33 (s, 3H), 1.25 – 1.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.5, 171.1, 170.5, 138.0, 137.4, 124.2, 90.3, 62.2, 61.7, 47.2, 33.2, 28.0, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.72 – 7.64 (m, 2H), 7.28 – 7.22 (m, 2H), 4.85 (d, *J* = 8.4, 1H), 4.16 – 4.10 (m, 2H), 3.77 – 3.68 (m, 1H), 3.19 (dd, *J* = 16.6, 12.3, 1H), 2.63 (dd, *J* = 16.8, 8.6, 1H), 2.33 (s, 3H), 1.24 – 1.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.4, 172.4, 169.2, 138.1, 137.5, 123.3, 89.8, 62.7, 62.2, 48.1, 32.9, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{15}H_{17}INO_4$ $[M+H]^+$ m/z 402.0202, found 402.0200.

Ethyl 3-acetyl-1-(4-nitrophenyl)-5-oxopyrrolidine-2-carboxylate (4n). Yellow oil, 50% yield (160 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.22 (d, *J* = 9.1, 2H), 7.71 (d, *J* = 8.9, 2H), 5.18 – 5.16 (m, 1H), 4.22 (q, *J* = 7.0, 2H), 3.42 – 3.37 (m, 1H), 3.08 (dd, *J* = 17.5, 10.5, 1H), 2.79 (dd, *J* =

17.6, 2.6, 1H), 2.34 (s, 3H), 1.22 (t, *J* = 7.0, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.4, 171.6, 170.1, 144.2, 143.4, 124.6, 120.6, 62.6, 61.2, 46.9, 33.4, 27.9, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.05 (d, *J* = 8.9, 1H), 7.76 (d, *J* = 9.1, 2H), 6.61 (d, *J* = 8.8, 1H), 4.98 (d, *J* = 8.3, 1H), 4.19 – 4.12 (m, 2H), 3.79 – 3.72 (m, 1H), 3.24 (dd, *J* = 16.8, 12.3, 1H), 2.69 (dd, *J* = 16.9, 8.4, 1H), 2.34 (s, 3H), 1.25 – 1.19 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.2, 172.8, 168.7, 143.9, 143.5, 124.8, 119.7, 62.5, 62.2, 47.7, 33.1, 30.0, 13.9. HRMS (ESI) exact mass calcd for $C_{15}H_{17}N_2O_6$ $[M+H]^+$ m/z 321.1087, found 321.1091.

Ethyl 3-acetyl-1-(4-cyanophenyl)-5-oxopyrrolidine-2-carboxylate (4o). light Yellow oil, 44% yield (132 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.67 – 7.61 (m, 4H), 5.14 – 5.11 (m, 1H), 4.20 (q, *J* = 7.1, 2H), 3.40 – 3.34 (m, 1H), 3.06 (dd, *J* = 17.5, 10.5, 1H), 2.80 – 2.73 (m, 1H), 2.33 (s, 3H), 1.23 – 1.19 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.4, 171.4, 170.2, 141.7, 133.0, 121.1, 118.5, 108.5, 62.5, 61.2, 47.0, 33.4, 28.0, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.72 – 7.62 (m, 4H), 4.92 (d, *J* = 8.3, 1H), 4.18 – 4.12 (m, 2H), 3.76 – 3.70 (m, 1H), 3.26 – 3.19 (m, 1H), 2.67 (dd, *J* = 16.9, 8.5, 1H), 2.33 (s, 3H), 1.23 – 1.19 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.2, 172.7, 168.8, 141.8, 133.1, 120.2, 118.4, 108.2, 62.1, 47.8, 33.1, 30.0, 13.9. HRMS (ESI) exact mass calcd for $C_{16}H_{17}N_2O_4$ $[M+H]^+$ m/z 301.1188, found 301.1190.

