Utilizing Carbonyl-Coordination of Native Amides for Pd– catalyzed C(sp³)–H Olefination

Hojoon Park, Yang Li, jin-quan yu

Submitted date: 15/05/2019 • Posted date: 16/05/2019

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Citation information: Park, Hojoon; Li, Yang; yu, jin-quan (2019): Utilizing Carbonyl-Coordination of Native Amides for Pd– catalyzed C(sp³)–H Olefination. ChemRxiv. Preprint.

Pd(II)–catalyzed C(sp³)–H olefination of native amide substrates was developed. To utilize the extremely weak-coordinating carbonyl-coordination of amides, an electron-deficient pyridinesulfonic acid ligand was designed. Structurally diverse amide substrates, including lactams, underwent olefination without the undesired cyclization. Olefination products were further diversified through synthetic transformations on the alkenyl moiety.

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Utilizing Carbonyl-Coordination of Native Amides for Pd-catalyzed C(sp³)-H Olefination

Hoon Park,^[a] Yang Li,^[a] and Jin-Quan Yu^{*[a]}

Abstract: Pd(II)-catalyzed C(sp³)-H olefination of weakly-coordinating native amides is reported. Three major drawbacks of previous C(sp³)-H olefination protocols – 1) *in situ* cyclization of products, 2) incompatibility with α -H-containing substrates, and 3) installation of exogenous directing groups – are addressed via harnessing the carbonyl-coordination of amides to direct C(sp³)-H activation. The method enables direct C(sp³)-H functionalization of a wide range of native amide substrates, including secondary, tertiary, and cyclic amides, for the first time. The utility of this process is demonstrated by diverse transformations of the olefination products.

The Mizoroki-Heck reaction^[1] has proven to be a powerful technology for C–C bond formation.^[2] While progress has been made for the alkyl-variant of the Mizoroki-Heck reaction,^[3] the well-known challenges of this process^[4] – undesired β -hydride elimination^[4a] and slow oxidative addition^[4b] – still limit its development and application. Recently, alkyl-Mizoroki-Heck reaction operating via alkyl hybrid organometallic-radical intermediates has been shown as a promising strategy.^[5] As an alternative approach, our group developed the Pd-catalyzed directed C(sp³)-H olefination (**Scheme 1A**).^[6a] Presumably, the intramolecular coordination of the directing group with the alkyl-Pd intermediate prevents premature β -hydride elimination. Since then, several reports on Pd-catalyzed C(sp³)-H olefination have been disclosed.^[6] However, the resulting olefination products often undergo subsequent cyclization.^[6a,6c-e,6h] For example, using the acidic amide directing group gives lactam products which require strongly basic conditions to restore the desired alkenyl moiety.^[6a] Even with a weakly-nucleophilic carboxylic acid, the product undergoes a facile cyclization to form a lactone.^[6h] While reversibly-cyclizing^[6b] and non-cyclizing^[6f,6g] C(sp³)-H olefination reactions have been reported, the directing groups that are used therein are either synthetically limited heterocycles or exogenous auxiliaries, and the substrate scopes are mostly limited to α - or β -quaternary substrates. Overall, C(sp³)-H olefination still remains largely underdeveloped compared to other extensively studied reactions such as C(sp³)-H arylation.

In order to develop a broadly useful C(sp³)-H olefination reaction, the following criteria must be met: 1) the installed alkenyl moiety remains intact without undergoing further reactions, 2) α -H-containing substrates are compatible, and 3) ideally, native functionalities are used as directing groups. To the best of our knowledge, there is no protocol reported that satisfies all three criteria above. The dilemma is that due to the inertness of C(sp³)-H bonds, directing groups used for C(sp³)-H activation – either nitrogen-based or anionic directing groups – require a certain deg-

A. C(sp³)-H olefination as an alternative approach for alkyl-Mizoroki-Heck reaction

B. Key Challenge: Utilizing carbonyl-coordination for C(sp³)-H activation (This work)

C. Structural diversity of amides: New classes of substrates for C(sp³)-H activation

Scheme 1. Pd-catalyzed C(sp³)-H Olefination.

ree of Lewis-basicity,^[7] which inevitably causes subsequent cyclization via addition to the double bond (**Scheme 1A**). However, utilizing a neutral, oxygen-based functional group that would not cyclize, such as a carbonyl, as a directing group for C(sp³)-H activation is substantially less effective due to the weakly-coordinating nature.

Recently, we reported the C(sp³)-H arylation of Weinreb amides enabled by a pyridine-3-sulfonic acid ligand.^[8] Both experimental and computational studies indicated that the non-coordinating anionic sulfonate group of the ligand is crucial in promoting the reaction via preserving the cationic character of the Pd center. While the scope of this method was limited to α -quaternary substrates, we reasoned that this is due to the unfavorable Pd(II)/Pd(IV) catalysis with weak-coordination. On the other hand, C(sp³)-H olefination involving Pd(II)/Pd(0) catalysis would benefit from weak-coordination and extend the scope to a broader range of native amides through carbonyl coordination (**Scheme 1B**). Amides are undoubtedly one of the most ubiquitous functional groups in organic chemistry,^[9] and thus the direct coupling of native amides with olefins through C(sp³)-H activation would be highly desirable. In terms of C–C bond disconnection strategy, such transformation extends the classical Michael addition disconnection from the α -position of a carbonyl to the β -position. Herein, we report the development of C(sp³)-H olefination of native amides enabled by 5-(trifluoromethyl)-pyridine-3-sulfonic acid ligand. Another unique advantage of utilizing the carbonyl-coordination, besides the non-cyclizing aspect, is that structurally diverse amides, including non-acidic secondary, tertiary, and cyclic amides, becomes available in the substrate scope (**Scheme 1C**).

[a] H. Park, Dr. Y. Li, Prof. Dr. J.-Q. Yu, Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037 (USA).
E-mail: yu200@scripps.edu

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Table 1. Evaluation of Ligands for C(sp³)-H Olefination^[a,b]

$\text{Pd(OAc)}_2 \text{ (10 mol\%), Ligand (10 mol\%), AgOAc (2 equiv.), HFIP (0.2 M), 70 °C, 24 h}$			
No Ligand	L1, 31%, >20:1	L2, 30%, >20:1	L3, 0%
L4, 17%	L5, 25%	L6, 48%, >20:1	L7, 45%, 15:1
L8, 65%, 20:1 (75%, 10:1) ^c	L9, 6%	L10, 38%	L11, 0%
L12, 9%	L13, <5%	L14, <5%	L12 + L14, 8%
L15, <5%	L16, 0%	L17, 9%	L18, <5%

[a] Conditions: **1o** (0.1 mmol), Pd(OAc)₂ (10 mol%), **Ligand** (10 mol%), ethyl acrylate (0.2 mmol), AgOAc (0.2 mmol), HFIP (0.5 mL), 70 °C, 24 h. [b] The yield and *mono:di* ratio was determined by ¹H NMR analysis of the crude product using CH₂Br₂ as the internal standard. [c] ethyl acrylate (0.4 mmol), AgOAc (0.3 mmol), HFIP (1.0 mL), 36 h, isolated yield/*mono:di* ratio.

To develop the proposed olefination reaction, we first investigated the ligand effect for the coupling of Weinreb amide **1o** and ethyl acrylate (**Table 1**). While no product was observed in the absence of ligand, using pyridinesulfonic acid ligands **L1** and **L2** enabled the reaction giving 31% and 30% yields of the product, respectively. This is in clear contrast with the previous arylation^[8] where α-H-containing substrates were incompatible, implying that unlike Pd(II)/Pd(IV) catalysis, Pd(II)/Pd(0) catalysis can benefit from weakly-coordinating substrates. Pyridine-2-sulfonic acid (**L3**) completely inhibited the reaction, supporting our hypothesis that the charge separation between Pd and ligand is crucial for reactivity. Next, substitution effect on the pyridine-3-sulfonic acid ligand was examined. While electron-donating substituents (**L4**, **L5**) decreased the yield, electron-withdrawing substituents (**L6**, **L7**) improved the yield. This trend led us to prepare -CF₃-containing pyridine-3-sulfonic acid ligands **L8–L10**. To our delight, **L8** was shown to be the superior ligand giving 65% yield, which was further improved to 75% isolated yield with high *mono*-selectivity under slightly modified reaction conditions. Interestingly, only 6% and 38% yields were observed with **L9** and **L10**, respectively, implying that the pyridine-coordination needs to be finely tuned through both sterics and electronics. An analogous carboxylic acid ligand **L11** was ineffective, showing the importance of the non-coordinating property of the sulfonate anion. Simple pyridine ligands (**L12**, **L13**) were ineffective in promoting the reaction. To show that the pyridinesulfonic acid ligands are not serving as simple sulfonic acid additives, 4-nitrobenzenesulfonic acid (**L14**) was tested, and only trace amount of product was observed. Using a combination of ligands **L12** and **L14** were also ineffective. Other X-type ligands (**L15–L18**) did not promote the reaction as well.

Table 2. Substrate Scope of Amides - A^[a,b,d]

$\text{Pd(OAc)}_2 \text{ (10 mol\%), L8 (10 mol\%), AgOAc (2–3 equiv.), HFIP (0.1–0.2 M), 70–80 °C, 24–36 h}$			
2a, 70%, 20:1	2b, 77%, 10:1	2c, 67%, 17:1	2d, 56%, 13:1
2e, 78%, 10:1	2f, 56%	2g, 62%	2h, 69%, 10:1
2i, 70%, 10:1	2j, 81%, 19:1 ^d	2k, 71%, >20:1	2l, 57% (dr 1:1)
2m, 69%, >20:1	2n, 79%, 10:1	2o, 75%, 10:1	2p+2p', 61%, 13:1 [R=H(2p):CH=CH-CO2Et(2p')=2:1]
2q, 74%, 5:1	2r, 77%, 12:1	2s, 77%, 8:1	2t, 71%, 7:1
2u, 50%	2v, 0%	2v', 81%	2w, 54%

Conditions: **1** (0.1–0.2 mmol), Pd(OAc)₂ (10 mol%), **L8** (10 mol%), ethyl acrylate (4 equiv.), AgOAc (2–3 equiv.), HFIP (0.1–0.2 M), 70–80 °C, 24–36 h. See Supporting Information for details. [b] Isolated yield/*mono:di* ratio. [c] The isolated *mono:di* ratio does not necessarily reflect the *mono:di* selectivity of the reaction. [d] 1.0 g (6.37 mmol) scale.

With the optimal ligand in hand, we evaluated the substrate scope of the olefination. First, isobutyramide substrates bearing diverse amino-groups were tested (**Table 2**). Simple *di*-alkyl amides with varying sterics were compatible (**2a–2e**). Amides containing a wide range of cyclic amino-groups were suitable substrates as well (**2f–2k**). A gram-scale reaction was conducted to give **2j** in good yield. Substrates derived from amino acids such as proline (**2l**), sarcosine (**2m**), and isonipecotic acid (**2n**) also provided the products in moderate to good yields. It is noteworthy that previous works on peptide/amino acid-directed C–H functionalization^[10] cannot utilize these amino acids due to the lack of nitrogen-coordinating site. As described in Table 1, Weinreb amide **1o** also gave good yield. With secondary amide (**1p**), expected primary olefination products and subsequent vinylic olefination products were obtained in 61% total yield (**2p**: **2p'** = 2:1). No cyclization was observed, implying that carbonyl-coordination was utilized instead of nitrogen-coordination. With secondary pivalamides (**1q–1u**), the desired olefination products were delivered in moderate to good yields (**2q–2u**) with trace amounts of vinylic olefination products. Lastly, we tested whether

Table 3. Substrate Scope of Amides - B [a,b,c]

[a] Conditions: **3** (0.1–0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L8** (10 mol%), ethyl acrylate (4 equiv.), $AgOAc$ (2–3 equiv.), HFIP (0.1–0.2 M), 70–80 °C, 24–36 h. See Supporting Information for details. [b] Isolated yield/*mono:di* ratio. [c] The isolated *mono:di* ratio does not necessarily reflect the *mono:di* selectivity of the reaction. [d] Phenyl vinyl sulfone was used for purification purpose.

a coordinating group as weak as an anilide-carbonyl could also serve as a directing group for $C(sp^3)-H$ activation. Anilides have only been used as substrates for $C(sp^3)-H$ activation through nitrogen-coordination via deprotonation of the acidic N–H.^[6a,11] With **1v**, only $C(sp^2)-H$ olefination product **2v'** was isolated. To our delight, with the *ortho*-positions of the phenyl ring blocked with methyl groups, **1w** underwent the reaction to give **2w** in 54% yield, demonstrating that $Pd/L8$ system can exploit extremely weak coordination for $C(sp^3)-H$ activation.

Next, the scope of the carboxyl component of amides was evaluated (Table 3). Various alkyl substituents (**4a–4d**), heteroatom-containing functional groups (**4e–4h**), and aromatic groups (**4i–4j**) on the substrate were tolerated. α -Quaternary amides (**4k–4m**) were suitable substrates as well. Cyclopropyl substrates (**4n–4q**) also gave moderate to good yields of the products. The formation of **4q** with 1-aminocyclopropane-1-carbo-

Table 4. Olefin Coupling Partner Scope [a,b]

[a] Conditions: **1j** (0.1–0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L8** (10 mol%), olefin (4 equiv.), $AgOAc$ (2–3 equiv.), HFIP (0.1–0.2 M), 70–80 °C, 24–36 h. See Supporting Information for details. [b] Isolated yield.

xylic acid (ACCA) amide substrate was particularly interesting, as 2-vinyl-ACCA is a motif that is present in numerous drug molecules, especially for the treatment of hepatitis C virus.^[12] Lastly, the advantage of utilizing carbonyl-coordination was further demonstrated with the $C(sp^3)-H$ olefination of lactam substrates (**4r–4u**). Both 6- (**4r–4t**) and 7-membered (**4u**) ring-size, as well as α -tertiary (**4t–4u**) and α -quaternary (**4r–4s**) structures, were tested and successfully provided the olefination products. Unfortunately, 4- or 5-membered lactams were not reactive, presumably due to the unfavorable geometry between directing group, catalyst, and C–H bond. Albeit low yield, *N*-alkyl pyridone also underwent the reaction to give the product **4v** in 23% yield.

Finally, the scope of the olefin coupling partner was investigated (Table 4). Commonly used Michael acceptors, including acrylate (**5a**), vinyl ketone (**5b**), vinyl phosphonate (**5c**), vinyl sulfonate (**5d–5e**), and vinyl sulfate (**5f**) were installed through $C(sp^3)-H$ olefination in moderate to good yields. Most interestingly, ethenesulfonyl fluoride (ESF)^[13] was also reactive and gave **5g** in good yield. ESF has been extensively utilized for the sulfur (VI) fluoride exchange (SuFEx) click reaction.^[14] To the best of our knowledge, there is no report of ESF being directly installed at an alkyl carbon center via either $C(sp^3)-H$ olefination^[15] or even aliphatic Mizoroki–Heck reaction.^[16] We anticipate this protocol to be applied to explore new Fsp^3 -rich substrates for SuFEx chemistry. Various di-substituted Michael acceptors were compatible with the reaction to give products **5h–5k**. It is noteworthy that fumarate and maleate were successfully employed as coupling partner for $C(sp^3)-H$ olefination for the first time (**5j**, **5k**). The formation of these tri-substituted olefins with carboxylate groups in either *E*- or *Z*-configuration could greatly facilitate complex olefin synthesis. Unfortunately, styrenes and aliphatic alkenes were generally not reactive under our reaction conditions. Only pentafluorostyrene successfully delivered the olefination product **5l** in 54% yield.

Scheme 2. Diversification of Olefination Products. (a) **2j** (0.1 mmol), dimethyl malonate (2 equiv.), Cs₂CO₃ (1 equiv.), CH₃CN (0.1 M), 70 °C, 32 h. (b) **2j** (0.1 mmol), DBU (1.5 equiv.), CH₃NO₂ (0.5 M), 0 °C, 3 h. (c) **2j** (0.1 mmol), PhSH (2 equiv.), K₂CO₃ (2.2 equiv.), THF (0.1 M), 70 °C, 32 h. (d) **2j** (0.96 mmol), 10% Pd/C (0.07 mmol), EtOAc (0.1 M), H₂ balloon (1 atm), r.t., 24 h. (e) **5g** (0.38 mmol), 10% Pd/C (0.03 mmol), EtOAc (0.1 M), H₂ balloon (1 atm), r.t., 48 h. (f) **5g** (0.1 mmol), *n*-amyamine (4 equiv.), CH₃CN (0.1 M), r.t., 30 min. (g) **2u** (0.49 mmol), DBU (1 equiv.), EtOH (0.25 M), reflux, 1 h. (h) **6d** (0.053 mmol), Ar-OTBS (1.05 equiv.), DBU (10 mol%), CH₃CN (0.1 M), r.t., 16 h.

The synthetic utility of the Mizoroki-Heck reaction largely comes from the versatile reactivity of an alkenyl group.^[2] To emphasize the value of preserving the alkenyl group during C(sp³)-H olefination, we conducted diverse transformation on the olefination products using the alkenyl group as the functional group handle (**Scheme 2**). Michael addition products were obtained from **2j** with both carbon-based (**6a–6b**) and heteroatom-based (**6c**) nucleophiles. Hydrogenation of **2j** and **5g** led to **3h** and **6d** in 97% and 93% yields, respectively. It is noteworthy that **3h** can undergo a 2nd C(sp³)-H olefination (**Table 3, 4h**) to install another synthetic handle for further transformation. We also demonstrated that **6d** can lead to sulfonate ester products **7a–7d** with various silyl-protected phenols under classical SuFEx conditions. **5g** was treated with *n*-amyamine to form the β-sultam product **6e** in 82% yield, demonstrating the potential “dual warhead” reactivity of vinyl sulfonyl fluorides.^[16b,17] With secondary amide **2u**, facile cyclization proceeds with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to form the lactam product **6f** in 89% yield. It is important to note that while previously reported C(sp³)-H olefination/*in situ* cyclization reactions produce auxiliary-embedded lactams,^[6a,6c,6d] our two-step protocol (olefination/DBU-mediated cyclization) can be used to prepare general *N*-alkyl lactams.

In summary, we have developed the Pd(II)-catalyzed C(sp³)-H olefination of native amides. To utilize the weak carbonyl-coordination, an electron-deficient pyridine-3-sulfonic acid ligand **L8** was designed. Among the known classes of ligands, only pyridinesulfonic acid ligands were effective in promoting the reaction, supporting our hypothesis on the role of the non-coordinating sulfonate group in generating a highly electrophilic catalyst. Using our method, structurally diverse amide substrates, including secondary, tertiary, and cyclic amides, were shown to undergo C(sp³)-H olefination without the undesired *in situ* cyclization. Finally, olefination products were further diversified

using both alkene transformation reactions and SuFEx chemistry. Combining the versatile reactivity of olefins with the combinatorial nature of amides (amine + carboxylic acid) would allow one to rapidly access diverse target compounds.

Acknowledgements

We gratefully acknowledge The Scripps Research Institute and the NIH (NIGMS, 2R01GM084019) for financial support. We thank Dr. Milan Gembicky (UCSD) for X-ray crystallographic analysis, and Dr. Jason Chen and Brittany Sanchez (Scripps Automated Synthesis Facility) for assistance with HRMS. H.P. thanks the Korea Foundation for Advanced Studies for a predoctoral fellowship. Y.L. thanks the National Natural Science Foundation of China (21602167), the China Scholarship Council (CSC) fellowship program, and Xi'an Jiaotong University for financial support.