Ethyl 3-acetyl-1-(4-(ethoxycarbonyl)phenyl)-5-oxopyrrolidine-2-carboxylate (4p). light Yellow oil, 57% yield (198 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.04 (d, *J* = 8.1, 2H), 7.58 (d, *J* = 8.0, 2H), 5.16 – 5.10 (m, 1H), 4.35 (q, *J* = 7.0, 2H), 4.18 (q, *J* = 7.1, 2H), 3.39 – 3.33 (m, 1H), 3.05 (dd, *J* = 17.4, 10.5, 1H), 2.77 (dd, *J* = 17.4, 2.5, 1H), 2.33 (s, 3H), 1.37 (t, *J* = 7.0, 3H), 1.19 (t, *J* = 7.1, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.4, 171.3, 170.5, 165.8, 141.6, 130.5, 127.3, 120.7, 62.3, 61.6, 60.9, 47.1, 33.4, 28.0, 14.3, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.07 – 8.00 (m, 2H), 7.62 (d, *J* = 8.2, 2H), 4.94 (d, *J* = 8.4, 1H), 4.33 – 4.28 (m, 2H), 4.16 – 4.10 (m, 2H), 3.77 – 3.69 (m, 1H), 3.23 (dd, *J* = 16.5, 12.3, 1H), 2.65 (dd, *J* = 16.8, 8.4, 1H), 2.33 (s, 3H), 1.40 – 1.35 (m, 3H), 1.22 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.3, 172.6, 169.1, 165.8, 141.7, 130.6, 127.0, 119.8, 62.5, 48.0, 33.1, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{18}H_{22}NO_6$ $[M+H]^+$ m/z 348.1447, found 348.1452.

Ethyl 3-acetyl-5-oxo-1-(m-tolyl)pyrrolidine-2-carboxylate (4q). light brown oil, 29% yield (84 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 – 7.18 (m, 3H), 7.03 (d, *J* = 7.3, 1H), 5.04 (d, *J* = 3.1, 1H), 4.18 (q, *J* = 7.1, 2H), 3.39 – 3.30 (m, 1H), 3.02 (dd, *J* = 17.2, 10.4, 1H), 2.75 (dd, *J* = 17.2, 4.1, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 1.20 (t, *J* = 7.1, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 171.2, 170.9, 139.0, 137.3, 128.8, 127.2, 123.7, 120.0, 62.4, 62.0, 47.5, 33.3, 28.0, 21.4, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.18 (m, 3H), 7.06 – 6.99 (m, 1H), 4.86 (d, *J* = 8.4, 1H), 4.15 – 4.10 (m, 2H), 3.77 – 3.69 (m, 1H), 3.21 (dd, *J* = 16.7, 11.9, 1H), 2.62 (dd, *J* = 16.7, 8.5, 1H), 2.36 – 2.30 (m, 6H), 1.23 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 172.5, 169.5, 139.0, 137.5, 128.9, 126.9, 123.0, 119.2, 63.4, 48.4, 32.9, 29.9, 21.5, 13.9. HRMS (ESI) exact mass calcd for $C_{16}H_{20}NO_4$ $[M+H]^+$ m/z 290.1392, found 290.1391.

Ethyl 3-acetyl-1-(3-isopropylphenyl)-5-oxopyrrolidine-2-carboxylate (4r).[2b] light Yellow oil, 48% yield (152 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 – 7.25 (m, 3H), 7.11 – 7.06 (m, 1H), 5.04 (d, *J* = 3.3, 1H), 4.21 – 4.14 (m, 2H), 3.39 – 3.33 (m, 1H), 3.03 (dd, *J* = 17.2, 10.3, 1H), 2.94 – 2.86 (m, 1H), 2.76 (dd, *J* = 17.2, 4.3, 1H), 2.32 (s, 3H), 1.24 (d, *J* = 6.9, 6H), 1.18 (t, *J* = 6.1, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 171.2, 170.9, 149.9, 137.4, 128.9, 124.3, 121.0, 120.4, 62.5, 62.0, 47.5, 34.1, 33.3, 28.0, 23.8, 23.8, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.21 (m, 3H), 7.13 – 7.04 (m, 1H), 4.87 (d, *J* = 8.4, 1H), 4.15 – 4.11 (m, 2H), 3.77 – 3.69 (m, 1H), 3.22 (dd, *J* = 16.6, 11.9, 1H), 2.96 – 2.84 (m, 1H), 2.64 (dd, *J* = 16.6, 8.5, 1H), 2.32 (s, 3H), 1.27 – 1.22 (m, 6H), 1.21 – 1.16 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.7, 172.4, 169.6, 150.0, 137.6, 129.0, 124.1, 120.3, 119.6, 63.4, 48.5, 34.1, 32.9, 29.8, 13.9. HRMS (ESI) exact mass calcd for $C_{18}H_{24}NO4$ $[M+H]^+$ m/z 318.1705, found 318.1711.