Keywords: C–H activation • Palladium catalysis • Ligand design • Amide • Mizoroki-Heck reaction

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1. General Information

Amide substrates were synthesized from corresponding carboxylic acids which were obtained from commercial sources or prepared following literature procedures. Pd(OAc)₂ was obtained from Strem. Solvents were obtained from Sigma-Aldrich, Alfa-Aesar, Oakwood, and Acros and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light. ¹H NMR was recorded on Bruker instrument (600 MHz). Chemical shifts were reported in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. ¹³C NMR was recorded on Bruker instrument (150 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to 77.16 ppm for center line of chloroform. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

2. Experimental Section

2.1. Preparation of substrates

- List of substrates

- General procedure A for the preparation of substrates **1a-1v**.

To a stirring solution of isobutyryl chloride (5 mmol) in DCM (20 mL) were added the corresponding amine R₁R₂NH (5.5 mmol) and diisopropylethylamine (960 μ L, 5.5 mmol) dropwise at 0 °C (11.0 mmol of diisopropylethylamine was added if hydrochloride salt of the amine was used). The reaction mixture was warm to room temperature and was stirred for 6 h. Upon completion, the organic layer was washed with 0.2 M HCl (aq) and sat. Na₂CO₃ (aq). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford substrate **1**.

***1a**, **1s** were commercially available.

*Pivaloyl chloride was used for **1r-1u**.

- Procedure for the preparation of **1w**.

S1 was prepared following the general procedure A. To a stirring solution of **S1** (573.8 mg, 3 mmol) in DMF (10 ml) under N₂ atmosphere was added sodium hydride (60% (w/w) dispersion in mineral oil, 180 mg, 4.5 mmol) in one portion at 0 °C. After stirring for 30 min at room temperature, the reaction mixture was cooled to 0 °C and iodomethane (280 uL, 4.5 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with dropwise addition of sat. NH₄Cl (aq.), diluted with EtOAc, and washed with water and brine. The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford substrate **1w**.

- General procedure B for the preparation of substrates **3a-3q**.

To a stirring solution of corresponding carboxylic acid (5 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.15 g, 6 mmol) in DCM (20 mL) were added morpholine (520 uL, 6 mmol) or *n*-pentylamine (700 uL, 6 mmol) and a small amount of 4-(dimethylamino)pyridine. The reaction was allowed to stir for 24 h at room temperature. Upon completion, the organic layer was washed with 0.2 M HCl (aq) and sat. Na₂CO₃ (aq). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford substrate **3**.

*See section 2.5 for the preparation of **3h**.

*Dimethylamine hydrochloride with diisopropylethylamine was used for the preparation of **3q**.

- General procedure C for the preparation of substrates **3r-3u**.

To a stirring solution of diisopropylamine (12 mmol, 1.7 mL) in THF (30 mL) was added 2.5 M *n*-BuLi solution (12.5 mmol, 5 mL) dropwise at -78 °C. The resulting solution was stirred for 30 min at 0 °C, and the corresponding lactam (10 mmol) was added dropwise. After stirring for 1 h at 0 °C, iodomethane (930 uL, 15 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was quenched with sat. NH₄Cl (aq.) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford lactam substrates **3r-3u**.

- Procedure for the preparation of **3v**.

3v was prepared following the literature procedure.¹

- Full characterization of new compounds

***N*-isopropyl-*N*-methylisobutyramide (1c) (1:0.84 mixture of rotamers)**

¹H NMR (600 MHz, CDCl₃, major rotamer): δ 4.90 (hept, *J* = 6.8 Hz, 1H), 2.84 (s, 3H), 2.82 (hept, *J* = 6.7 Hz, 1H), 1.11 (d, *J* = 6.7 Hz, 6H), 1.07 (d, *J* = 6.8 Hz, 6H).

¹H NMR (600 MHz, CDCl₃, minor rotamer): δ 4.16 (hept, *J* = 6.5 Hz, 1H), 2.77 (s, 3H), 2.75 (hept, *J* = 6.7 Hz, 1H), 1.20 (d, *J* = 6.7 Hz, 6H), 1.13 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (150 MHz, CDCl₃, mixture of rotamers): δ 176.54, 176.53, 47.46, 43.74, 30.96, 30.46, 28.02, 26.06, 20.86, 19.98, 19.56, 19.36.

HRMS (ESI-TOF): *m/z* calculated for C₈H₁₈NO⁺ [M+H]⁺ 144.1383, found 144.1384.

***N*-(2-methoxyethyl)-*N*-methylisobutyramide (1e) (1:0.65 mixture of rotamers)**

¹H NMR (600 MHz, CDCl₃, major rotamer): δ 3.56 – 3.51 (m, 4H), 3.34 (s, 3H), 3.11 (s, 3H), 2.81 (hept, *J* = 6.7 Hz, 1H), 1.12 (d, *J* = 6.8 Hz, 6H).

¹H NMR (600 MHz, CDCl₃, minor rotamer): δ 3.52 – 3.47 (m, 4H), 3.35 (s, 3H), 2.96 (s, 3H), 2.87 (hept, *J* = 6.7 Hz, 1H), 1.12 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (150 MHz, CDCl₃, major rotamer): δ 177.16, 71.32, 58.92, 48.05, 36.94, 30.50, 19.29.

¹³C NMR (150 MHz, CDCl₃, minor rotamer): δ 177.80, 70.66, 59.29, 49.55, 34.26, 30.06, 19.82.

HRMS (ESI-TOF): *m/z* calculated for C₈H₁₈NO₂⁺ [M+H]⁺ 160.1332, found 160.1327.

1-(azetidin-1-yl)-2-methylpropan-1-one (1f)

¹H NMR (600 MHz, CDCl₃): δ 4.16 (t, *J* = 7.6 Hz, 2H), 4.01 (t, *J* = 7.8 Hz, 2H), 2.43 (hept, *J* = 6.8 Hz, 1H), 2.26 (p, *J* = 7.7 Hz, 2H), 1.09 (d, *J* = 6.8 Hz, 6H).

¹³C NMR (150 MHz, CDCl₃): δ 177.05, 50.22, 47.88, 29.60, 18.93, 15.27.

HRMS (ESI-TOF): *m/z* calculated for C₇H₁₄NO⁺ [M+H]⁺ 128.1070, found 128.1071.

1-(azepan-1-yl)-2-methylpropan-1-one (1i)

¹H NMR (600 MHz, CDCl₃): δ 3.52 (t, *J* = 6.1 Hz, 2H), 3.46 (t, *J* = 6.1 Hz, 2H), 2.79 (hept, *J* = 6.7 Hz, 1H), 1.74 – 1.68 (m, 4H), 1.61 – 1.52 (m, 4H), 1.13 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (150 MHz, CDCl₃): δ 176.92, 47.84, 46.32, 30.33, 29.77, 27.75, 27.07, 26.92, 19.89.

HRMS (ESI-TOF): *m/z* calculated for C₁₀H₂₀NO⁺ [M+H]⁺ 170.1539, found 170.1542.

2-methyl-1-(4-(2,2,2-trifluoroacetyl)piperazin-1-yl)propan-1-one (1k)

¹H NMR (600 MHz, CDCl₃): δ 3.70 (br s, 4H), 3.61 (br s, 4H), 2.79 (br s, 1H), 1.15 (d, *J* = 6.8 Hz, 6H).

¹³C NMR (150 MHz, CDCl₃, mixture of rotamers*): δ 175.84, 116.43 (q, *J* = 288.1 Hz), 46.03 (*minor*), 45.86 (*major*), 45.41 (*minor*), 44.88 (*major*), 43.63 (*major*), 43.44 (*minor*), 41.71 (*major*), 41.13 (*minor*), 30.31, 19.47. (Carbonyl peak for trifluoroacetyl group was not found)

¹⁹F NMR (376 MHz, CDCl₃, mixture of rotamers) δ –69.12 (*minor*), –69.22 (*major*).

HRMS (ESI-TOF): *m/z* calculated for C₁₀H₁₆F₃N₂O₂⁺ [M+H]⁺ 253.1158, found 253.1164.

(*Relative geometry between two amide groups lead to rotameric peaks in ¹³C and ¹⁹F NMR)

ethyl *N*-isobutyryl-*N*-methylglycinate (1m) (1:0.24 mixture of rotamers)

¹H NMR (600 MHz, CDCl₃, major rotamer): δ 4.18 (q, *J* = 7.1 Hz, 2H), 4.10 (s, 2H), 3.12 (s, 3H), 2.87 (hept, *J* = 6.7 Hz, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 6.8 Hz, 6H).

¹H NMR (600 MHz, CDCl₃, minor rotamer): δ 4.23 (q, *J* = 7.1 Hz, 2H), 4.08 (s, 2H), 2.98 (s, 3H), 2.63

(hept, $J = 6.7$ Hz, 1H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.12 (d, $J = 6.7$ Hz, 6H).

^{13}C NMR (150 MHz, CDCl_3 , major rotamer): δ 177.80, 169.61, 61.18, 49.79, 36.55, 30.31, 19.17, 14.29.

^{13}C NMR (150 MHz, CDCl_3 , minor rotamer): δ 177.69, 169.35, 61.72, 51.72, 35.24, 30.39, 19.64, 14.32.

HRMS (ESI-TOF): m/z calculated for $\text{C}_9\text{H}_{18}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 188.1281, found 188.1289.

ethyl 1-isobutyrylpiperidine-4-carboxylate (1n)

^1H NMR (600 MHz, CDCl_3): δ 4.45 (d, $J = 13.1$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.90 (d, $J = 13.2$ Hz, 1H), 3.12 (t, $J = 11.7$ Hz, 1H), 2.83 – 2.76 (m, 2H), 2.53 (tt, $J = 10.8, 4.0$ Hz, 1H), 1.98 – 1.90 (m, 2H), 1.73 – 1.57 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.13 (d, $J = 6.6$ Hz, 3H), 1.12 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.45, 174.42, 60.76, 44.80, 41.33, 41.26, 30.24, 28.86, 28.14, 19.70, 19.50, 14.35.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{12}\text{H}_{22}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 228.1594, found 228.1598.

N-octylisobutyramide (1p)

^1H NMR (600 MHz, CDCl_3): δ 5.42 (br s, 1H), 3.25 – 3.21 (m, 2H), 2.32 (hept, $J = 6.9$ Hz, 1H), 1.49 (p, $J = 7.3$ Hz, 2H), 1.33 – 1.23 (m, 10H), 1.15 (d, $J = 6.9$ Hz, 6H), 0.88 (t, $J = 7.0$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 176.93, 39.55, 35.90, 31.93, 29.84, 29.40, 29.34, 27.04, 22.78, 19.83, 14.23.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{12}\text{H}_{26}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 200.2009, found 200.2013.

methyl pivaloylglycinate (1u)

^1H NMR (600 MHz, CDCl_3): δ 6.17 (br s, 1H), 4.03 (d, $J = 4.9$ Hz, 2H), 3.77 (s, 3H), 1.23 (s, 9H).

^{13}C NMR (150 MHz, CDCl_3): δ 178.78, 170.88, 52.46, 41.48, 38.81, 27.58.

HRMS (ESI-TOF): m/z calculated for $\text{C}_8\text{H}_{16}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 174.1125, found 174.1128.

N-(2,6-dimethylphenyl)-N-methylisobutyramide (1w)

^1H NMR (600 MHz, CDCl_3): δ 7.18 – 7.11 (m, 3H), 3.13 (s, 3H), 2.24 (hept, $J = 6.7$ Hz, 1H), 2.22 (s, 6H), 1.02 (d, $J = 6.7$ Hz, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ 177.92, 141.52, 135.91, 129.02, 127.98, 34.77, 31.26, 20.03, 17.93.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{20}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 206.1539, found 206.1543.

2-methyl-1-morpholinopentan-1-one (3b)

^1H NMR (600 MHz, CDCl_3): δ 3.70 – 3.60 (m, 6H), 3.56 – 3.47 (m, 2H), 2.66 (h, $J = 6.8$ Hz, 1H), 1.70 – 1.62 (m, 1H), 1.40 – 1.26 (m, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.90 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.46, 67.25, 67.02, 46.19, 42.22, 36.35, 35.00, 20.73, 17.65, 14.26.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{10}\text{H}_{20}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 186.1489, found 186.1489.

2-cyclohexyl-1-morpholinopropan-1-one (3c)

^1H NMR (600 MHz, CDCl_3): δ 3.70 – 3.60 (m, 6H), 3.58 – 3.49 (m, 2H), 2.44 (dq, $J = 8.1, 6.9$ Hz, 1H), 1.87 – 1.80 (m, 1H), 1.78 – 1.72 (m, 1H), 1.71 – 1.62 (m, 3H), 1.62 – 1.54 (m, 1H), 1.29 – 1.20 (m, 2H), 1.12 (ddd, $J = 16.2, 8.3, 3.6$ Hz, 1H), 1.08 (d, $J = 6.8$ Hz, 3H), 0.94 – 0.85 (m, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.50, 67.31, 67.05, 46.47, 42.21, 40.94, 40.83, 32.12, 29.82, 26.57, 26.47, 26.41, 14.99.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{24}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 226.1802, found 226.1806.

2-(adamantan-1-yl)-1-morpholinopropan-1-one (3d)

^1H NMR (600 MHz, CDCl_3): δ 3.70 – 3.63 (m, 6H), 3.63 – 3.55 (m, 2H), 2.43 (q, J = 6.9 Hz, 1H), 1.97 (br s, 3H), 1.74 (dq, J = 12.0, 2.7 Hz, 3H), 1.71 – 1.67 (m, 3H), 1.66 – 1.61 (m, 3H), 1.52 (dq, J = 12.0, 2.6 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.43, 67.37, 67.00, 47.25, 44.23, 42.05, 40.06, 37.18, 35.62, 28.80, 11.98.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{17}\text{H}_{28}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 278.2115, found 278.2122.

2-(5-methyl-6-morpholino-6-oxohexyl)isoindoline-1,3-dione (3e)

^1H NMR (600 MHz, CDCl_3): δ 7.84 (dd, J = 5.4, 3.0 Hz, 2H), 7.71 (dd, J = 5.5, 3.0 Hz, 2H), 3.70 – 3.60 (m, 8H), 3.57 – 3.46 (m, 2H), 2.65 (h, J = 6.8 Hz, 1H), 1.74 (ddd, J = 15.4, 13.3, 7.3 Hz, 1H), 1.67 (ddp, J = 10.6, 7.1, 3.4 Hz, 2H), 1.43 (ddt, J = 13.1, 9.1, 6.6 Hz, 1H), 1.33 (p, J = 7.7 Hz, 2H), 1.10 (d, J = 6.8 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.09, 168.55, 134.05, 132.29, 123.33, 67.22, 67.03, 46.21, 42.24, 37.94, 35.07, 33.55, 28.73, 24.86, 17.70.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{19}\text{H}_{25}\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 345.1809, found 345.1808.

6-(benzyloxy)-2-methyl-1-morpholinohexan-1-one (3f)

^1H NMR (600 MHz, CDCl_3): δ 7.36 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 4.49 (s, 2H), 3.67 – 3.61 (m, 6H), 3.52 – 3.49 (m, 2H), 3.48 – 3.44 (m, 2H), 2.64 (h, J = 6.8 Hz, 1H), 1.74 – 1.67 (m, 1H), 1.67 – 1.56 (m, 2H), 1.44 – 1.30 (m, 3H), 1.11 (d, J = 6.8 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.29, 138.72, 128.50, 127.78, 127.67, 73.07, 70.31, 67.23, 67.00, 46.19, 42.22, 35.26, 33.95, 29.96, 24.29, 17.70.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{18}\text{H}_{28}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 306.2064, found 306.207.

6-fluoro-2-methyl-1-morpholinohexan-1-one (3g)

^1H NMR (600 MHz, CDCl_3): δ 4.52 – 4.35 (m, 2H), 3.71 – 3.60 (m, 6H), 3.56 – 3.48 (m, 2H), 2.66 (h, J = 6.9 Hz, 1H), 1.78 – 1.61 (m, 3H), 1.47 – 1.33 (m, 3H), 1.13 (d, J = 6.8 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.08, 84.04 (d, J = 164.47 Hz), 67.21, 66.99, 46.18, 42.24, 35.32, 33.69, 30.62 (d, J = 19.7 Hz), 23.40 (d, J = 5.1 Hz), 17.79.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{11}\text{H}_{21}\text{FNO}_2^+$ $[\text{M}+\text{H}]^+$ 218.1551, found 218.1554.

3-(2,6-difluorophenyl)-2-methyl-1-morpholinopropan-1-one (3i)

^1H NMR (600 MHz, CDCl_3): δ 7.20 – 7.15 (m, 1H), 6.89 – 6.83 (m, 2H), 3.72 – 3.52 (m, 5H), 3.49 – 3.39 (m, 3H), 3.06 – 2.99 (m, 1H), 2.96 – 2.90 (m, 1H), 2.88 – 2.82 (m, 1H), 1.13 (d, J = 6.6 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.15, 161.89 (dd, J = 247.0, 8.8 Hz), 128.21 (t, J = 10.3 Hz), 115.46 (t, J = 20.2 Hz), 111.26 (dd, J = 21.0, 5.2 Hz), 67.11, 66.83, 46.14, 42.30, 34.95, 26.85 (t, J = 1.5 Hz), 16.96.

^{19}F NMR (376 MHz, CDCl_3) δ -114.74.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{18}\text{F}_2\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 270.1300, found 270.1303.

2-(2,6-difluorophenyl)-1-morpholinopropan-1-one (3j)

^1H NMR (600 MHz, CDCl_3): δ 7.23 (tt, J = 8.4, 6.3 Hz, 1H), 6.93 – 6.88 (m, 2H), 4.09 (q, J = 7.0 Hz, 1H), 3.75 – 3.64 (m, 2H), 3.62 – 3.54 (m, 2H), 3.52 – 3.46 (m, 1H), 3.33 – 3.25 (m, 1H), 3.21 – 3.11 (m, 2H), 1.49 (d, J = 7.0 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 170.72, 160.68 (dd, J = 248.6, 8.2 Hz), 128.86 (t, J = 10.4 Hz), 118.01 (t, J = 18.2 Hz), 111.99 (dd, J = 21.6, 4.6 Hz), 67.02, 66.34, 46.01, 42.86, 33.05, 17.27 (t, J = 1.1 Hz).

^{19}F NMR (376 MHz, CDCl_3) δ -114.74.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{16}\text{F}_2\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 256.1144, found 256.1146.

2,2-dimethyl-N-pentylbutanamide (3k)

^1H NMR (600 MHz, CDCl_3): δ 5.58 (br s, 1H), 3.26 – 3.22 (m, 2H), 1.54 (q, J = 7.4 Hz, 2H), 1.50 (p, J = 7.2 Hz, 2H), 1.37 – 1.26 (m, 4H), 1.15 (s, 6H), 0.90 (t, J = 7.1 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 177.65, 42.47, 39.63, 34.05, 29.53, 29.25, 25.14, 22.50, 14.14, 9.33.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{11}\text{H}_{24}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 186.1852, found 186.1856.

2-ethyl-2-methyl-N-pentylbutanamide (3l)

^1H NMR (600 MHz, CDCl_3): δ 5.58 (br s, 1H), 3.27 – 3.23 (m, 2H), 1.69 – 1.61 (m, 2H), 1.50 (p, J = 7.4 Hz, 2H), 1.41 (q, J = 7.5 Hz, 1H), 1.39 (q, J = 7.4 Hz, 1H), 1.36 – 1.27 (m, 4H), 1.09 (s, 3H), 0.90 (t, J = 7.1 Hz, 3H), 0.83 (t, J = 7.5 Hz, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ 176.85, 46.35, 39.59, 32.51, 29.57, 29.27, 22.49, 19.98, 14.14, 9.03.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{12}\text{H}_{26}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 200.2009, found 200.2010.

5-(1,3-dioxoisindolin-2-yl)-2,2-dimethyl-N-pentylpentanamide (3m)

^1H NMR (600 MHz, CDCl_3): δ 7.84 (dd, J = 5.4, 3.0 Hz, 2H), 7.71 (dd, J = 5.4, 3.0 Hz, 2H), 5.56 (br s, 1H), 3.66 (t, J = 7.0 Hz, 2H), 3.23 – 3.18 (m, 2H), 1.67 – 1.61 (m, 2H), 1.58 – 1.54 (m, 2H), 1.47 (p, J = 7.4 Hz, 2H), 1.35 – 1.23 (m, 4H), 1.15 (s, 6H), 0.88 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 177.07, 168.52, 134.02, 132.28, 123.34, 41.88, 39.71, 38.42, 38.37, 29.47, 29.25, 25.54, 24.34, 22.49, 14.14.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{20}\text{H}_{29}\text{N}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 345.2173, found 345.2177.

(1-methylcyclopropyl)(morpholino)methanone (3o)

^1H NMR (600 MHz, CDCl_3): δ 3.69 – 3.63 (m, 8H), 1.31 (s, 3H), 0.94 – 0.92 (m, 2H), 0.61 – 0.58 (m, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.09, 66.93, 44.52, 22.02, 20.17, 12.80.

HRMS (ESI-TOF): m/z calculated for $\text{C}_9\text{H}_{16}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 170.1176, found 170.1178.

(2,2-dimethylcyclopropyl)(morpholino)methanone (3p)

^1H NMR (600 MHz, CDCl_3): δ 3.81 – 3.74 (m, 2H), 3.74 – 3.69 (m, 1H), 3.65 – 3.56 (m, 4H), 3.52 – 3.47 (m, 1H), 1.47 (dd, J = 8.0, 5.3 Hz, 1H), 1.20 (s, 3H), 1.19 (t, J = 5.0 Hz, 1H), 1.05 (s, 3H), 0.72 (dd, J = 8.0, 4.4 Hz, 1H).

^{13}C NMR (150 MHz, CDCl_3): δ 170.14, 67.30, 67.17, 46.23, 42.44, 27.48, 26.48, 20.60, 19.82, 19.01.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{10}\text{H}_{18}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 184.1332, found 184.1334.

1-(1,3-dioxoisindolin-2-yl)-N,N-dimethylcyclopropane-1-carboxamide (3q)

^1H NMR (600 MHz, CDCl_3): δ 7.85 (dd, J = 5.5, 3.0 Hz, 2H), 7.75 (dd, J = 5.5, 3.0 Hz, 2H), 2.99 (s, 6H), 1.75 – 1.71 (m, 2H), 1.50 – 1.47 (m, 2H).

^{13}C NMR (150 MHz, CDCl_3): δ 169.11, 168.19, 134.54, 131.41, 123.66, 37.45, 34.54, 14.34.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{15}\text{N}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$ 259.1077, found 259.1084.

1,3,3-trimethylpiperidin-2-one (3r)

^1H NMR (600 MHz, CDCl_3): δ 3.28 (t, J = 6.2 Hz, 2H), 2.91 (s, 3H), 1.84 (p, J = 6.1 Hz, 2H), 1.70 – 1.67 (m, 2H), 1.21 (s, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ 176.22, 50.78, 38.28, 36.51, 35.22, 27.70, 19.71.

HRMS (ESI-TOF): m/z calculated for $\text{C}_8\text{H}_{16}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 142.1226, found 142.1227.

1,3-dimethylpiperidin-2-one (3t)

^1H NMR (600 MHz, CDCl_3): δ 3.28 (dhept, J = 17.8, 5.3 Hz, 2H), 2.92 (s, 3H), 2.39 (h, J = 7.1 Hz, 1H), 1.97 – 1.92 (m, 1H), 1.91 – 1.85 (m, 1H), 1.81 – 1.74 (m, 1H), 1.52 (q, J = 10.5 Hz, 1H), 1.24 (d, J = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.51, 50.49, 36.62, 34.99, 29.79, 21.76, 18.10.

HRMS (ESI-TOF): m/z calculated for $\text{C}_7\text{H}_{14}\text{NO}^+$ $[\text{M}+\text{H}]^+$ 128.1070, found 128.1070.

2.2 Preparation of Ligands

- **L1**, **L3**, and **L11–L18** were obtained from commercial sources. **L2**² was synthesized following literature procedures.

- General procedures for the preparation of **L4–L10**. (Note: for the preparation of **L9**, the pyridine-3-sulfonyl chloride was purchased from commercial source)

A reaction vessel with magnetic stir bar was charged with Pd_2dba_3 (36.6 mg, 0.04 mmol), Xantphos (46.3 mg, 0.08 mmol), and the corresponding 3-bromopyridine (2.0 mmol). The mixture was back-filled with N_2 , and toluene (5.0 mL), benzyl mercaptan (250 μL , 2.1 mmol), and diisopropylethylamine (760 μL , 4.4 mmol) was added via syringe (if the corresponding 3-bromopyridine is in liquid state, it was added at this stage). The reaction mixture was stirred for 3 h at 80 $^\circ\text{C}$. Upon completion, the reaction mixture was filtered through a pad of silica and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford the 3-(benzylthio)pyridine intermediates.

To a mixture of the corresponding 3-(benzylthio)pyridine (1.5 mmol), acetic acid (2.3 mL), and H_2O (0.75 mL) was added *N*-chlorosuccinimide (0.8 g, 6.0 mmol) portionwise at 0 $^\circ\text{C}$. The mixture was allowed to warm to room temperature, and the reaction progress was monitored by TLC. Upon completion, acetic acid was removed *in vacuo* and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified by flash

chromatography to afford the pyridine-3-sulfonyl chloride intermediates.

To a solution of the corresponding pyridine-3-sulfonyl chloride (0.75 mmol) in CH₃CN (3 mL) was added 6 N HCl (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. Upon completion, the reaction mixture was concentrated *in vacuo*. While the obtained pyridine-3-sulfonic acids are usually pure at this stage, further purification can be done by reverse-phase chromatography (H₂O:MeOH, 100:0→0:100) or recrystallization from H₂O/EtOH.

- Full characterization of new compounds

5-methylpyridine-3-sulfonic acid (L4)

¹H NMR (500 MHz, D₂O): δ 8.98 (s, 1H), 8.77 (s, 1H), 8.75 (s, 1H), 2.62 (s, 3H).

¹³C NMR (150 MHz, D₂O): δ 143.31, 142.83, 141.86, 139.46, 135.99, 17.22.

HRMS (ESI-TOF): *m/z* calculated for C₆H₆NO₃S⁻ [M-H]⁻ 172.0074, found 172.0069.

5-methoxypyridine-3-sulfonic acid (L5)

¹H NMR (500 MHz, D₂O): δ 8.74 (s, 1H), 8.61 (s, 1H), 8.37 (s, 1H), 4.08 (s, 3H).

¹³C NMR (150 MHz, D₂O): δ 157.73, 143.04, 131.84, 131.23, 126.60, 56.84.

HRMS (ESI-TOF): *m/z* calculated for C₆H₆NO₄S⁻ [M-H]⁻ 188.0023, found 188.0018.

5-fluoropyridine-3-sulfonic acid (L6)

¹H NMR (500 MHz, D₂O): δ 8.93 (s, 1H), 8.81 (s, 1H), 8.39 (d, *J* = 7.6 Hz, 1H).

¹³C NMR (150 MHz, D₂O): δ 159.10 (d, *J* = 258.6 Hz), 142.36 (d, *J* = 4.1 Hz), 138.54 (d, *J* = 4.5 Hz), 136.20 (d, *J* = 30.4 Hz), 126.41 (d, *J* = 20.2 Hz).

¹⁹F NMR (376 MHz, D₂O): δ -119.12.

HRMS (ESI-TOF): *m/z* calculated for C₅H₃FNO₃S⁻ [M-H]⁻ 175.9823, found 175.9818.

5-chloropyridine-3-sulfonic acid (L7)

¹H NMR (500 MHz, D₂O): δ 8.97 (s, 1H), 8.88 (s, 1H), 8.61 (s, 1H).

¹³C NMR (150 MHz, D₂O): δ 146.50, 141.31, 140.65, 138.02, 133.41.

HRMS (ESI-TOF): *m/z* calculated for C₅H₃ClNO₃S⁻ [M-H]⁻ 191.9528, found 191.9526.

5-(trifluoromethyl)pyridine-3-sulfonic acid (L8)

¹H NMR (500 MHz, D₂O): δ 9.23 (s, 1H), 9.15 (s, 1H), 8.75 (s, 1H).

¹³C NMR (150 MHz, D₂O): δ 146.96, 145.79 (q, *J* = 4.1 Hz), 140.38, 134.33 (q, *J* = 3.4 Hz), 127.33 (q, *J* = 34.8 Hz), 121.77 (q, *J* = 272.7 Hz).

¹⁹F NMR (376 MHz, D₂O): δ -62.96.

HRMS (ESI-TOF): *m/z* calculated for C₆H₃F₃NO₃S⁻ [M-H]⁻ 225.9791, found 225.9786.

6-(trifluoromethyl)pyridine-3-sulfonic acid (L9)

¹H NMR (500 MHz, D₂O): δ 9.05 – 8.98 (m, 1H), 8.44 – 8.38 (m, 1H), 8.03 – 7.96 (m, 1H).

¹³C NMR (150 MHz, D₂O): δ 148.02 (q, *J* = 35.4 Hz), 146.06, 141.60, 136.04, 121.15, 120.45 (q, *J* = 270.8 Hz).

¹⁹F NMR (376 MHz, D₂O): δ -68.05.

HRMS (ESI-TOF): *m/z* calculated for C₆H₃F₃NO₃S⁻ [M-H]⁻ 225.9791, found 225.9789.

4-(trifluoromethyl)pyridine-3-sulfonic acid (L10)

¹H NMR (500 MHz, D₂O): δ 9.35 (s, 1H), 9.02 (d, *J* = 5.5 Hz, 1H), 8.14 (d, *J* = 5.5 Hz, 1H).

¹³C NMR (150 MHz, D₂O): δ 151.97 – 151.67 (m), 149.29 – 148.75 (m), 140.31 (d, *J* = 35.2 Hz), 139.97, 125.75 (q, *J* = 5.0, 4.5 Hz), 123.37 (q, *J* = 275.2 Hz).

¹⁹F NMR (376 MHz, D₂O): δ –61.08.

HRMS (ESI-TOF): *m/z* calculated for C₆H₃F₃NO₃S[–] [M–H][–] 225.9791, found 225.9789.

2.3 General Procedure for Pd-catalyzed C–H Olefination

2.3.1 Substrate scope A, B

Conditions A: A sealed tube with magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 4.5 mg), **L8** (10 mol%, 4.5 mg), AgOAc (0.4 mmol, 66.8 mg), and substrate **1** (0.2 mmol). Then, HFIP (1.0 mL) and ethyl acrylate (84 uL, 0.8 mmol) were added. The reaction mixture was stirred at 70 °C for 24 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a celite/silica plug, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography to afford the desired products.

Conditions B: A sealed tube with magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 4.5 mg), **L8** (10 mol%, 4.5 mg), AgOAc (0.6 mmol, 100.2 mg), and substrate **1** (0.2 mmol). Then, HFIP (2.0 mL) and ethyl acrylate (84 uL, 0.8 mmol) were added. The reaction mixture was stirred at 70 °C for 36 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a celite/silica plug, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography to afford the desired product.

*Note: Most products were isolated as mixtures of *mono*- and *di*-olefinated products, where only the *mono*-olefinated products were characterized due to the 1) high *mono:di* ratio (~10:1) and 2) difficulty of chromatographic separation. If possible, analytical samples of pure *mono*-olefinated products were isolated and characterized. Selected examples of *di*-olefinated products were characterized (**2q-di**, **2s-di**, **4k-di**).

ethyl (*E*)-6-(dimethylamino)-5-methyl-6-oxohex-2-enoate (**2a**)

2a was obtained as a colorless oil under *Conditions A*. (*mono:di* = 20:1, 30.4 mg, 70% yield)

¹H NMR (600 MHz, CDCl₃): δ 6.89 (ddd, *J* = 15.6, 7.9, 6.8 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.05 (s, 3H), 2.96 (s, 3H), 2.84 (h, *J* = 6.9 Hz, 1H), 2.61 (dtd, *J* = 14.5, 7.0, 1.6 Hz, 1H), 2.27 (dddd, *J* = 14.5, 7.9, 6.8, 1.4 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 175.10, 166.54, 146.60, 123.07, 60.31, 37.25, 36.45, 35.78, 35.12, 17.46, 14.36.

HRMS (ESI-TOF): *m/z* calculated for C₁₁H₂₀NO₃⁺ [M+H]⁺ 214.1438, found 214.1442.

ethyl (*E*)-6-(isopropyl(methyl)amino)-5-methyl-6-oxohex-2-enoate (**2b**)

2b was obtained as a colorless oil under *Conditions A*. (*mono:di* = 10:1, 38.3 mg, 77% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.88 (ddd, $J = 15.2, 8.0, 6.9$ Hz, 1H), 5.85 (dt, $J = 15.6, 1.4$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.42 – 3.29 (m, 4H), 2.75 (h, $J = 6.8$ Hz, 1H), 2.58 (dtd, $J = 14.2, 7.1, 1.6$ Hz, 1H), 2.28 (dddd, $J = 14.6, 8.0, 6.8, 1.3$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.2$ Hz, 3H), 1.16 (d, $J = 6.8$ Hz, 3H), 1.10 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.49, 166.50, 146.48, 123.16, 60.29, 42.02, 40.53, 36.90, 35.15, 18.06, 15.06, 14.36, 13.17.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{24}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 242.1751, found 242.1754.

ethyl (E)-6-(isopropyl(methyl)amino)-5-methyl-6-oxohex-2-enoate (2c)

2c was obtained as a colorless oil under *Conditions A*. (*mono:di* = 17:1, 32.9 mg, 67% yield)

^1H NMR (600 MHz, CDCl_3 , 1:1 mixture of rotamers): δ 6.92 – 6.85 (m, 1H), 5.85 (dt, $J = 7.4, 1.4$ Hz, 0.5H), 5.83 (dt, $J = 7.4, 1.4$ Hz, 0.5H), 4.89 (hept, $J = 6.8$ Hz, 0.5H), 4.17 (q, $J = 7.1$ Hz, 2H), 4.12 (dt, $J = 13.3, 6.6$ Hz, 0.5H), 2.84 (s, 1.5H), 2.88 – 2.75 (m, 1H), 2.78 (s, 1.5H), 2.63 – 2.56 (m, 1H), 2.32 – 2.24 (m, 1H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.21 (d, $J = 6.7$ Hz, 1.5H), 1.19 (d, $J = 6.7$ Hz, 1.5H), 1.15 (d, $J = 6.8$ Hz, 1.5H), 1.14 (d, $J = 6.8$ Hz, 1.5H), 1.08 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3 , 1:1 mixture of rotamers): δ 174.62/174.59, 166.53/166.49, 146.65/146.63, 123.08/122.99, 60.30, 47.71/44.00, 36.81/36.59, 35.63/35.24, 28.19/26.17, 20.86/20.84, 19.55/19.47, 18.13/17.41, 14.35. (Due to similar peak intensity, rotamers cannot be distinguished. Therefore rotameric carbon peaks were grouped together)

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{24}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 242.1751, found 242.1755.

ethyl (E)-6-(diisopropylamino)-5-methyl-6-oxohex-2-enoate (2d)

2d was obtained as a colorless oil under *Conditions A*. (*mono:di* = 13:1, 31.0 mg, 56% yield)

Analytical sample of pure **2d** was isolated for characterization.

^1H NMR (600 MHz, CDCl_3): δ 6.90 (ddd, $J = 15.6, 8.0, 6.7$ Hz, 1H), 5.84 (dt, $J = 15.6, 1.5$ Hz, 1H), 4.18 (q, $J = 7.1$, 1H), 4.17 (q, $J = 7.1$, 1H), 3.98 (br s, 1H), 3.55 (br s, 1H), 2.74 (h, $J = 6.8$ Hz, 1H), 2.59 (dtd, $J = 14.1, 7.0, 1.6$ Hz, 1H), 2.28 – 2.22 (m, 1H), 1.35 (t, $J = 7.1$ Hz, 6H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.23 (d, $J = 6.8$ Hz, 3H), 1.21 (d, $J = 6.8$ Hz, 3H), 1.13 (d, $J = 6.8$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.29, 166.54, 146.88, 122.95, 60.27, 48.03, 45.90, 36.88, 36.53, 21.56, 21.47, 20.85, 20.69, 18.00, 14.37.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{15}\text{H}_{28}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 270.2064, found 270.2069.

ethyl (E)-6-((2-methoxyethyl)(methyl)amino)-5-methyl-6-oxohex-2-enoate (2e)

2e was obtained as a colorless oil under *Conditions A*. (*mono:di* = 10:1, 41.8 mg, 78% yield)

^1H NMR (600 MHz, CDCl_3 , 1.5:1 mixture of rotamers): δ 6.92 – 6.86 (m, 1H), 5.86 (dt, $J = 15.6, 1.4$ Hz, 0.4H), 5.84 (dt, $J = 15.5, 1.5$ Hz, 0.6H), 4.18 (q, $J = 7.1$ Hz, 1.2H), 4.17 (q, $J = 7.1$ Hz, 0.8H), 3.64 – 3.55 (m, 1H), 3.55 – 3.47 (m, 3H), 3.34 (s, 1.2H), 3.33 (s, 1.8H), 3.11 (s, 1.8H), 2.96 (s, 1.2H), 2.95 (h, $J = 6.9$ Hz, 0.4H), 2.84 (h, $J = 6.8$ Hz, 0.6H), 2.64 – 2.58 (m, 1H), 2.30 – 2.23 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 1.8H), 1.28 (t, $J = 7.1$ Hz, 1.2H), 1.15 (d, $J = 6.9$ Hz, 1.8H), 1.14 (d, $J = 6.9$ Hz, 1.2H).

^{13}C NMR (150 MHz, CDCl_3 , major rotamer): δ 175.17, 166.52, 146.55, 123.04, 71.17, 60.31, 58.90, 48.15, 37.04, 36.42, 35.20, 17.38, 14.36.