Ethyl 3-acetyl-1-(3-chlorophenyl)-5-oxopyrrolidine-2-carboxylate (4s).[2b] light Yellow oil, 47% yield (145 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.53 (t, *J* = 1.9, 1H), 7.35 – 7.32 (m, 1H), 7.30 – 7.26 (m, 1H), 7.19 – 7.16 (m, 1H), 5.04 (d, *J* = 3.0, 1H), 4.22 – 4.16 (m, 2H), 3.37 – 3.33 (m, 1H), 3.02 (dd, *J* = 17.4, 10.4, 1H), 2.74 (dd, *J* = 17.4, 3.6, 1H), 2.32 (s, 3H), 1.22 – 1.19 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.5, 171.1, 170.5, 138.7, 134.6, 130.0, 126.1, 122.6, 120.3, 62.3, 61.9, 47.3, 33.2, 28.0, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.60 – 7.57 (m, 1H), 7.36 –

7.32 (m, 1H), 7.30 – 7.26 (m, 1H), 7.19 – 7.14 (m, 1H), 4.86 (d, *J* = 8.4, 1H), 4.17 – 4.12 (m, 2H), 3.75 – 3.68 (m, 1H), 3.19 (dd, *J* = 16.8, 12.0, 1H), 2.63 (dd, *J* = 16.8, 8.5, 1H), 2.32 (s, 3H), 1.23 – 1.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.4, 172.4, 169.1, 138.8, 134.7, 130.1, 125.8, 121.7, 119.4, 62.8, 48.2, 32.9, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{15}H_{17}ClNO_4$ $[M+H]^+$ m/z 310.0846, found 310.0843.

Ethyl 3-acetyl-1-(3-nitrophenyl)-5-oxopyrrolidine-2-carboxylate (4t). light Yellow oil, 57% yield (182 mg). Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.31 (s, 1H), 8.05 (d, *J* = 8.3, 1H), 7.95 (d, *J* = 8.1, 1H), 7.55 (t, *J* = 8.2, 1H), 5.16 – 5.14 (m, 1H), 4.25 – 4.18 (m, 2H), 3.44 – 3.40 (m, 1H), 3.07 (dd, *J* = 17.4, 10.5, 1H), 2.82 – 2.74 (m, 1H), 2.35 (s, 3H), 1.26 – 1.20 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.4, 171.4, 170.2, 148.5, 138.8, 129.9, 127.6, 120.3, 116.5, 62.5, 61.5, 47.1, 33.2, 28.0, 14.0. Minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.34 (s, 1H), 8.08 – 7.99 (m, 1H), 7.96 – 7.92 (m, 1H), 7.58 – 7.52 (m, 1H), 4.97 (d, *J* = 8.3, 1H), 4.19 – 4.13 (m, 2H), 3.81 – 3.73 (m, 1H), 3.24 (dd, *J* = 16.6, 12.0, 1H), 2.69 (dd, *J* = 16.7, 8.4, 1H), 2.35 (s, 3H), 1.27 – 1.19 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.3, 172.7, 168.9, 148.5, 138.9, 130.0, 126.9, 120.0, 115.7, 62.4, 48.0, 32.9, 30.0, 13.9. HRMS (ESI) exact mass calcd for $C_{15}H_{17}N_2O_6$ $[M+H]^+$ m/z 321.1087, found 321.1085.

Ethyl 3-acetyl-1-(3,4-dimethylphenyl)-5-oxopyrrolidine-2-carboxylate (4v).[2b] light Yellow oil, 55% yield (167 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 (s, 1H), 7.13 – 7.08 (m, 2H), 5.00 (d, *J* = 3.1, 1H), 4.18 (q, *J* = 7.1, 2H), 3.38 – 3.29 (m, 1H), 3.01 (dd, *J* = 17.2, 10.4, 1H), 2.73 (dd, *J* = 17.2, 4.1, 1H), 2.32 (s, 3H), 2.23 (d, *J* = 8.8, 6H), 1.24 – 1.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 171.2, 170.9, 137.4, 135.1, 135.0, 130.1, 124.6, 120.7, 62.6, 62.0, 47.6, 33.2, 28.0, 19.9, 19.3, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25 – 7.22 (m, 1H), 7.13 – 7.07 (m, 2H), 4.82 (d, *J* = 8.4, 1H), 4.15 – 4.10 (m, 2H), 3.77 – 3.68 (m, 1H), 3.19 (dd, *J* = 16.6, 11.9, 1H), 2.61 (dd, *J* = 16.6, 8.5, 1H), 2.32 (s, 3H), 2.26 – 2.21 (m, 6H), 1.23 – 1.17 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.8, 172.5, 169.6, 137.5, 135.1, 134.8, 130.1, 124.0, 120.0, 63.6, 48.5, 32.8, 29.9, 19.9, 19.3, 13.9. HRMS (ESI) exact mass calcd for $C_{17}H_{22}NO_4$ $[M+H]^+$ m/z 304.1549, found 304.1551.