^{13}C NMR (150 MHz, CDCl_3 , minor rotamer): δ 175.93, 166.59, 146.81, 122.88, 70.22, 60.25, 59.24, 49.70, 36.72, 34.81, 34.14, 17.95, 14.36.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{24}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 258.1700, found 258.1705.

ethyl (E)-6-(azetidin-1-yl)-5-methyl-6-oxohex-2-enoate (2f)

2f was obtained as a colorless oil under *Conditions A* in 0.1 mmol scale. (**2f:1f** = 12:1, 13.2 mg, 56% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.87 (ddd, J = 15.5, 7.8, 7.0 Hz, 1H), 5.85 (dt, J = 15.6, 1.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.16 (t, J = 8.5 Hz, 2H), 4.02 (t, J = 7.8 Hz, 2H), 2.53 (dtd, J = 14.4, 7.2, 1.5 Hz, 1H), 2.42 (h, J = 6.9 Hz, 1H), 2.27 (dt, J = 14.7, 7.3 Hz, 2H), 2.23 (dddd, J = 14.4, 7.9, 6.6, 1.4 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.88, 166.55, 146.26, 123.22, 60.36, 50.21, 47.89, 36.04, 34.40, 17.10, 15.22, 14.38.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{12}\text{H}_{20}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 226.1438, found 226.1442.

ethyl (E)-5-methyl-6-oxo-6-(pyrrolidin-1-yl)hex-2-enoate (2g)

2g was obtained as a yellow oil under *Conditions A*. (28.3 mg, 62% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.90 (ddd, J = 15.6, 7.9, 6.7 Hz, 1H), 5.85 (dt, J = 15.6, 1.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.50 – 3.43 (m, 4H), 2.66 (h, J = 6.7 Hz, 1H), 2.60 (dtd, J = 14.1, 7.0, 1.6 Hz, 1H), 2.27 (dddd, J = 14.4, 8.0, 6.6, 1.3 Hz, 1H), 1.96 (pd, J = 6.7, 1.3 Hz, 2H), 1.86 (p, J = 6.5 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.7 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.75, 166.60, 146.63, 123.10, 60.35, 46.58, 45.94, 37.45, 36.40, 26.28, 24.41, 17.31, 14.39.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{22}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 240.1594, found 240.1594.

ethyl (E)-5-methyl-6-oxo-6-(piperidin-1-yl)hex-2-enoate (2h)

2h was obtained as a colorless oil under *Conditions A*. (*mono:di* = 10:1, 36.3 mg, 69% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.90 (ddd, J = 15.6, 7.9, 6.8 Hz, 1H), 5.85 (dt, J = 15.6, 1.5 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.56 (ddt, J = 24.3, 12.9, 6.5 Hz, 2H), 3.48 – 3.40 (m, 2H), 2.83 (h, J = 6.9 Hz, 1H), 2.61 (dtd, J = 14.5, 6.9, 1.6 Hz, 1H), 2.27 (dddd, J = 14.7, 8.1, 6.9, 1.4 Hz, 1H), 1.68 – 1.63 (m, 2H), 1.59 – 1.51 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.39, 166.57, 146.80, 123.05, 60.33, 46.74, 43.09, 36.60, 34.85, 26.89, 25.81, 24.76, 17.80, 14.40.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{24}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 254.1751, found 254.1753.

ethyl (E)-6-(azepan-1-yl)-5-methyl-6-oxohex-2-enoate (2i)

2i was obtained as a colorless oil under *Conditions A*. (*mono:di* = 10:1, 38.5 mg, 70% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.89 (ddd, J = 15.4, 8.0, 6.8 Hz, 1H), 5.86 (dt, J = 15.6, 1.4 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.65 (ddd, J = 13.7, 7.0, 5.1 Hz, 1H), 3.55 – 3.48 (m, 1H), 3.44 – 3.37 (m, 2H), 2.80 (h, J = 6.8 Hz, 1H), 2.61 (dtd, J = 14.3, 7.3, 1.5 Hz, 1H), 2.27 (dddd, J = 14.5, 8.0, 6.6, 1.3 Hz, 1H), 1.75 – 1.65 (m, 4H), 1.60 – 1.51 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.8 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.90, 166.52, 146.70, 123.12, 60.30, 48.01, 46.41, 36.82, 35.33, 29.61, 27.76, 26.85, 26.84, 18.09, 14.37.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{15}\text{H}_{26}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 268.1907, found 268.1908.

ethyl (E)-5-methyl-6-morpholino-6-oxohex-2-enoate (2j)

2j was obtained as a colorless oil under *Conditions A* in 6.37 mmol (1.0 g) scale. (*mono:di* = 19:1, 1.36 g, 81% yield)

Analytical sample of pure **2j** was isolated for characterization.

^1H NMR (600 MHz, CDCl_3): δ 6.88 (ddd, J = 15.6, 7.8, 6.9 Hz, 1H), 5.86 (dt, J = 15.6, 1.5 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.70 – 3.61 (m, 6H), 3.55 – 3.45 (m, 2H), 2.79 (h, J = 6.9 Hz, 1H), 2.61 (dtd, J = 14.3, 7.0, 1.6 Hz, 1H), 2.30 (dddd, J = 14.5, 8.0, 6.8, 1.4 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.80, 166.48, 146.22, 123.37, 67.15, 66.89, 60.45, 46.21, 42.32, 36.44, 34.76, 17.77, 14.41.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{22}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 256.1543, found 256.1546.

ethyl (E)-5-methyl-6-oxo-6-(4-(2,2,2-trifluoroacetyl)piperazin-1-yl)hex-2-enoate (2k)

2k was obtained as a colorless oil under *Conditions B*. (*mono:di* >20:1, **2k-mono:1k** = 6.4:1, 55.6 mg, 71% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.86 (dt, J = 15.1, 7.4 Hz, 1H), 5.87 (dt, J = 15.6, 1.5 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.81 – 3.53 (m, 8H), 2.87 – 2.76 (m, 1H), 2.62 (dtd, J = 14.4, 7.3, 1.6 Hz, 1H), 2.31 (dddd, J = 14.4, 7.8, 6.5, 1.4 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3 , mixture of rotamers*): δ 173.98, 166.37, 145.74, 123.60, 116.37 (q, J = 287.8 Hz), 60.50, 45.92 (*minor*), 45.81 (*major*), 45.51 (*minor*), 44.98 (*major*), 43.51 (*major*), 43.38 (*minor*), 41.81 (*major*), 41.24 (*minor*), 36.40, 35.08 (*minor*), 34.99 (*major*), 17.83, 14.36. (Carbonyl peak for trifluoroacetyl group was not found)

HRMS (ESI-TOF): m/z calculated for $\text{C}_{15}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$ 351.1526, found 351.1530.

(*Relative geometry between two amide groups lead to rotameric peaks in ^{13}C NMR)

ethyl ((E)-6-ethoxy-2-methyl-6-oxohex-4-enoyl)-L-prolinate (2l)

2l was obtained as a colorless oil under *Conditions B*. (35.8 mg, 57% yield, dr 1:1)

Analytical sample of one of the diastereomers was characterized.

^1H NMR (600 MHz, CDCl_3 , 5:1 mixture of rotamers, only major rotamer is characterized): δ 6.95 (ddd, J = 15.5, 8.3, 6.4 Hz, 1H), 5.87 (dt, J = 15.6, 1.5 Hz, 1H), 4.47 (dd, J = 8.8, 4.1 Hz, 1H), 4.23 – 4.14 (m, 4H), 3.68 (ddd, J = 9.9, 8.0, 5.2 Hz, 1H), 3.55 (dt, J = 9.6, 7.0 Hz, 1H), 2.69 (h, J = 6.7 Hz, 1H), 2.61 (dtd, J = 14.5, 6.4, 1.7 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.24 – 2.15 (m, 1H), 2.12 – 2.04 (m, 1H), 1.99 (dddd, J = 12.3, 9.0, 6.6, 5.0 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.7 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3 , mixture of rotamers, only major rotamer is characterized): δ 173.97, 172.40, 166.61, 146.49, 123.19, 61.15, 60.38, 58.92, 46.99, 37.33, 36.02, 29.18, 24.96, 17.23, 14.41, 14.28.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{16}\text{H}_{26}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$ 312.1805, found 312.1809.

ethyl (E)-6-((2-ethoxy-2-oxoethyl)(methyl)amino)-5-methyl-6-oxohex-2-enoate (2m)

2m was obtained as a colorless oil under *Conditions B*. (*mono:di* > 20:1, 39.3 mg, 69% yield)

^1H NMR (600 MHz, CDCl_3 , 4:1 mixture of rotamers, only major rotamer is characterized): δ 6.91 (ddd, J

= 15.0, 7.8, 6.7 Hz, 1H), 5.86 (dt, J = 15.6, 1.2 Hz, 1H), 4.21 – 4.16 (m, 5H), 4.03 (d, J = 17.2 Hz, 1H), 3.12 (s, 3H), 2.89 (h, J = 6.9 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.32 – 2.25 (m, 1H), 1.28 (t, J = 7.4 Hz, 3H), 1.27 (t, J = 7.4 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3 , mixture of rotamers, only major rotamer is characterized): δ 175.89, 169.31, 166.52, 146.30, 123.24, 61.25, 60.35, 49.87, 36.66, 36.21, 35.04, 17.18, 14.36, 14.26.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{24}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$ 286.1649, found 286.1654.

ethyl (E)-1-(6-ethoxy-2-methyl-6-oxohex-4-enoyl)piperidine-4-carboxylate (2n)

2n was obtained as a colorless oil under *Conditions B*. (*mono:di* = 10:1, 53.1 mg, 79% yield)

Analytical sample of pure **2n** was isolated for characterization.

^1H NMR (600 MHz, CDCl_3): δ 6.88 (dtd, J = 15.0, 7.4, 3.7 Hz, 1H), 5.85 (dd, J = 15.5, 7.3 Hz, 1H), 4.42 (dd, J = 12.8, 4.7 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.89 – 3.82 (m, 1H), 3.19 – 3.10 (m, 1H), 2.90 – 2.77 (m, 2H), 2.65 – 2.51 (m, 2H), 2.28 (dq, J = 15.0, 7.7 Hz, 1H), 1.99 – 1.91 (m, 2H), 1.72 – 1.66 (m, 1H), 1.66 – 1.57 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.16 – 1.12 (m, 3H).

^{13}C NMR (150 MHz, CDCl_3 , mixture of rotamers): δ 174.30/174.18, 173.57/173.51, 166.57/166.47, 146.60/146.38, 123.33/123.16, 60.80, 60.39, 44.95/44.89, 41.42/41.34, 41.18/41.14, 36.51, 34.98/34.93, 28.85/28.79, 28.13/28.09, 17.96, 17.57, 14.40/14.34. (Corresponding carbon peaks between rotamers are grouped)

HRMS (ESI-TOF): m/z calculated for $\text{C}_{17}\text{H}_{28}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$ 326.1962, found 326.1968.

ethyl (E)-6-(methoxy(methyl)amino)-5-methyl-6-oxohex-2-enoate (2o)

2o was obtained as a colorless oil under *Conditions B*. (*mono:di* = 10:1, 35.5 mg, 75% yield)

Analytical sample of pure **2o** was isolated for characterization.

^1H NMR (600 MHz, CDCl_3): δ 6.89 (ddd, J = 15.5, 7.7, 7.0 Hz, 1H), 5.86 (dt, J = 15.6, 1.5 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.69 (s, 3H), 3.19 (s, 3H), 3.08 – 2.95 (m, 1H), 2.58 (dtd, J = 14.3, 7.1, 1.6 Hz, 1H), 2.29 – 2.23 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 176.56, 166.54, 146.40, 123.17, 61.68, 60.34, 36.10, 34.72, 32.38, 17.35, 14.38.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{11}\text{H}_{20}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 230.1387, found 230.1397.

ethyl (E)-5-methyl-6-(octylamino)-6-oxohex-2-enoate (2p)

2p was obtained as a colorless oil under *Conditions B*. (*mono:di* = 13:1, 25.0 mg, 41%)

^1H NMR (600 MHz, CDCl_3): δ 6.87 (dt, J = 15.5, 7.3 Hz, 1H), 5.85 (dt, J = 15.6, 1.4 Hz, 1H), 5.44 (br s, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.28 – 3.18 (m, 2H), 2.60 – 2.53 (m, 1H), 2.33 – 2.25 (m, 2H), 1.48 (p, J = 7.0 Hz, 2H), 1.32 – 1.22 (m, 10H), 1.28 (t, J = 7.1 Hz, 3H), 1.18 (d, J = 6.7 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.85, 166.50, 146.07, 123.40, 60.41, 40.80, 39.65, 36.63, 31.93, 29.80, 29.37, 29.32, 27.02, 22.77, 17.89, 14.39, 14.23.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{17}\text{H}_{32}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 298.2377, found 298.2376.

diethyl (2E,4E)-3-(2-methyl-3-(octylamino)-3-oxopropyl)hexa-2,4-dienedioate (2p'-E)

2p'-E was isolated as a white solid along with **2p**. (7.6 mg, 10% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.25 (d, *J* = 15.9 Hz, 1H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.09 (s, 1H), 6.01 (t, *J* = 5.0 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.24 – 3.16 (m, 2H), 3.12 (dd, *J* = 12.9, 6.1 Hz, 1H), 2.75 (dd, *J* = 12.9, 8.4 Hz, 1H), 2.49 (h, *J* = 6.8 Hz, 1H), 1.50 – 1.43 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.33 – 1.24 (m, 10H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 175.15, 166.44, 166.23, 152.97, 145.98, 125.74, 124.54, 61.04, 60.72, 41.83, 39.62, 32.38, 31.95, 29.72, 29.41, 29.38, 27.06, 22.80, 17.17, 14.36, 14.24 (two –Me peaks overlap).

HRMS (ESI-TOF): *m/z* calculated for C₂₂H₃₈NO₅⁺ [M+H]⁺ 396.2744, found 396.2748.

diethyl (2Z,4E)-3-(2-methyl-3-(octylamino)-3-oxopropyl)hexa-2,4-dienedioate (2p'-Z)

2p'-Z was isolated as a colorless oil along with **2p**. (7.8 mg, 10% yield)

¹H NMR (600 MHz, CDCl₃): δ 8.54 (d, *J* = 16.3 Hz, 1H), 6.19 – 6.12 (m, 1H), 5.93 (s, 1H), 5.34 (t, *J* = 5.2 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.26 – 3.13 (m, 2H), 2.74 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.40 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.34 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.45 (tp, *J* = 13.9, 7.2, 6.5 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.34 – 1.24 (m, 10H), 1.18 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 174.53, 166.58, 165.38, 148.61, 139.50, 124.89, 124.16, 61.01, 60.63, 41.03, 39.69, 38.39, 31.94, 29.79, 29.36, 29.32, 27.03, 22.78, 18.29, 14.42, 14.35, 14.23.

HRMS (ESI-TOF): *m/z* calculated for C₂₂H₃₈NO₅⁺ [M+H]⁺ 396.2744, found 396.2745.

ethyl (E)-5,5-dimethyl-6-(methylamino)-6-oxohex-2-enoate (2q)

2q was obtained as a colorless oil under *Conditions A* with 2.5 equiv. of AgOAc. (26.4 mg, 62% yield)

¹H NMR (600 MHz, CDCl₃): δ 6.85 (dt, *J* = 15.5, 7.7 Hz, 1H), 5.85 (dt, *J* = 15.5, 1.4 Hz, 1H), 5.77 (br s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.81 (d, *J* = 4.8 Hz, 3H), 2.43 (dd, *J* = 7.8, 1.4 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 6H).

¹³C NMR (150 MHz, CDCl₃): δ 177.21, 166.38, 144.90, 124.31, 60.37, 43.29, 42.27, 26.66, 25.34, 14.35.

HRMS (ESI-TOF): *m/z* calculated for C₁₁H₂₀NO₃⁺ [M+H]⁺ 214.1438, found 214.1438.

diethyl (2E,7E)-5-methyl-5-(methylcarbamoyl)nona-2,7-dienedioate (2q-di)

2q-di was isolated as a colorless oil along with **2q**. (7.4 mg, 12% yield)

¹H NMR (600 MHz, CDCl₃): δ 6.81 (ddd, *J* = 15.5, 8.3, 7.2 Hz, 2H), 5.87 (dt, *J* = 15.5, 1.3 Hz, 2H), 5.67 (q, *J* = 4.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 4H), 2.82 (d, *J* = 4.8 Hz, 3H), 2.63 (ddd, *J* = 13.8, 7.2, 1.4 Hz, 2H), 2.29 (ddd, *J* = 13.8, 8.3, 1.2 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H), 1.18 (s, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 175.12, 166.22, 143.69, 124.96, 60.52, 45.85, 42.12, 26.73, 21.05, 14.37.

HRMS (ESI-TOF): *m/z* calculated for C₁₆H₂₆NO₅⁺ [M+H]⁺ 312.1805, found 312.1803.

ethyl (E)-6-(isopropylamino)-5,5-dimethyl-6-oxohex-2-enoate (2r)

2r was obtained as a yellow oil under *Conditions A*. (*mono:di* = 12:1, 38.4 mg, 77% yield)

¹H NMR (600 MHz, CDCl₃): δ 6.86 (dt, *J* = 15.5, 7.8 Hz, 1H), 5.84 (dt, *J* = 15.5, 1.4 Hz, 1H), 5.40 (d, *J* = 6.7 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.07 (ddt, *J* = 13.1, 7.8, 6.6 Hz, 1H), 2.41 (dd, *J* = 7.8, 1.4 Hz, 2H),

1.27 (t, $J = 7.1$ Hz, 3H), 1.19 (s, 6H), 1.14 (d, $J = 6.6$ Hz, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.52, 166.33, 144.86, 124.34, 60.35, 43.38, 42.13, 41.48, 25.29, 22.84, 14.36.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{24}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 242.1751, found 242.1756.

ethyl (*E*)-6-(tert-butylamino)-5,5-dimethyl-6-oxohex-2-enoate (2s)

2s was obtained as a colorless oil under *Conditions A*. (33.0 mg, 68% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.86 (dt, $J = 15.6, 7.8$ Hz, 1H), 5.84 (dt, $J = 15.5, 1.4$ Hz, 1H), 5.39 (br s, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.39 (dd, $J = 7.8, 1.4$ Hz, 2H), 1.34 (s, 9H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.17 (s, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.71, 166.33, 144.98, 124.27, 60.32, 51.21, 43.48, 42.60, 28.81, 25.41, 14.36.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{26}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 256.1907, found 256.1911.

diethyl (2*E*,7*E*)-5-(tert-butylcarbamoyl)-5-methylnona-2,7-dienedioate (2s-di)

2s-di was isolated as a white solid along with **2s**. (6.3 mg, 9% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.83 (ddd, $J = 15.5, 8.3, 7.2$ Hz, 2H), 5.86 (dt, $J = 15.5, 1.3$ Hz, 2H), 5.36 (br s, 1H), 4.18 (qd, $J = 7.1, 2.0$ Hz, 4H), 2.62 (ddd, $J = 13.7, 7.2, 1.3$ Hz, 2H), 2.23 (ddd, $J = 13.7, 8.4, 1.2$ Hz, 2H), 1.33 (s, 9H), 1.28 (t, $J = 7.1$ Hz, 6H), 1.14 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.55, 166.20, 143.84, 124.90, 60.46, 51.69, 46.13, 42.32, 28.78, 21.04, 14.38.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{19}\text{H}_{32}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$ 354.2275, found 354.2283.

ethyl (*E*)-6-((2-methoxyethyl)amino)-5,5-dimethyl-6-oxohex-2-enoate (2t)

2t was obtained as a colorless oil under *Conditions A*. (*mono:di* = 7:1, 38.2 mg, 71% yield)

Analytical sample of pure **2t** was isolated for characterization.

^1H NMR (600 MHz, CDCl_3): δ 6.86 (dt, $J = 15.5, 7.8$ Hz, 1H), 6.02 (br s, 1H), 5.85 (dt, $J = 15.5, 1.4$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.46 – 3.43 (m, 4H), 3.36 (s, 3H), 2.43 (dd, $J = 7.8, 1.4$ Hz, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.21 (s, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ 176.59, 166.33, 144.80, 124.39, 71.33, 60.37, 58.93, 43.33, 42.34, 39.44, 25.35, 14.39.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{24}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 258.1700, found 258.1706.

ethyl (*E*)-6-((2-methoxy-2-oxoethyl)amino)-5,5-dimethyl-6-oxohex-2-enoate (2u)

2u was obtained as a colorless oil under *Conditions A* in 1.0 mmol scale. (134.5 mg, 50% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.88 (dt, $J = 15.5, 7.7$ Hz, 1H), 6.15 (br s, 1H), 5.88 – 5.83 (m, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 4.04 (d, $J = 5.0$ Hz, 2H), 3.77 (s, 3H), 2.45 (d, $J = 7.7$ Hz, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.24 (s, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ 176.89, 170.63, 166.35, 144.56, 124.60, 60.44, 52.56, 43.23, 42.31, 41.55, 25.27, 14.39.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{22}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$ 272.1492, found 272.1496.

ethyl (E)-3-(2-(N-methylisobutyramido)phenyl)acrylate (2v')

2v' was obtained as a white solid under *Conditions A* in 0.1 mmol scale. (22.4 mg, 81% yield)

^1H NMR (600 MHz, CDCl_3): δ 7.72 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.66 (d, $J = 16.1$ Hz, 1H), 7.45 (td, $J = 7.6$, 1.6 Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.20 (dd, $J = 7.8$, 1.2 Hz, 1H), 6.46 (d, $J = 16.1$ Hz, 1H), 4.26 (qd, $J = 7.1$, 4.3 Hz, 2H), 3.21 (s, 3H), 2.28 (hept, $J = 6.7$ Hz, 1H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.99 (d, $J = 6.5$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 177.68, 166.34, 143.41, 138.60, 132.52, 131.56, 128.90, 128.76, 127.85, 121.61, 60.90, 37.32, 31.64, 19.81, 19.65, 14.42.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{16}\text{H}_{22}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 276.1594, found 276.1699.

ethyl (E)-6-((2,6-dimethylphenyl)(methyl)amino)-5-methyl-6-oxohex-2-enoate (2w)

2w was obtained as a colorless oil under *Conditions A*. (32.8 mg, 54% yield)

^1H NMR (600 MHz, CDCl_3 , 16:1 mixture of rotamers, only major rotamer is characterized): δ 7.17 (dd, $J = 8.0$, 6.9 Hz, 1H), 7.14 – 7.10 (m, 2H), 6.72 (ddd, $J = 15.5$, 8.1, 6.8 Hz, 1H), 5.77 (dt, $J = 15.5$, 1.3 Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.14 (s, 3H), 2.49 – 2.43 (m, 1H), 2.28 – 2.21 (m, 2H), 2.23 (s, 3H), 2.19 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.00 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3 , 16:1 mixture of rotamers, only major rotamer is characterized): δ 175.97, 166.44, 146.47, 140.99, 135.80, 135.71, 129.20, 129.14, 128.27, 123.44, 60.36, 36.87, 36.16, 34.96, 18.01, 17.98, 17.46, 14.40.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{18}\text{H}_{26}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 304.1907, found 304.1911.

ethyl (E)-5-(morpholine-4-carbonyl)hept-2-enoate (4a)

4a was obtained as a colorless oil under *Conditions B*. (45.5 mg (2:1 mixture with **3a**), 66% yield)

Analytical sample of pure **4a** was isolated for characterization.

^1H NMR (600 MHz, CDCl_3): δ 6.86 (dt, $J = 15.5$, 7.4 Hz, 1H), 5.84 (dt, $J = 15.6$, 1.4 Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.73 – 3.60 (m, 6H), 3.53 (tq, $J = 13.4$, 8.5, 6.3 Hz, 2H), 2.70 (tt, $J = 8.1$, 5.6 Hz, 1H), 2.56 (dddd, $J = 14.4$, 8.5, 7.2, 1.5 Hz, 1H), 2.37 – 2.31 (m, 1H), 1.75 – 1.66 (m, 1H), 1.57 – 1.49 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.90 (t, $J = 7.4$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.12, 166.41, 146.21, 123.23, 67.24, 66.92, 60.40, 46.37, 42.36, 41.52, 34.92, 25.80, 14.38, 11.78.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{24}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 270.1700, found 270.1697.

ethyl (E)-5-(morpholine-4-carbonyl)oct-2-enoate (4b)

4b was obtained as a colorless oil under *Conditions B* at 80 °C. (43.4 mg (3:1 mixture with **3b**), 63% yield)

Analytical sample of pure **4b** was isolated for characterization.

^1H NMR (600 MHz, CDCl_3): δ 6.86 (dt, $J = 15.5$, 7.4 Hz, 1H), 5.84 (dt, $J = 15.6$, 1.4 Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.74 – 3.57 (m, 6H), 3.56 – 3.48 (m, 2H), 2.76 (tt, $J = 8.3$, 5.5 Hz, 1H), 2.56 (dddd, $J = 14.3$, 8.6, 7.2, 1.5 Hz, 1H), 2.33 (dddd, $J = 14.4$, 7.4, 5.6, 1.4 Hz, 1H), 1.68 (dddd, $J = 13.4$, 10.4, 8.2, 5.4 Hz, 1H), 1.48 – 1.41 (m, 1H), 1.35 – 1.23 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.90 (t, $J = 7.3$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.32, 166.42, 146.18, 123.24, 67.24, 66.92, 60.41, 46.38, 42.38, 39.88,

35.35, 35.05, 20.62, 14.39, 14.22.

HRMS (ESI-TOF): m/z calculated for $C_{15}H_{26}NO_4^+$ $[M+H]^+$ 284.1856, found 284.1860.

ethyl (*E*)-5-cyclohexyl-6-morpholino-6-oxohex-2-enoate (4c)

4c was obtained as a colorless oil under *Conditions B* at 80 °C. (50.3 mg (4:1 mixture with **3c**), 66% yield)
Analytical sample of pure **4c** was isolated for characterization.

1H NMR (600 MHz, $CDCl_3$): δ 6.82 (dt, J = 14.5, 6.1 Hz, 1H), 5.83 (d, J = 15.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.82 – 3.77 (m, 1H), 3.71 – 3.64 (m, 2H), 3.63 – 3.45 (m, 5H), 2.58 – 2.51 (m, 2H), 2.43 (p, J = 9.0, 8.2 Hz, 1H), 1.85 (d, J = 12.1 Hz, 1H), 1.76 – 1.58 (m, 5H), 1.27 (t, J = 7.1 Hz, 3H), 1.31 – 1.19 (m, 2H), 1.17 – 1.07 (m, 1H), 0.98 – 0.89 (m, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.03, 166.39, 146.70, 123.09, 67.29, 66.89, 60.35, 46.64, 46.08, 42.29, 40.61, 32.67, 31.65, 30.41, 26.41, 26.36, 26.32, 14.39.

HRMS (ESI-TOF): m/z calculated for $C_{18}H_{30}NO_4^+$ $[M+H]^+$ 324.2169, found 324.2172.

ethyl (*E*)-5-(adamantan-1-yl)-6-morpholino-6-oxohex-2-enoate (4d)

4d was obtained as a white solid under *Conditions A* in 0.8 mmol scale. (217.4 mg, 72% yield)

1H NMR (600 MHz, $CDCl_3$): δ 6.80 (dt, J = 15.3, 7.4 Hz, 1H), 5.82 (dt, J = 15.6, 1.3 Hz, 1H), 4.17 (qd, J = 7.1, 1.0 Hz, 2H), 3.93 – 3.87 (m, 1H), 3.70 (tdd, J = 11.1, 5.1, 3.1 Hz, 2H), 3.64 – 3.59 (m, 1H), 3.57 – 3.52 (m, 2H), 3.48 (ddd, J = 12.9, 7.9, 2.9 Hz, 1H), 3.44 (ddd, J = 13.4, 8.0, 3.2 Hz, 1H), 2.66 (dddd, J = 13.1, 11.5, 7.7, 1.2 Hz, 1H), 2.43 (dd, J = 11.4, 2.8 Hz, 1H), 2.37 (dddd, J = 13.4, 7.2, 2.8, 1.4 Hz, 1H), 1.98 (br s, 3H), 1.79 – 1.74 (m, 3H), 1.72 – 1.67 (m, 3H), 1.65 – 1.61 (m, 3H), 1.52 – 1.48 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 171.93, 166.42, 147.36, 123.03, 67.42, 66.93, 60.36, 50.30, 47.35, 42.21, 40.28, 37.01, 35.96, 29.82, 28.73, 14.43.

HRMS (ESI-TOF): m/z calculated for $C_{22}H_{34}NO_4^+$ $[M+H]^+$ 376.2482, found 376.2485.

ethyl (*E*)-9-(1,3-dioxoisindolin-2-yl)-5-(morpholine-4-carbonyl)non-2-enoate (4e)

4e was obtained as a colorless oil under *Conditions B* in 0.1 mmol scale at 80 °C. (29.3 mg, 66% yield)

1H NMR (600 MHz, $CDCl_3$): δ 7.84 (dd, J = 5.4, 3.0 Hz, 2H), 7.72 (dd, J = 5.5, 3.0 Hz, 2H), 6.87 – 6.79 (m, 1H), 5.83 (dt, J = 15.6, 1.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.71 – 3.56 (m, 8H), 3.52 (t, J = 4.8 Hz, 2H), 2.76 (tt, J = 8.5, 5.5 Hz, 1H), 2.55 (dddd, J = 14.4, 8.6, 7.3, 1.4 Hz, 1H), 2.35 – 2.29 (m, 1H), 1.74 (dtt, J = 10.6, 8.3, 5.3 Hz, 1H), 1.66 (p, J = 7.4 Hz, 2H), 1.55 – 1.48 (m, 1H), 1.39 – 1.29 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.02, 168.53, 166.38, 145.88, 134.10, 132.24, 123.41, 123.35, 67.21, 66.93, 60.46, 46.42, 42.42, 39.89, 37.79, 35.36, 32.32, 28.69, 24.75, 14.41.

HRMS (ESI-TOF): m/z calculated for $C_{24}H_{31}N_2O_6^+$ $[M+H]^+$ 443.2177, found 443.2176.

ethyl (*E*)-9-(benzyloxy)-5-(morpholine-4-carbonyl)non-2-enoate (4f)

4f was obtained as a colorless oil under *Conditions B* in 0.1 mmol scale at 80 °C. (27.1 mg (7:1 mixture with **3f**), 61% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.36 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 6.88 – 6.80 (m, 1H), 5.84 (dt, *J* = 15.6, 1.4 Hz, 1H), 4.48 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.73 – 3.68 (m, 1H), 3.66 – 3.56 (m, 5H), 3.53 – 3.41 (m, 2H), 3.47 – 3.41 (m, 2H), 2.75 (tt, *J* = 8.3, 5.5 Hz, 1H), 2.55 (dddd, *J* = 14.3, 8.6, 7.3, 1.4 Hz, 1H), 2.32 (dddd, *J* = 14.4, 7.3, 5.6, 1.3 Hz, 1H), 1.74 – 1.67 (m, 1H), 1.59 (dtd, *J* = 13.3, 6.6, 2.3 Hz, 2H), 1.48 (dtd, *J* = 13.4, 8.0, 5.5 Hz, 1H), 1.38 – 1.31 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 173.20, 166.40, 146.05, 138.63, 128.51, 127.79, 127.71, 123.33, 73.08, 70.09, 67.23, 66.91, 60.45, 46.40, 42.41, 40.07, 35.36, 32.69, 29.89, 24.17, 14.41.

HRMS (ESI-TOF): *m/z* calculated for C₂₃H₃₄NO₅⁺ [M+H]⁺ 404.2431, found 404.2441.

ethyl (E)-9-fluoro-5-(morpholine-4-carbonyl)non-2-enoate (4g)

4g was obtained as a colorless oil under *Conditions B* at 80 °C. (47.8 mg (2:1 mixture with **3g**), 56% yield) Analytical sample of pure **4g** was isolated for characterization.

¹H NMR (600 MHz, CDCl₃): δ 6.85 (dt, *J* = 15.4, 7.4 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.4 Hz, 1H), 4.50 – 4.35 (m, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.76 – 3.71 (m, 1H), 3.70 – 3.61 (m, 4H), 3.60 – 3.48 (m, 3H), 2.77 (tt, *J* = 8.4, 5.5 Hz, 1H), 2.56 (dddd, *J* = 14.3, 8.5, 7.4, 1.4 Hz, 1H), 2.37 – 2.31 (m, 1H), 1.80 – 1.73 (m, 1H), 1.72 – 1.63 (m, 2H), 1.55 – 1.48 (m, 1H), 1.42 – 1.35 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 173.00, 166.32, 145.75, 123.46, 83.83 (d, *J* = 164.6 Hz), 67.21, 66.89, 60.46, 46.39, 42.41, 40.05, 35.42, 32.40, 30.54 (d, *J* = 19.7 Hz), 23.29 (d, *J* = 5.0 Hz), 14.38.

HRMS (ESI-TOF): *m/z* calculated for C₁₆H₂₇FO₄⁺ [M+H]⁺ 316.1919, found 316.1926.

diethyl (E)-5-(morpholine-4-carbonyl)non-2-enedioate (4h)

4h was obtained as a colorless oil under *Conditions B* in 0.1 mmol scale at 80 °C. (32.2 mg (1.5:1 mixture with **3a**), 61 % yield)

Analytical sample of pure **4h** was isolated for characterization.

¹H NMR (600 MHz, CDCl₃): δ 6.84 (dt, *J* = 15.4, 7.4 Hz, 1H), 5.84 (dt, *J* = 15.6, 1.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.73 – 3.57 (m, 6H), 3.56 – 3.48 (m, 2H), 2.78 (tt, *J* = 8.2, 5.5 Hz, 1H), 2.56 (dddd, *J* = 14.4, 8.5, 7.4, 1.4 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.33 – 2.24 (m, 2H), 1.75 – 1.68 (m, 1H), 1.59 (p, *J* = 7.6 Hz, 2H), 1.54 – 1.47 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 173.29, 172.81, 166.32, 145.71, 123.48, 67.20, 66.89, 60.52, 60.46, 46.39, 42.42, 39.95, 35.24, 34.18, 32.13, 22.73, 14.39, 14.37.

HRMS (ESI-TOF): *m/z* calculated for C₁₈H₃₀NO₆⁺ [M+H]⁺ 356.2068, found 356.2068.

ethyl (E)-5-(2,6-difluorobenzyl)-6-morpholino-6-oxohex-2-enoate (4i)

4i was obtained as a colorless oil under *Conditions A* in 0.1 mmol scale. (20.5 mg, 56% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.20 (tt, *J* = 8.3, 6.5 Hz, 1H), 6.88 (ddt, *J* = 10.0, 6.1, 3.0 Hz, 2H), 6.81 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.82 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.67 – 3.60 (m, 2H), 3.59 – 3.50 (m, 3H), 3.45 (ddd, *J* = 13.9, 7.4, 3.0 Hz, 1H), 3.32 (ddt, *J* = 16.1, 11.4, 3.4 Hz, 2H), 3.11 (dtd, *J* = 9.0, 7.4, 5.0 Hz, 1H), 2.96 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.89 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.74 (dddd, *J* = 14.7, 8.8, 7.1, 1.4 Hz, 1H), 2.32 (dddd, *J* = 14.1, 7.0, 5.0, 1.3 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 172.04, 166.35, 161.78 (dd, *J* = 247.3, 8.5 Hz), 145.61, 128.68 (t, *J* = 10.2

Hz), 123.45, 114.69 (t, $J = 20.1$ Hz), 111.41 (dd, $J = 21.0, 5.1$ Hz), 67.09, 66.72, 60.42, 46.24, 42.46, 39.57, 34.60, 25.94 (t, $J = 1.9$ Hz), 14.40.

HRMS (ESI-TOF): m/z calculated for $C_{19}H_{24}F_2NO_4^+$ $[M+H]^+$ 368.1668, found 386.1675.

(E)-2-(2,6-difluorophenyl)-1-morpholino-5-(phenylsulfonyl)pent-4-en-1-one (4j)

4j was obtained as a white solid under *Conditions B* in 0.1 mmol scale with phenyl vinyl sulfone instead of ethyl acrylate. (21.8 mg, 52% yield)

1H NMR (600 MHz, $CDCl_3$): δ 7.78 (dd, $J = 8.5, 1.2$ Hz, 2H), 7.62 – 7.58 (m, 1H), 7.51 (tt, $J = 6.7, 1.1$ Hz, 2H), 7.21 (tt, $J = 8.4, 6.4$ Hz, 1H), 6.93 (dt, $J = 15.1, 7.6$ Hz, 1H), 6.85 (t, $J = 8.3$ Hz, 2H), 6.23 (dt, $J = 15.0, 1.3$ Hz, 1H), 4.12 – 4.09 (m, 1H), 3.70 – 3.62 (m, 2H), 3.60 – 3.51 (m, 2H), 3.50 – 3.45 (m, 1H), 3.29 – 3.22 (m, 1H), 3.15 – 3.02 (m, 2H), 3.06 (dtd, $J = 14.6, 6.7, 1.5$ Hz, 1H), 2.74 (dtd, $J = 14.5, 8.2, 1.0$ Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 168.36, 160.51 (dd, $J = 249.2, 7.7$ Hz), 143.70, 140.51, 133.35, 132.92, 129.86 (t, $J = 10.4$ Hz), 129.27, 127.75, 114.65 (t, $J = 18.0$ Hz), 112.15 (dd, $J = 21.7, 4.1$ Hz), 66.90, 66.19, 45.91, 42.98, 37.56, 33.47.

HRMS (ESI-TOF): m/z calculated for $C_{21}H_{22}F_2NO_4S^+$ $[M+H]^+$ 422.1232, found 422.1234.

ethyl (E)-5-methyl-5-(pentylcarbamoyl)hept-2-enoate (4k-mono)

4k-mono was obtained as a colorless oil under *Conditions B* at 80 °C. (36.1 mg, 64% yield)

1H NMR (600 MHz, $CDCl_3$): δ 6.85 (ddd, $J = 15.5, 8.3, 7.2$ Hz, 1H), 5.85 (dt, $J = 15.5, 1.4$ Hz, 1H), 5.60 (br s, 1H), 4.17 (q, $J = 7.2$ Hz, 2H), 3.25 (ddd, $J = 13.1, 7.2, 6.0$ Hz, 2H), 2.57 (ddd, $J = 13.8, 7.2, 1.4$ Hz, 1H), 2.30 – 2.24 (m, 1H), 1.72 (dt, $J = 14.8, 7.4$ Hz, 1H), 1.49 (p, $J = 7.3$ Hz, 2H), 1.46 – 1.39 (m, 1H), 1.37 – 1.25 (m, 4H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.13 (s, 3H), 0.90 (t, $J = 7.1$ Hz, 3H), 0.85 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 175.55, 166.36, 144.96, 124.32, 60.36, 46.13, 41.87, 39.75, 32.52, 29.47, 29.22, 22.45, 20.92, 14.39, 14.10, 8.96.

HRMS (ESI-TOF): m/z calculated for $C_{16}H_{30}NO_3^+$ $[M+H]^+$ 284.2220, found 284.2226.

diethyl (2E,7E)-5-ethyl-5-(pentylcarbamoyl)nona-2,7-dienedioate (4k-di)

4k-di was isolated as a colorless oil along with **4k-mono**. (7.8 mg, 10% yield)

1H NMR (600 MHz, $CDCl_3$): δ 6.81 (dt, $J = 15.5, 7.7$ Hz, 2H), 5.88 (dt, $J = 15.5, 1.3$ Hz, 2H), 5.57 (t, $J = 5.3$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 4H), 3.29 – 3.24 (m, 2H), 2.51 (ddd, $J = 14.2, 7.7, 1.4$ Hz, 2H), 2.42 (ddd, $J = 14.3, 7.7, 1.4$ Hz, 2H), 1.61 – 1.58 (m, 2H), 1.49 (p, $J = 7.4$ Hz, 2H), 1.35 – 1.27 (m, 4H), 1.28 (t, $J = 7.1$ Hz, 6H), 0.90 (t, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 173.89, 166.16, 143.53, 124.96, 60.54, 49.43, 39.93, 37.45, 29.44, 29.23, 27.81, 22.45, 14.39, 14.09, 8.44.