Ethyl 3-acetyl-1-(3-fluoro-4-methylphenyl)-5-oxopyrrolidine-2-carboxylate (4w).[2b] light brown oil, 58% yield (178 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 – 7.26 (m, 1H), 7.16 (t, *J* =

8.3, 1H), 7.07 (dd, *J* = 8.2, 2.1, 1H), 5.02 (d, *J* = 3.0, 1H), 4.20 (q, *J* = 7.1, 2H), 3.38 – 3.31 (m, 1H), 3.02 (dd, *J* = 17.3, 10.4, 1H), 2.74 (dd, *J* = 17.3, 4.0, 1H), 2.32 (s, 3H), 2.24 (s, 3H), 1.25 – 1.19 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.5, 171.1, 170.6, 161.8, 160.1, 136.5, 136.4, 131.4, 131.4, 117.4, 117.4, 109.9, 109.7, 62.2, 62.0, 47.3, 33.2, 28.0, 14.1, 14.1, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 – 7.31 (m, 1H), 7.19 – 7.12 (m, 1H), 7.10 – 7.03 (m, 1H), 4.84 (d, *J* = 8.4, 1H), 4.17 – 4.12 (m, 2H), 3.77 – 3.68 (m, 1H), 3.20 (dd, *J* = 16.7, 12.0, 1H), 2.63 (dd, *J* = 16.7, 8.5, 1H), 2.32 (s, 3H), 2.24 (s, 3H), 1.25 – 1.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.5, 172.3, 169.3, 131.5, 131.5, 116.5, 116.5, 109.1, 108.9, 63.0, 48.2, 32.9, 29.9, 13.9. HRMS (ESI) exact mass calcd for $C_{16}H_{19}FNO_4$ $[M+H]^+$ m/z 308.1298, found 308.1299.

Ethyl 3-acetyl-1-(3-chloro-4-methylphenyl)-5-oxopyrrolidine-2-carboxylate (4x).[2b] light brown oil, 55% yield (178 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 1.8, 1H), 7.27 – 7.19 (m, 2H), 5.02 (d, *J* = 2.6, 1H), 4.23 – 4.16 (m, 2H), 3.39 – 3.31 (m, 1H), 3.02 (dd, *J* = 17.3, 10.4, 1H), 2.73 (dd, *J* = 17.3, 4.0, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 1.22 (t, *J* = 7.1, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.6, 171.2, 170.6, 136.2, 134.5, 134.0, 131.0, 123.3, 120.9, 62.2, 62.0, 47.3, 33.1, 28.0, 19.5, 14.0. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 – 7.52 (m, 1H), 7.25 – 7.19 (m, 2H), 4.84 (d, *J* = 8.4, 1H), 4.17 – 4.12 (m, 2H), 3.77 – 3.68 (m, 1H), 3.19 (dd, *J* = 16.7, 12.0, 1H), 2.63 (dd, *J* = 16.7, 8.5, 1H), 2.36 – 2.30 (m, 6H), 1.28 – 1.18 (m, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 203.5, 172.4, 169.2, 136.4, 134.6, 133.7, 131.1, 122.5, 120.0, 63.0, 62.1, 48.2, 32.8, 29.9, 19.5, 13.9. HRMS (ESI) exact mass calcd for $C_{16}H_{19}ClNO_4$ $[M+H]^+$ m/z 324.1003, found 324.0998.

4-Acetyl-5-benzoyl-1-(p-tolyl)pyrrolidin-2-one (4y). light brown oil, 47% yield (151 mg). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (dd, *J* = 8.3, 1.2, 2H), 7.63 (dd, *J* = 10.6, 4.3, 1H), 7.50 (t, *J* = 7.7, 2H), 7.35 (d, *J* = 8.4, 2H), 7.13 (d, *J* = 8.3, 2H), 6.25 (d, *J* = 2.2, 1H), 3.21 – 3.15 (m, 1H), 3.10 (dd, *J* = 16.8, 10.9, 1H), 2.74 (dd, *J* = 16.8, 2.5, 1H), 2.29 (d, *J* = 6.8, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.2, 195.8, 171.6, 136.0, 135.1, 134.4, 133.6, 129.6, 129.2, 128.5, 123.2, 63.7, 47.6, 33.5, 27.8, 20.9. HRMS (ESI) exact mass calcd for $C_{15}H_{17}N_2O_6$ $[M+H]^+$ m/z 321.1087, found 321.1088.

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Supporting Information Available: Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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