HRMS (ESI-TOF): m/z calculated for $C_{21}H_{36}NO_5^+$ $[M+H]^+$ 382.2588, found 382.2592.

ethyl (E)-5-ethyl-5-(pentylcarbamoyl)hept-2-enoate (4l)

4l was obtained as a colorless oil under *Conditions B* at 80 °C. (28.1 mg, 47% yield)

1H NMR (600 MHz, $CDCl_3$): δ 6.82 (dt, $J = 15.5, 7.8$ Hz, 1H), 5.87 (dt, $J = 15.5, 1.4$ Hz, 1H), 5.59 (t, $J =$

5.4 Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.29 – 3.23 (m, 2H), 2.47 (dd, $J = 7.8, 1.4$ Hz, 2H), 1.61 – 1.57 (m, 2H), 1.53 – 1.46 (m, 4H), 1.37 – 1.27 (m, 4H), 1.28 (t, $J = 7.1$ Hz, 3H), 0.90 (t, $J = 7.1$ Hz, 3H), 0.83 (t, $J = 7.4$ Hz, 6H).

^{13}C NMR (150 MHz, CDCl_3): δ 175.24, 166.42, 144.92, 124.19, 60.40, 49.64, 39.75, 35.96, 29.51, 29.26, 27.85, 22.47, 14.40, 14.12, 8.47.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{17}\text{H}_{32}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 298.2377, found 298.2384.

ethyl (*E*)-8-(1,3-dioxoisindolin-2-yl)-5-methyl-5-(pentylcarbamoyl)oct-2-enoate (4m)

4m was obtained as a colorless oil under *Conditions B* in 0.1 mmol scale. (*mono:di* = 20:1, 31.7 mg, 72% yield)

^1H NMR (600 MHz, CDCl_3): δ 7.83 (dd, $J = 5.4, 3.1$ Hz, 2H), 7.71 (dd, $J = 5.5, 3.0$ Hz, 2H), 6.80 (ddd, $J = 15.5, 8.4, 7.1$ Hz, 1H), 5.83 (dt, $J = 15.5, 1.2$ Hz, 1H), 5.59 (t, $J = 5.5$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.70 – 3.62 (m, 2H), 3.22 (tt, $J = 7.3, 5.6$ Hz, 2H), 2.59 (ddd, $J = 13.8, 7.1, 1.3$ Hz, 1H), 2.23 (ddd, $J = 13.8, 8.4, 1.1$ Hz, 1H), 1.76 (td, $J = 12.5, 4.4$ Hz, 1H), 1.71 – 1.56 (m, 2H), 1.50 – 1.40 (m, 3H), 1.36 – 1.28 (m, 2H), 1.28 – 1.24 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.14 (s, 3H), 0.88 (t, $J = 7.2$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.96, 168.46, 166.22, 144.38, 134.06, 132.20, 124.57, 123.35, 60.37, 45.50, 42.26, 39.82, 38.22, 37.12, 29.39, 29.20, 23.92, 22.43, 21.13, 14.37, 14.08.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{25}\text{H}_{35}\text{N}_2\text{O}_5^+$ $[\text{M}+\text{H}]^+$ 443.2540, found 443.2543.

ethyl (*E*)-3-(2-(morpholine-4-carbonyl)cyclopropyl)acrylate (4n)

4n was obtained as a yellow solid under *Conditions B*. (**4n:3n** = 9:1, 34.2 mg, 64% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.61 (dd, $J = 15.5, 10.3$ Hz, 1H), 5.98 (d, $J = 15.5$ Hz, 1H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.87 – 3.82 (m, 1H), 3.75 – 3.61 (m, 4H), 3.60 – 3.50 (m, 3H), 3.43 (ddd, $J = 12.8, 7.8, 3.0$ Hz, 1H), 2.18 (td, $J = 8.1, 6.2$ Hz, 1H), 2.02 (dtd, $J = 10.2, 8.5, 6.1$ Hz, 1H), 1.64 – 1.59 (m, 1H), 1.31 (td, $J = 8.1, 5.0$ Hz, 1H), 1.27 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 167.75, 165.96, 147.16, 122.10, 67.09, 60.31, 46.04, 42.65, 22.44, 22.09, 14.41, 13.59.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{13}\text{H}_{20}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 254.1387, found 254.1393.

ethyl (*E*)-3-(2-methyl-2-(morpholine-4-carbonyl)cyclopropyl)acrylate (4o)

4o was obtained as a colorless oil under *Conditions B* at 80 °C. (30.3 mg, 57% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.40 (dd, $J = 15.4, 10.6$ Hz, 1H), 5.93 (d, $J = 15.5$ Hz, 1H), 4.21 – 4.14 (m, 2H), 3.92 – 3.82 (m, 1H), 3.76 – 3.65 (m, 2H), 3.61 – 3.44 (m, 4H), 3.41 – 3.29 (m, 1H), 1.78 (ddd, $J = 10.6, 8.3, 5.5$ Hz, 1H), 1.42 (t, $J = 5.4$ Hz, 1H), 1.38 (s, 3H), 1.27 (t, $J = 7.1$ Hz, 3H), 1.12 (dd, $J = 8.3, 5.2$ Hz, 1H).

^{13}C NMR (150 MHz, CDCl_3): δ 170.01, 165.94, 148.78, 121.07, 67.02, 60.43, 46.33, 42.61, 30.13, 29.84, 29.60, 22.22, 21.23, 14.46.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{22}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$ 268.1543, found 268.1545.

ethyl (*E*)-3-(2,2-dimethyl-3-(morpholine-4-carbonyl)cyclopropyl)acrylate (4p)

4p was obtained as a colorless oil under *Conditions B* at 80 °C. (41.4 mg, 74% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.11 (dd, *J* = 15.5, 10.6 Hz, 1H), 5.97 – 5.93 (m, 1H), 4.18 (qd, *J* = 7.1, 1.6 Hz, 2H), 3.67 – 3.59 (m, 6H), 3.58 – 3.47 (m, 2H), 1.87 (d, *J* = 8.6 Hz, 1H), 1.80 (dd, *J* = 10.5, 8.7 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.27 (s, 3H), 1.26 (s, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 167.83, 166.17, 146.44, 122.01, 67.16, 67.05, 60.23, 46.26, 42.08, 34.91, 33.46, 28.18, 27.19, 16.79, 14.49.

HRMS (ESI-TOF): *m/z* calculated for C₁₅H₂₄NO₄⁺ [M+H]⁺ 282.1700, found 282.1703.

ethyl (*E*)-3-(2-(dimethylcarbamoyl)-2-(1,3-dioxoisindolin-2-yl)cyclopropyl)acrylate (4q**)**

4q was obtained as a colorless oil under *Conditions A* in 0.1 mmol scale. (11.7 mg, 32% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.86 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.76 (dd, *J* = 5.5, 3.0 Hz, 2H), 6.53 (dd, *J* = 15.5, 9.8 Hz, 1H), 6.21 (d, *J* = 15.4 Hz, 1H), 4.22 – 4.16 (m, 2H), 3.16 (td, *J* = 9.7, 7.8 Hz, 1H), 2.97 (s, 6H), 2.28 (dd, *J* = 7.6, 6.2 Hz, 1H), 1.42 (dd, *J* = 9.7, 6.1 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 167.72, 165.97, 165.89, 143.81, 134.71, 131.26, 124.54, 123.80, 60.52, 41.92, 37.17, 27.52, 21.28, 14.40.

HRMS (ESI-TOF): *m/z* calculated for C₁₉H₂₁N₂O₅⁺ [M+H]⁺ 357.1445, found 357.1452.

diethyl (*E*)-3-(2-(dimethylcarbamoyl)-2-(1,3-dioxoisindolin-2-yl)cyclopropyl)hexa-2,4-dienedioate (4q'**)**

4q' was isolated as a colorless oil along with **4q**. (7.4 mg, 16% yield)

¹H NMR (600 MHz, CDCl₃): δ 8.66 (d, *J* = 16.2 Hz, 1H), 7.89 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.32 (d, *J* = 16.2 Hz, 1H), 5.85 (s, 1H), 4.33 – 4.27 (m, 2H), 4.24 – 4.15 (m, 2H), 3.47 (t, *J* = 9.2 Hz, 1H), 2.85 (s, 6H), 2.57 (dd, *J* = 8.2, 6.3 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 167.89, 167.01, 165.38, 164.57, 143.94, 140.16, 134.83, 131.21, 125.61, 124.20, 123.97, 60.94, 60.80, 42.88, 37.48, 27.53, 19.51, 14.51, 14.31.

HRMS (ESI-TOF): *m/z* calculated for C₂₄H₂₇N₂O₇⁺ [M+H]⁺ 455.1813, found 455.1818.

ethyl (*E*)-4-(1,3-dimethyl-2-oxopiperidin-3-yl)but-2-enoate (4r**)**

4r was obtained as a colorless oil under *Conditions A*. (*mono:di* = 8:1, 34.9 mg, 69% yield)

Analytical sample of pure **4r** was isolated for characterization.

¹H NMR (600 MHz, CDCl₃): δ 6.88 (ddd, *J* = 15.5, 8.4, 7.1 Hz, 1H), 5.86 (dt, *J* = 15.5, 1.4 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.31 (ddd, *J* = 12.1, 8.9, 5.1 Hz, 1H), 3.27 – 3.23 (m, 1H), 2.92 (s, 3H), 2.62 (ddd, *J* = 13.9, 7.1, 1.5 Hz, 1H), 2.40 (ddd, *J* = 13.9, 8.4, 1.3 Hz, 1H), 1.91 – 1.84 (m, 1H), 1.82 – 1.75 (m, 2H), 1.61 – 1.56 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 174.47, 166.42, 145.25, 124.40, 60.34, 50.48, 42.62, 41.67, 35.33, 33.02, 25.70, 19.38, 14.38.

HRMS (ESI-TOF): *m/z* calculated for C₁₃H₂₂NO₃⁺ [M+H]⁺ 240.1594, found 240.1592.

ethyl (*E*)-4-(1,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)but-2-enoate (4s**)**

4s was obtained as a colorless oil under *Conditions A* in 0.1 mmol scale. (*mono:di* = 11:1, 17.5 mg, 60% yield)

Analytical sample of pure **4s** was isolated for characterization.

^1H NMR (600 MHz, CDCl_3): δ 7.27 (td, $J = 7.8, 1.5$ Hz, 1H), 7.15 – 7.12 (m, 1H), 7.03 (td, $J = 7.4, 1.0$ Hz, 1H), 6.97 (d, $J = 8.1$ Hz, 1H), 6.92 (dt, $J = 15.5, 7.8$ Hz, 1H), 5.82 (dt, $J = 15.5, 1.3$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.37 (s, 3H), 2.86 (d, $J = 15.6$ Hz, 1H), 2.67 (d, $J = 15.6$ Hz, 1H), 2.50 (ddd, $J = 13.9, 7.5, 1.4$ Hz, 1H), 2.39 (ddd, $J = 13.9, 8.1, 1.3$ Hz, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.14 (s, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.76, 166.26, 144.33, 139.89, 128.54, 127.66, 124.93, 124.35, 123.12, 114.31, 60.45, 40.85, 39.76, 37.32, 30.22, 22.43, 14.40.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{17}\text{H}_{22}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 288.1594, found 288.1599.

ethyl (*E*)-4-(1-methyl-2-oxopiperidin-3-yl)but-2-enoate (**4t**)

4t was obtained as a colorless oil under *Conditions A*. (9.1 mg, 20% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.95 – 6.89 (m, 1H), 5.87 (d, $J = 15.6$ Hz, 1H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.36 – 3.23 (m, 2H), 2.94 (s, 3H), 2.88 (dddd, $J = 14.1, 6.8, 3.4, 1.6$ Hz, 1H), 2.46 – 2.35 (m, 2H), 1.95 – 1.86 (m, 2H), 1.82 – 1.72 (m, 1H), 1.55 – 1.48 (m, 1H), 1.29 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 171.24, 166.53, 147.16, 123.37, 60.37, 50.22, 40.90, 35.13, 34.77, 26.68, 21.91, 14.41.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{12}\text{H}_{20}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$ 226.1438, found 226.1443.

diethyl (*2E,4E*)-3-((1-methyl-2-oxopiperidin-3-yl)methyl)hexa-2,4-dienedioate (**4t'-E**)

4t'-E was isolated as a colorless oil along with **4t**. (9.6 mg, 15% yield)

^1H NMR (600 MHz, CDCl_3): δ 7.21 (d, $J = 16.0$ Hz, 1H), 6.49 (d, $J = 15.9$ Hz, 1H), 6.12 (s, 1H), 4.22 (qd, $J = 7.1, 0.8$ Hz, 2H), 4.19 (q, $J = 7.2$ Hz, 2H), 3.42 (dd, $J = 13.0, 11.1$ Hz, 1H), 3.31 (ddd, $J = 12.2, 8.9, 5.0$ Hz, 1H), 3.25 (dd, $J = 6.3, 4.5$ Hz, 1H), 3.23 – 3.21 (m, 1H), 2.94 (s, 3H), 2.49 – 2.42 (m, 1H), 1.98 – 1.88 (m, 1H), 1.79 – 1.73 (m, 1H), 1.71 – 1.64 (m, 1H), 1.63 – 1.56 (m, 1H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 171.48, 166.65, 166.04, 151.87, 145.49, 126.66, 124.27, 60.91, 60.46, 50.25, 41.18, 35.14, 29.28, 26.12, 21.67, 14.35 (two –Me peaks overlap).

HRMS (ESI-TOF): m/z calculated for $\text{C}_{17}\text{H}_{26}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$ 324.1805, found 324.1811.

diethyl (*2Z,4E*)-3-((1-methyl-2-oxopiperidin-3-yl)methyl)hexa-2,4-dienedioate (**4t'-Z**)

4t'-Z was isolated as a colorless oil along with **4t**. (12.3 mg, 19% yield)

^1H NMR (600 MHz, CDCl_3): δ 8.51 (d, $J = 16.3$ Hz, 1H), 6.45 – 6.29 (m, 1H), 5.90 (s, 1H), 4.26 – 4.18 (m, 4H), 3.48 – 3.44 (m, 1H), 3.33 – 3.24 (m, 2H), 2.95 (s, 3H), 2.43 (tt, $J = 10.0, 4.6$ Hz, 1H), 2.13 (dd, $J = 13.9, 10.9$ Hz, 1H), 1.87 (ttdd, $J = 11.8, 8.9, 6.0, 3.7$ Hz, 2H), 1.77 – 1.70 (m, 1H), 1.47 – 1.39 (m, 1H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 171.19, 166.71, 165.32, 149.75, 139.11, 124.93, 124.38, 60.87, 60.66, 50.17, 40.73, 36.81, 35.18, 26.76, 21.81, 14.40, 14.38.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{17}\text{H}_{26}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$ 324.1805, found 324.1804.

ethyl (*E*)-4-(1-methyl-2-oxoazepan-3-yl)but-2-enoate (**4u**)

4u was obtained as a colorless oil under *Conditions B*. (22.0 mg, 46% yield)

¹H NMR (600 MHz, CDCl₃): δ 6.97 (ddd, *J* = 15.6, 8.1, 6.1 Hz, 1H), 5.85 (dt, *J* = 15.6, 1.5 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.62 (dd, *J* = 15.2, 11.4 Hz, 1H), 3.16 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.99 (s, 3H), 2.75 (dtd, *J* = 14.6, 6.3, 1.7 Hz, 1H), 2.68 – 2.63 (m, 1H), 2.26 – 2.20 (m, 1H), 1.94 (dp, *J* = 13.8, 3.3 Hz, 1H), 1.78 (dq, *J* = 13.5, 4.1 Hz, 1H), 1.69 (dt, *J* = 13.9, 3.9 Hz, 1H), 1.58 (qt, *J* = 13.7, 3.9 Hz, 1H), 1.48 – 1.40 (m, 1H), 1.41 – 1.30 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 175.81, 166.72, 147.91, 122.86, 60.29, 50.56, 42.81, 35.96, 35.36, 29.87, 29.31, 27.03, 14.38.

HRMS (ESI-TOF): *m/z* calculated for C₁₃H₂₂NO₃⁺ [M+H]⁺ 240.1594, found 240.1593.

ethyl (*E*)-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)but-2-enoate (**4v**)

4v was obtained as a colorless oil under *Conditions B* in 0.1 mmol scale at 80 °C. (5.0 mg, 23% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.22 (dd, *J* = 6.7, 2.0 Hz, 1H), 7.19 – 7.17 (m, 1H), 7.07 (dt, *J* = 15.6, 6.9 Hz, 1H), 6.12 (t, *J* = 6.8 Hz, 1H), 5.88 (dt, *J* = 15.6, 1.6 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.56 (s, 3H), 3.44 (d, *J* = 6.9 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 166.59, 162.63, 145.73, 137.25, 136.82, 129.71, 123.10, 105.64, 60.39, 38.00, 33.25, 14.41.

HRMS (ESI-TOF): *m/z* calculated for C₁₂H₁₆NO₃⁺ [M+H]⁺ 222.1125, found 222.1128.

2.3.2 Olefin coupling partner scope

Conditions C: A sealed tube with magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 4.5 mg), **L8** (10 mol%, 4.5 mg), AgOAc (0.4 mmol, 66.8 mg), and **2j** (0.2 mmol, 31.4 mg). Then, HFIP (1.0 mL) and corresponding olefin (0.8 mmol) were added. The reaction mixture was stirred at 70 °C for 24 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a celite/silica plug, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography to afford the desired products.

Conditions D: A sealed tube with magnetic stir bar was charged with Pd(OAc)₂ (10 mol%, 4.5 mg), **L8** (10 mol%, 4.5 mg), AgOAc (0.6 mmol, 100.2 mg), and **2j** (0.2 mmol, 31.4 mg). Then, HFIP (2.0 mL) and corresponding olefin (0.8 mmol) were added. The reaction mixture was stirred at 80 °C for 36 hours. Upon completion, the reaction mixture was cooled to room temperature, diluted with EtOAc, filtered through a celite/silica plug, and concentrated *in vacuo*. The crude reaction mixture was purified by flash chromatography to afford the desired product.

phenyl (*E*)-5-methyl-6-morpholino-6-oxohex-2-enoate (**5a**)

5a was obtained as a colorless oil under *Conditions D* in 0.1 mmol scale. (16.4 mg, 54% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.40 – 7.37 (m, 2H), 7.25 – 7.21 (m, 1H), 7.10 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.09 (ddd, *J* = 15.6, 7.7, 6.9 Hz, 1H), 6.07 (dt, *J* = 15.6, 1.5 Hz, 1H), 3.74 – 3.63 (m, 6H), 3.58 – 3.48 (m, 2H), 2.85 (h, *J* = 6.8 Hz, 1H), 2.72 (dtd, *J* = 14.3, 7.1, 1.6 Hz, 1H), 2.39 (dddd, *J* = 14.4, 7.8, 6.5, 1.4 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 173.65, 164.79, 150.79, 148.70, 129.54, 125.90, 122.56, 121.70, 67.16, 66.90, 46.23, 42.36, 36.59, 34.75, 17.89.

HRMS (ESI-TOF): m/z calculated for $C_{17}H_{22}NO_4^+$ $[M+H]^+$ 304.1543, found 304.1545.

(E)-2-methyl-1-morpholino-4-ene-1,6-dione (5b)

5b was obtained as a colorless oil under *Conditions D*. (28.0 mg, 59% yield)

1H NMR (600 MHz, $CDCl_3$): δ 6.77 (ddd, J = 15.8, 7.6, 6.9 Hz, 1H), 6.14 (dt, J = 15.8, 1.4 Hz, 1H), 3.70 – 3.60 (m, 6H), 3.54 – 3.49 (m, 2H), 2.81 (h, J = 6.9 Hz, 1H), 2.63 (dtd, J = 14.3, 7.1, 1.5 Hz, 1H), 2.55 (q, J = 7.3 Hz, 2H), 2.30 (dddd, J = 14.4, 7.7, 6.5, 1.3 Hz, 1H), 1.16 (d, J = 6.9 Hz, 3H), 1.09 (t, J = 7.3 Hz, 3H).
 ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.90, 173.72, 143.80, 131.59, 67.08, 66.85, 46.15, 42.27, 36.50, 34.80, 33.65, 17.76, 8.13.

HRMS (ESI-TOF): m/z calculated for $C_{13}H_{22}NO_3^+$ $[M+H]^+$ 240.1594, found 240.1595.

diethyl (E)-(4-methyl-5-morpholino-5-oxopent-1-en-1-yl)phosphonate (5c)

5c was obtained as a colorless oil under *Conditions D* in 0.1 mmol scale. (22.9 mg, 72% yield)

1H NMR (600 MHz, $CDCl_3$): δ 6.74 – 6.64 (m, 1H), 5.71 (ddt, J = 20.6, 17.1, 1.4 Hz, 1H), 4.10 – 4.02 (m, 4H), 3.74 – 3.57 (m, 6H), 3.55 – 3.46 (m, 2H), 2.79 (h, J = 6.8 Hz, 1H), 2.64 (dtd, J = 14.1, 7.0, 1.8 Hz, 1H), 2.34 – 2.28 (m, 1H), 1.32 (td, J = 7.1, 1.6 Hz, 6H), 1.15 (d, J = 6.9 Hz, 3H).
 ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.69, 150.70 (d, J = 4.6 Hz), 119.46 (d, J = 187.1 Hz), 67.11, 66.89, 61.85 (d, J = 2.4 Hz), 61.81 (d, J = 2.5 Hz), 46.20, 42.31, 38.43 (d, J = 22.5 Hz), 34.60 (d, J = 1.3 Hz), 17.73, 16.55, 16.50.

HRMS (ESI-TOF): m/z calculated for $C_{14}H_{27}NO_5P^+$ $[M+H]^+$ 320.1621, found 320.1623.

(E)-2-methyl-1-morpholino-5-(phenylsulfonyl)pent-4-en-1-one (5d)

5d was obtained as a colorless oil under *Conditions C*. (48.9 mg, 76% yield)

1H NMR (600 MHz, $CDCl_3$): δ 7.88 – 7.85 (m, 2H), 7.64 – 7.60 (m, 1H), 7.57 – 7.51 (m, 2H), 6.91 (ddd, J = 15.0, 7.8, 7.1 Hz, 1H), 6.38 (dt, J = 15.0, 1.4 Hz, 1H), 3.70 – 3.53 (m, 6H), 3.52 – 3.43 (m, 2H), 2.82 (dq, J = 13.8, 6.9 Hz, 1H), 2.67 (dddd, J = 14.6, 7.7, 7.1, 1.5 Hz, 1H), 2.31 (dddd, J = 14.2, 7.7, 6.2, 1.3 Hz, 1H), 1.14 (d, J = 6.9 Hz, 3H).
 ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.10, 144.23, 140.54, 133.46, 132.38, 129.37, 127.64, 66.98, 66.80, 46.13, 42.27, 35.53, 34.59, 17.84.

HRMS (ESI-TOF): m/z calculated for $C_{16}H_{22}NO_4S^+$ $[M+H]^+$ 324.1264, found 324.1271.

(E)-2-methyl-5-(methylsulfonyl)-1-morpholinopent-4-en-1-one (5e)

5e was obtained as a colorless oil under *Conditions D* in 0.1 mmol scale. (17.6 mg, 67% yield)

1H NMR (600 MHz, $CDCl_3$): δ 6.86 (ddd, J = 14.9, 7.7, 7.1 Hz, 1H), 6.42 (dt, J = 15.1, 1.4 Hz, 1H), 3.74 – 3.58 (m, 6H), 3.55 – 3.46 (m, 2H), 2.92 (s, 3H), 2.82 (h, J = 6.9 Hz, 1H), 2.72 (dtd, J = 14.5, 7.3, 1.5 Hz, 1H), 2.36 (dddd, J = 14.3, 7.6, 6.1, 1.3 Hz, 1H), 1.18 (d, J = 6.9 Hz, 3H).
 ^{13}C NMR (150 MHz, $CDCl_3$): δ 173.09, 145.78, 131.48, 67.07, 66.84, 46.19, 42.96, 42.36, 35.50, 34.62, 17.92.

HRMS (ESI-TOF): m/z calculated for $C_{11}H_{20}NO_4S^+$ $[M+H]^+$ 262.1108, found 262.1111.

phenyl (*E*)-4-methyl-5-morpholino-5-oxopent-1-ene-1-sulfonate (5f)

5f was obtained as a colorless oil under *Conditions D*. (39.4 mg, 58% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.40 – 7.36 (m, 2H), 7.32 – 7.28 (m, 1H), 7.24 – 7.21 (m, 2H), 6.78 (ddd, *J* = 14.9, 7.8, 6.8 Hz, 1H), 6.38 (dt, *J* = 15.1, 1.4 Hz, 1H), 3.70 – 3.54 (m, 6H), 3.47 – 3.43 (m, 2H), 2.78 – 2.67 (m, 2H), 2.36 – 2.31 (m, 1H), 1.11 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 172.88, 149.60, 148.33, 129.93, 127.34, 125.88, 122.53, 67.05, 66.81, 46.15, 42.36, 35.65, 34.53, 17.90.

HRMS (ESI-TOF): *m/z* calculated for C₁₆H₂₂NO₅S⁺ [M+H]⁺ 340.1213, found 340.1217.

(*E*)-4-methyl-5-morpholino-5-oxopent-1-ene-1-sulfonyl fluoride (5g)

5g was obtained as a colorless oil under *Conditions D*. (40.7 mg, 77% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.14 – 7.07 (m, 1H), 6.46 – 6.40 (m, 1H), 3.73 – 3.59 (m, 6H), 3.55 – 3.46 (m, 2H), 2.88 – 2.78 (m, 2H), 2.47 – 2.40 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 172.56, 151.66, 123.81 (d, *J* = 26.9 Hz), 67.07, 66.82, 46.19, 42.41, 35.69, 34.56, 18.01.

¹⁹F NMR (376 MHz, CDCl₃): δ 59.57.

HRMS (ESI-TOF): *m/z* calculated for C₁₀H₁₇FO₄S⁺ [M+H]⁺ 266.0857, found 266.0865.

(*E*)-2,5-dimethyl-6-morpholino-6-oxohex-2-enal (5h-endo)

5h-endo was obtained as a colorless oil under *Conditions D*. (15.1 mg, 34% yield)

¹H NMR (600 MHz, CDCl₃): δ 9.40 (s, 1H), 6.45 (ddq, *J* = 8.1, 6.8, 1.3 Hz, 1H), 3.70 – 3.58 (m, 6H), 3.54 – 3.50 (m, 2H), 2.85 (h, *J* = 6.9 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.54 – 2.48 (m, 1H), 1.78 (q, *J* = 0.9 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 195.15 (d, *J* = 2.7 Hz), 173.68, 151.43, 140.82, 67.13, 66.90, 46.21, 42.34, 34.99, 33.03, 17.87, 9.54.

HRMS (ESI-TOF): *m/z* calculated for C₁₂H₂₀NO₃⁺ [M+H]⁺ 226.1438, found 226.1443.

5-methyl-2-methylene-6-morpholino-6-oxohexanal (5h-exo)

5h-exo was isolated along with **5h-endo** as a colorless oil. (12.9 mg, 29% yield)

¹H NMR (600 MHz, CDCl₃): δ 9.54 (s, 1H), 6.29 (q, *J* = 1.2 Hz, 1H), 6.02 (d, *J* = 0.6 Hz, 1H), 3.70 – 3.62 (m, 6H), 3.54 – 3.46 (m, 2H), 2.66 (h, *J* = 6.9 Hz, 1H), 2.30 – 2.16 (m, 2H), 1.88 (dddd, *J* = 13.2, 10.4, 7.5, 5.5 Hz, 1H), 1.54 (ddt, *J* = 13.3, 10.4, 6.0 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 194.73 (d, *J* = 3.2 Hz), 174.66, 149.91, 134.52, 67.18, 66.96, 46.15, 42.25, 35.21, 32.05, 25.92, 17.77.

HRMS (ESI-TOF): *m/z* calculated for C₁₂H₂₀NO₃⁺ [M+H]⁺ 226.1438, found 226.1444.

dimethyl (*E*)-2-(3-methyl-4-morpholino-4-oxobutylidene)succinate (5i)

5i was obtained as a colorless oil under *Conditions D*. (34.6 mg, 58% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.91 (t, $J = 7.7$ Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.68 – 3.58 (m, 6H), 3.58 – 3.45 (m, 2H), 3.40 (d, $J = 3.1$ Hz, 2H), 2.83 (h, $J = 6.9$ Hz, 1H), 2.59 (dt, $J = 14.8, 7.4$ Hz, 1H), 2.30 (ddd, $J = 14.7, 8.0, 6.6$ Hz, 1H), 1.17 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.83, 171.35, 167.28, 143.04, 127.08, 67.12, 66.90, 52.21, 52.17, 46.23, 42.34, 34.93, 33.31, 32.24, 18.01.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{15}\text{H}_{24}\text{NO}_6^+$ $[\text{M}+\text{H}]^+$ 314.1598, found 314.1601.

dimethyl 2-(2-methyl-3-morpholino-3-oxopropyl)maleate (**5j**)

5j was obtained as a colorless oil under *Conditions D* with dimethyl fumarate. (30.9 mg, 52% yield)

^1H NMR (600 MHz, CDCl_3): δ 5.90 (t, $J = 1.2$ Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.70 – 3.61 (m, 5H), 3.59 – 3.53 (m, 2H), 3.47 (dt, $J = 13.2, 5.0$ Hz, 1H), 3.01 – 2.94 (m, 1H), 2.83 (ddd, $J = 13.8, 8.2, 1.2$ Hz, 1H), 2.35 (ddd, $J = 13.8, 5.9, 1.2$ Hz, 1H), 1.15 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 173.26, 169.10, 165.34, 147.18, 122.19, 67.08, 66.88, 52.56, 52.01, 46.15, 42.35, 38.59, 33.67, 17.98.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{22}\text{NO}_6^+$ $[\text{M}+\text{H}]^+$ 300.1442, found 300.1441.

dimethyl 2-(2-methyl-3-morpholino-3-oxopropyl)fumarate (**5k**)

5k was obtained as a colorless oil under *Conditions D* with dimethyl maleate in 0.1 mmol scale. (12.0 mg, 40% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.84 (s, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.70 – 3.61 (m, 6H), 3.58 – 3.51 (m, 2H), 3.10 – 3.00 (m, 2H), 2.96 – 2.92 (m, 1H), 1.08 (d, $J = 6.6$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.06, 167.47, 165.96, 144.94, 128.56, 67.12, 67.05, 52.79, 52.04, 46.18, 42.34, 34.87, 31.52, 16.58.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{14}\text{H}_{22}\text{NO}_6^+$ $[\text{M}+\text{H}]^+$ 300.1442, found 300.1449.

(*E*)-2-methyl-1-morpholino-5-(perfluorophenyl)pent-4-en-1-one (**5l**)

5l was obtained as a colorless oil under *Conditions D* in 0.1 mmol scale. (18.8 mg, 54% yield)

^1H NMR (600 MHz, CDCl_3): δ 6.49 (dt, $J = 16.2, 7.2$ Hz, 1H), 6.32 (dt, $J = 16.3, 1.3$ Hz, 1H), 3.70 – 3.62 (m, 6H), 3.57 – 3.49 (m, 2H), 2.84 (h, $J = 6.8$ Hz, 1H), 2.68 (dt, $J = 14.3, 7.1$ Hz, 1H), 2.36 (dt, $J = 14.1, 6.9$ Hz, 1H), 1.19 (d, $J = 6.9$ Hz, 3H).

^{13}C NMR (150 MHz, CDCl_3): δ 174.07, 144.68 (d, $J = 249.4$ Hz), 139.69 (d, $J = 253.8$ Hz), 138.09 (td, $J = 7.5, 2.4$ Hz), 137.78 (d, $J = 247.4$ Hz), 116.27, 112.23 (td, $J = 14.6, 4.3$ Hz), 67.20, 66.95, 46.24, 42.32, 38.55, 35.31, 17.71.

HRMS (ESI-TOF): m/z calculated for $\text{C}_{16}\text{H}_{17}\text{F}_5\text{NO}_2^+$ $[\text{M}+\text{H}]^+$ 350.1174, found 350.1178.

2.4 Diversification of Olefination Products

3-ethyl 1,1-dimethyl 2-(2-methyl-3-morpholino-3-oxopropyl)propane-1,1,3-tricarboxylate (**6a**)

To a solution of **2j** (0.1 mmol, 25.5 mg) in CH₃CN (1.0 ml) was added dimethyl malonate (0.2 mmol, 23 uL) and Cs₂CO₃ (0.1 mmol, 32.6 mg). The resulting mixture was heated at 70 °C for 32 h. Upon cooling, the reaction mixture was diluted with EtOAc, filtered through Celite, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford **6a** (33.0 mg, 85% yield, dr 1.2:1).

¹H NMR (600 MHz, CDCl₃, 1.2:1 mixture of diastereomers): δ 4.13 (q, *J* = 7.2, Hz, 0.9H), 4.12 (q, *J* = 7.1 Hz, 1.1H), 3.74 (s, 1.65H), 3.74 (s, 1.35H), 3.73 (s, 1.35H), 3.73 (s, 1.65H), 3.71 – 3.60 (m, 7H), 3.58 – 3.53 (m, 1H), 3.52 – 3.46 (m, 1H), 2.80 (hept, *J* = 6.7 Hz, 1H), 2.66 – 2.57 (m, 1.45H), 2.54 (dd, *J* = 16.4, 6.4 Hz, 0.55H), 2.45 (dd, *J* = 16.4, 5.7 Hz, 0.55H), 2.49 – 2.38 (m, 0.45H), 1.90 (ddd, *J* = 13.8, 7.9, 5.9 Hz, 0.45H), 1.82 (ddd, *J* = 14.6, 8.3, 6.6 Hz, 0.55H), 1.51 (ddd, *J* = 14.2, 7.4, 4.9 Hz, 0.55H), 1.49 – 1.44 (m, 0.45H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃, mixture of diastereomers): δ 174.63/174.37, 172.42/172.29, 169.08/169.03, 169.00/168.96, 67.16/67.13, 66.99/66.94, 60.73/60.71, 54.91/54.37, 52.68/52.65, 52.64/52.56, 46.16/46.13, 42.33/42.31, 36.86/36.74, 36.47/36.10, 33.43/33.34, 33.15/33.09, 17.97/17.55, 14.38/14.35.

(Corresponding carbon peaks between diastereomers are grouped)

HRMS (ESI-TOF): *m/z* calculated for C₁₈H₃₀NO₈⁺ [M+H]⁺ 388.1966, found 388.1962.

ethyl 5-methyl-6-morpholino-3-(nitromethyl)-6-oxohexanoate (**6b**)

To a solution of **2j** (0.1 mmol, 25.5 mg) in CH₃NO₂ (200 uL) was added DBU (0.15 mmol, 22 uL) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 3h. The reaction was quenched with water and extracted with EtOAc. The combined organic layers were washed with 0.1 N HCl (aq.), dried with Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford **6b** (16.0 mg, 51% yield, dr 1.2:1).

¹H NMR (600 MHz, CDCl₃, 1.2:1 mixture of diastereomers): δ 4.55 – 4.45 (m, 2H), 4.16 (qd, *J* = 7.1, 1.4 Hz, 1.1H), 4.15 (q, *J* = 7.1 Hz, 0.9H), 3.74 – 3.60 (m, 6H), 3.58 – 3.46 (m, 2H), 2.86 – 2.80 (m, 0.55H), 2.80 – 2.73 (m, 0.45H), 2.61 (tq, *J* = 13.1, 7.0 Hz, 1H), 2.47 (dd, *J* = 16.6, 6.6 Hz, 0.55H), 2.47 (dd, *J* = 6.3, 3.4 Hz, 0.9H), 2.40 (dd, *J* = 16.6, 6.2 Hz, 0.55H), 1.97 – 1.89 (m, 1H), 1.52 – 1.44 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 1.65H), 1.27 (t, *J* = 7.1 Hz, 1.35H), 1.13 (d, *J* = 7.1 Hz, 1.65H), 1.12 (d, *J* = 7.1 Hz, 1.35H).

¹³C NMR (150 MHz, CDCl₃, mixture of diastereomers): δ 173.93/173.81, 171.47/171.46, 78.80/78.69, 67.10, 66.90, 61.03/60.99, 46.15/46.11, 42.39/42.36, 36.63/36.60, 36.06/35.76, 33.25/33.02, 32.55/32.43, 18.31/18.18, 14.33/14.32.

(Corresponding carbon peaks between diastereomers are grouped)

HRMS (ESI-TOF): *m/z* calculated for C₁₄H₂₅N₂O₆⁺ [M+H]⁺ 317.1707, found 317.1712.

ethyl 5-methyl-6-morpholino-6-oxo-3-(phenylthio)hexanoate (**6c**)

To a solution of **2j** (0.1 mmol, 25.5 mg) in THF (1.0 mL) was added thiophenol (0.2 mmol, 20 uL) and K₂CO₃ (0.22 mmol, 30.4 mg). The resulting mixture was stirred at 70 °C for 32 h. The reaction was quenched with 1 N HCl (aq.) and extracted with DCM. The combined organic layers were dried with

Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford **6c** (16.8 mg, 46% yield, dr 1.5:1).

(*Note: The starting material was no longer being consumed further after several hours, indicating that the reaction was under equilibrium.)

¹H NMR (600 MHz, CDCl₃, 1.5:1 mixture of diastereomers): δ 7.45 – 7.42 (m, 0.8H), 7.41 – 7.38 (m, 1.2H), 7.33 – 7.27 (m, 2.2H), 7.27 – 7.23 (m, 0.8H), 4.16 – 4.08 (m, 2H), 3.70 – 3.66 (m, 1.8H), 3.64 – 3.50 (m, 5.4H), 3.48 – 3.40 (m, 1.2H), 3.36 (ddd, *J* = 13.6, 6.6, 3.2 Hz, 0.6H), 3.19 (dq, *J* = 10.6, 7.0, 3.7 Hz, 0.6H), 3.08 (dq, *J* = 8.7, 6.7, 4.6 Hz, 0.4H), 2.64 (dd, *J* = 16.0, 6.3 Hz, 0.4H), 2.57 (d, *J* = 7.0 Hz, 1.2H), 2.52 (dd, *J* = 16.0, 7.9 Hz, 0.4H), 2.21 (ddd, *J* = 13.9, 10.2, 3.7 Hz, 0.6H), 1.87 (ddd, *J* = 14.7, 10.4, 4.5 Hz, 0.4H), 1.78 (ddd, *J* = 14.5, 8.9, 4.1 Hz, 0.4H), 1.50 (ddd, *J* = 14.0, 11.1, 3.6 Hz, 0.6H), 1.24 (t, *J* = 7.1 Hz, 1.2H), 1.24 (t, *J* = 7.1 Hz, 1.8H), 1.15 (d, *J* = 6.8 Hz, 1.2H), 1.11 (d, *J* = 7.0 Hz, 1.8H).

¹³C NMR (150 MHz, CDCl₃, mixture of diastereomers): δ 174.80/74.15, 171.26/171.09, 134.06/133.87, 132.55/132.30, 129.26/129.14, 127.66/127.44, 67.12, 66.95/66.92, 60.87/60.78, 46.19/46.04, 43.86/43.36, 42.31/42.22, 41.76/41.45, 39.52/38.62, 33.12/32.92, 18.71/16.88, 14.34/14.33.

(Corresponding carbon peaks between diastereomers are grouped)

HRMS (ESI-TOF): *m/z* calculated for C₁₉H₂₈NO₄S⁺ [M+H]⁺ 366.1734, found 366.1737.

ethyl 5-methyl-6-morpholino-6-oxohexanoate (**3h**)

To a N₂-filled flask charged with 10% Pd/C (0.07 mmol, 75 mg), a solution of **2j** (0.96 mmol, 245.0 mg) in EtOAc (10 mL) was added. The reaction flask was back-filled for three times with a H₂ balloon, and the reaction mixture was stirred for 24 h at room temperature. Upon completion, the reaction mixture was filtered through Celite and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford **3h** (238.8 mg, 97% yield).

¹H NMR (600 MHz, CDCl₃): δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.69 – 3.61 (m, 6H), 3.56 – 3.48 (m, 2H), 2.66 (h, *J* = 6.8 Hz, 1H), 2.35 – 2.25 (m, 2H), 1.76 – 1.69 (m, 1H), 1.61 (tdq, *J* = 18.4, 13.2, 6.3, 5.7 Hz, 2H), 1.42 (ddd, *J* = 13.7, 11.0, 6.2 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 174.91, 173.58, 67.20, 66.98, 60.44, 46.17, 42.24, 35.21, 34.33, 33.44, 22.97, 17.66, 14.39.

HRMS (ESI-TOF): *m/z* calculated for C₁₃H₂₄NO₄⁺ [M+H]⁺ 258.1700, found 258.1697.

4-methyl-5-morpholino-5-oxopentane-1-sulfonyl fluoride (**6d**)

To a N₂-filled flask charged with 10% Pd/C (0.07 mmol, 75 mg), a solution of **5g** (0.38 mmol, 101.0 mg) in EtOAc (4 mL) was added. The reaction flask was back-filled for three times with a H₂ balloon, and the reaction mixture was stirred for 48 h at room temperature. Upon completion, the reaction mixture was filtered through Celite and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford **6d** (94.3 mg, 93% yield).

¹H NMR (600 MHz, CDCl₃): δ 3.72 – 3.65 (m, 5H), 3.64 – 3.58 (m, 1H), 3.55 – 3.47 (m, 2H), 3.41 (dtd, *J* = 14.5, 7.3, 6.3, 4.1 Hz, 1H), 3.34 (dtd, *J* = 14.7, 8.4, 7.5, 4.3 Hz, 1H), 2.72 – 2.66 (m, 1H), 1.97 – 1.89 (m, 3H), 1.63 – 1.52 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 173.81, 67.15, 66.93, 51.05 (d, *J* = 16.4 Hz), 46.17, 42.34, 35.27, 31.96, 21.81, 18.01.

¹⁹F NMR (376 MHz, CDCl₃): δ 53.47.

HRMS (ESI-TOF): *m/z* calculated for C₁₀H₁₉FNO₄S⁺ [M+H]⁺ 268.1013, found 268.1011.

3-(1,1-dioxido-2-pentyl-1,2-thiazetidin-3-yl)-2-methyl-1-morpholinopropan-1-one (6e)

To a solution of **5g** (0.1 mmol, 26.5 mg) in CH₃CN (1 mL) was added *n*-amylamine (0.4 mmol, 46 μ L). The reaction mixture was stirred for 30 min at room temperature. Upon completion, the reaction mixture was diluted with EtOAc, filtered through Celite, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford **6e** (27.3 mg, 82% yield, dr 1:1).

¹H NMR (600 MHz, CDCl₃, 1:1 mixture of diastereomers): δ 4.02 (ddd, *J* = 21.7, 12.4, 7.8 Hz, 1H), 3.79 (dd, *J* = 12.5, 6.4 Hz, 0.5H), 3.76 – 3.63 (m, 5.5H), 3.63 – 3.58 (m, 0.5H), 3.57 – 3.48 (m, 2.5H), 3.24 – 3.16 (m, 1.5H), 3.15 (dt, *J* = 12.6, 7.3 Hz, 0.5H), 2.85 – 2.79 (m, 0.5H), 2.81 – 2.75 (m, 1H), 2.72 (dt, *J* = 12.5, 7.9 Hz, 0.5H), 2.45 (ddd, *J* = 13.1, 9.5, 3.2 Hz, 0.5H), 2.35 (ddd, *J* = 14.1, 9.2, 6.7 Hz, 0.5H), 1.74 (dt, *J* = 14.1, 4.3 Hz, 0.5H), 1.67 – 1.56 (m, 2.5H), 1.41 – 1.29 (m, 4H), 1.17 (d, *J* = 7.1 Hz, 1.5H), 1.15 (d, *J* = 7.1 Hz, 1.5H), 0.91 (t, *J* = 6.9 Hz, 1.5H), 0.90 (t, *J* = 6.9 Hz, 1.5H).

¹³C NMR (150 MHz, CDCl₃): δ 173.51/173.39, 67.06/66.84, 62.29, 61.81, 47.22/46.68, 46.53/46.35, 46.15/46.09, 42.43/42.33, 37.43/37.11, 32.07/31.62, 29.48/29.39, 28.38/28.36, 22.42/22.34, 18.72/18.68, 14.08/14.07.

(Corresponding carbon peaks between diastereomers are grouped)

HRMS (ESI-TOF): *m/z* calculated for C₁₅H₂₉N₂O₄S⁺ [M+H]⁺ 333.1843, found 333.1847.

diethyl 2,2'-(4,4-dimethyl-5-oxopyrrolidine-1,2-diyl)diacetate (6f)

To a solution of **2u** (0.49 mmol, 132.1 mg) in EtOH (2 mL) was added DBU (0.49 mmol, 73 μ L). The reaction mixture was stirred under reflux for 1 h. Upon cooling, the reaction mixture was concentrated *in vacuo*. The crude residue was diluted with EtOAc and washed with 0.1 N HCl (aq.). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography to afford **6f** (124.6 mg, 89% yield).

¹H NMR (600 MHz, CDCl₃): δ 4.38 (d, *J* = 17.8 Hz, 1H), 4.18 (qd, *J* = 7.2, 0.7 Hz, 2H), 4.15 (ddt, *J* = 10.4, 7.1, 3.3 Hz, 2H), 4.12 – 4.07 (m, 1H), 3.70 (d, *J* = 17.7 Hz, 1H), 2.68 (dd, *J* = 15.7, 5.9 Hz, 1H), 2.42 (dd, *J* = 15.7, 7.0 Hz, 1H), 2.19 (dd, *J* = 12.7, 7.0 Hz, 1H), 1.61 (dd, *J* = 12.7, 8.0 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.22 (s, 3H), 1.19 (s, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 180.76, 170.81, 168.84, 61.46, 61.08, 51.69, 42.60, 41.35, 40.13, 39.50, 25.49, 24.96, 14.31, 14.28.

HRMS (ESI-TOF): *m/z* calculated for C₁₄H₂₄NO₅⁺ [M+H]⁺ 286.1649, found 286.1658.

2.5 SuFEx reaction with 6d

To a solution of **6d** (0.053 mmol, 14.1 mg) and TBSO–Ar (0.055 mmol) in CH₃CN (0.5 ml) was added DBU (10 mol%, 1.6 μ L). The resulting mixture was stirred for 24 h at room temperature. Upon completion, the reaction mixture was diluted with EtOAc, filtered through silica/Celite, and concentrated *in vacuo*. The crude residue was purified by preparatory TLC to afford **7**.

4-fluorophenyl 4-methyl-5-morpholino-5-oxopentane-1-sulfonate (7a, 18.0 mg, 95% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.26 – 7.23 (m, 2H), 7.13 – 7.06 (m, 2H), 3.72 – 3.57 (m, 6H), 3.55 – 3.48 (m, 2H), 3.27 (dt, *J* = 14.9, 7.4 Hz, 1H), 3.21 (dt, *J* = 14.3, 7.4 Hz, 1H), 2.70 (h, *J* = 6.9 Hz, 1H), 1.98 – 1.88 (m, 3H), 1.60 – 1.54 (m, 1H), 1.15 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 174.05, 161.27 (d, *J* = 246.9 Hz), 144.84 (d, *J* = 3.0 Hz), 123.91 (d, *J* = 8.8 Hz), 116.86 (d, *J* = 23.8 Hz), 67.14, 66.94, 50.46, 46.17, 42.32, 35.30, 32.27, 21.86, 18.00.

HRMS (ESI-TOF): *m/z* calculated for C₁₆H₂₃FNO₅S⁺ [M+H]⁺ 360.1275, found 360.1271.

4-methoxyphenyl 4-methyl-5-morpholino-5-oxopentane-1-sulfonate (7b, 20.0 mg, >99% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.18 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.2 Hz, 2H), 3.81 (s, 3H), 3.71 – 3.58 (m, 6H), 3.52 (td, *J* = 11.6, 9.6, 4.7 Hz, 2H), 3.27 – 3.21 (m, 1H), 3.21 – 3.14 (m, 1H), 2.73 – 2.66 (m, 1H), 1.97 – 1.87 (m, 3H), 1.57 (ddt, *J* = 11.8, 6.1, 3.2 Hz, 1H), 1.15 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 174.12, 158.53, 142.59, 123.21, 115.01, 67.14, 66.94, 55.80, 50.03, 46.16, 42.31, 35.25, 32.31, 21.85, 17.95.

HRMS (ESI-TOF): *m/z* calculated for C₁₇H₂₆NO₆S⁺ [M+H]⁺ 372.1475, found 372.1475.

methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(4-(((4-methyl-5-morpholino-5-oxopentyl)sulfonyl)oxy)phenyl)propanoate (7c, 27.7 mg, 97% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.21 – 7.16 (m, 4H), 5.01 (d, *J* = 7.1 Hz, 0.9H), 4.74 (br s, 0.1H), 4.62 – 4.56 (m, 0.9H), 4.39 (br s, 0.1H), 3.72 (s, 3H), 3.70 – 3.58 (m, 6H), 3.55 – 3.48 (m, 2H), 3.26 (dt, *J* = 14.3, 7.2 Hz, 1H), 3.20 (dt, *J* = 14.3, 7.3 Hz, 1H), 3.14 (dd, *J* = 13.7, 5.6 Hz, 1H), 3.04 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.73 – 2.66 (m, 1H), 1.97 – 1.88 (m, 3H), 1.61 – 1.54 (m, 1H), 1.42 (s, 9H), 1.15 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 174.09, 172.13, 155.14, 148.22, 135.61, 131.00, 122.20, 80.27, 67.14, 66.94, 54.42, 52.50, 50.47, 46.17, 42.31, 37.90, 35.26, 32.27, 28.43, 21.85, 17.96.

HRMS (ESI-TOF): *m/z* calculated for C₂₅H₃₈N₂O₉SNa⁺ [M+Na]⁺ 565.2190, found 565.2195.

(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-methyl-5-morpholino-5-oxopentane-1-sulfonate (7d, 24.2 mg, 89% yield)

¹H NMR (600 MHz, CDCl₃): δ 7.31 (d, *J* = 8.4 Hz, 1H), 7.02 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.00 (d, *J* = 1.8 Hz, 1H), 3.71 – 3.64 (m, 5H), 3.63 – 3.58 (m, 1H), 3.56 – 3.47 (m, 2H), 3.26 (dt, *J* = 14.4, 7.0 Hz, 1H), 3.22 – 3.17 (m, 1H), 2.93 (dd, *J* = 8.5, 3.7 Hz, 2H), 2.74 – 2.67 (m, 1H), 2.51 (dd, *J* = 19.1, 8.3 Hz, 1H), 2.42 – 2.37 (m, 1H), 2.29 (td, *J* = 10.8, 3.9 Hz, 1H), 2.19 – 2.11 (m, 1H), 2.09 – 2.01 (m, 2H), 1.99 – 1.87 (m, 4H), 1.67 – 1.40 (m, 7H), 1.15 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 3H).

¹³C NMR (150 MHz, CDCl₃): δ 220.67, 174.13, 147.13, 139.17, 138.95, 127.03, 122.15, 119.16, 67.14, 66.94, 50.54, 50.33, 48.03, 46.16, 44.26, 42.30, 38.02, 35.96, 35.26, 32.31, 31.65, 29.53, 26.34, 25.86, 21.85, 21.71, 17.96, 13.95.

HRMS (ESI-TOF): *m/z* calculated for C₂₈H₃₉NO₆SNa⁺ [M+Na]⁺ 540.2390, found 540.2396.

2.6 X-Ray Crystallographic Data of 4d

Experimental Summary

The single crystal X-ray diffraction studies were carried out on a Bruker X8 APEX II CCD diffractometer equipped with Mo K_α radiation (λ = 0.71073). Crystals of the subject compound were used as received (grown by vapor diffusion of Pentane into DCM solution). A 0.220 x 0.060 x 0.060 mm colorless crystal was mounted on a Cryoloop with Paratone oil.

Data were collected in a nitrogen gas stream at 100(2) K using ϕ and ω scans. Crystal-to-detector distance was 50 mm using exposure time 10s with a scan width of 0.7°. Data collection was 99.9% complete to 25.242° in θ . A total of 25887 reflections were collected covering the indices,

-13<=*h*<=13, -15<=*k*<=15, -18<=*l*<=18. 20365 reflections were found to be symmetry independent,

with a R_{int} of 0.0287. Indexing and unit cell refinement indicated a Primitive **Orthorhombic** lattice. The space group was found to be ***P2₁***. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.

Notes: Proposed structure in agreement with model derived from X-ray data.

Two molecules in asymmetric unit.

TWIN : Final refinement using HKLF 5 file format

Table 1. Crystal data and structure refinement for **4d** (CCDC 1909341).

Report date	2019-04-09	
Identification code	yu108	
Empirical formula	C ₂₂ H ₃₃ N O ₄	
Molecular formula	C ₂₂ H ₃₃ N O ₄	
Formula weight	375.49	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.0347(12) Å	α = 96.454(2)°.
	b = 12.8460(14) Å	β = 90.210(2)°.
	c = 14.7618(16) Å	γ = 106.811(2)°.
Volume	1988.9(4) Å ³	
Z	4	
Density (calculated)	1.254 Mg/m ³	
Absorption coefficient	0.085 mm ⁻¹	
F(000)	816	
Crystal size	0.22 x 0.06 x 0.06 mm ³	
Crystal color, habit	colorless plank	
Theta range for data collection	1.389 to 25.731°.	
Index ranges	-13 ≤ h ≤ 13, -15 ≤ k ≤ 15, -18 ≤ l ≤ 16	
Reflections collected	25887	
Independent reflections	10546 [R(int) = 0.0287]	
Completeness to theta = 25.242°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.924 and 0.823	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	10546 / 0 / 490	
Goodness-of-fit on F ²	1.025	
Final R indices [I > 2σ(I)]	R1 = 0.0429, wR2 = 0.0929	
R indices (all data)	R1 = 0.0643, wR2 = 0.1028	
Largest diff. peak and hole	0.299 and -0.245 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Yu108. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4848(1)	6226(1)	1246(1)	32(1)
O(2)	6272(1)	3161(1)	2000(1)	18(1)
O(3)	5042(1)	1204(1)	-1476(1)	19(1)
O(4)	3081(1)	1333(1)	-1198(1)	19(1)
N(1)	4992(1)	4152(1)	1637(1)	16(1)
C(1)	6028(2)	6081(2)	1508(2)	30(1)
C(2)	6057(2)	4918(2)	1239(1)	22(1)
C(3)	3845(2)	5515(2)	1685(2)	30(1)
C(4)	3772(2)	4322(2)	1435(1)	20(1)
C(5)	5195(2)	3263(1)	1962(1)	13(1)
C(6)	4080(2)	2381(1)	2283(1)	13(1)
C(7)	4029(2)	1294(1)	1694(1)	16(1)
C(8)	3711(2)	1337(1)	715(1)	15(1)
C(9)	4467(2)	1258(1)	32(1)	16(1)
C(10)	4095(2)	1280(1)	-924(1)	15(1)
C(11)	4824(2)	1239(2)	-2439(1)	20(1)
C(12)	6098(2)	1460(2)	-2864(1)	23(1)
C(13)	4162(2)	2346(1)	3332(1)	13(1)
C(14)	2927(2)	1545(1)	3617(1)	14(1)
C(15)	2917(2)	1532(2)	4654(1)	15(1)
C(16)	3012(2)	2681(2)	5118(1)	19(1)
C(17)	4245(2)	3487(2)	4860(1)	19(1)
C(18)	4252(2)	3497(1)	3820(1)	16(1)
C(19)	5379(2)	3134(2)	5169(1)	23(1)
C(20)	5284(2)	1982(2)	4706(1)	19(1)
C(21)	5287(2)	1989(2)	3665(1)	16(1)
C(22)	4048(2)	1177(2)	4965(1)	18(1)
O(1')	9855(1)	6187(1)	4008(1)	32(1)
O(2')	11264(1)	3130(1)	2624(1)	18(1)
O(3')	10051(1)	1258(1)	5712(1)	18(1)
O(4')	8087(1)	1390(1)	5462(1)	19(1)

N(1')	9995(1)	4117(1)	3193(1)	16(1)
C(1')	8842(2)	5476(2)	3432(2)	29(1)
C(2')	8776(2)	4283(2)	3441(1)	21(1)
C(3')	11032(2)	6043(2)	3710(2)	30(1)
C(4')	11065(2)	4879(2)	3740(1)	22(1)
C(5')	10189(2)	3233(1)	2684(1)	14(1)
C(6')	9071(2)	2362(1)	2182(1)	13(1)
C(7')	9006(2)	1267(2)	2549(1)	16(1)
C(8')	8672(2)	1304(1)	3536(1)	16(1)
C(9')	9449(2)	1284(2)	4215(1)	16(1)
C(10')	9092(2)	1323(1)	5178(1)	15(1)
C(11')	9858(2)	1297(2)	6683(1)	19(1)
C(12')	11147(2)	1567(2)	7146(1)	20(1)
C(13')	9164(2)	2334(1)	1126(1)	13(1)
C(14')	10274(2)	1948(2)	736(1)	18(1)
C(15')	10285(2)	1947(2)	-305(1)	22(1)
C(16')	10413(2)	3107(2)	-544(1)	28(1)
C(17')	9294(2)	3484(2)	-177(1)	24(1)
C(18')	9289(2)	3487(2)	864(1)	19(1)
C(19')	8055(2)	2697(2)	-606(1)	21(1)
C(20')	7924(2)	1544(1)	-369(1)	15(1)
C(21')	7921(2)	1551(2)	671(1)	15(1)
C(22')	9037(2)	1162(2)	-736(1)	19(1)

Table 3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for Yu108.

O(1)-C(1)	1.426(3)	C(13)-C(14)	1.544(2)
O(1)-C(3)	1.426(2)	C(13)-C(18)	1.546(2)
O(2)-C(5)	1.234(2)	C(13)-C(21)	1.539(3)
O(3)-C(10)	1.346(2)	C(14)-H(14A)	0.9900
O(3)-C(11)	1.450(2)	C(14)-H(14B)	0.9900
O(4)-C(10)	1.211(2)	C(14)-C(15)	1.533(2)
N(1)-C(2)	1.470(2)	C(15)-H(15)	1.0000
N(1)-C(4)	1.460(2)	C(15)-C(16)	1.530(2)
N(1)-C(5)	1.361(2)	C(15)-C(22)	1.532(3)
C(1)-H(1A)	0.9900	C(16)-H(16A)	0.9900
C(1)-H(1B)	0.9900	C(16)-H(16B)	0.9900
C(1)-C(2)	1.511(3)	C(16)-C(17)	1.532(3)
C(2)-H(2A)	0.9900	C(17)-H(17)	1.0000
C(2)-H(2B)	0.9900	C(17)-C(18)	1.537(3)
C(3)-H(3A)	0.9900	C(17)-C(19)	1.534(3)
C(3)-H(3B)	0.9900	C(18)-H(18A)	0.9900
C(3)-C(4)	1.514(3)	C(18)-H(18B)	0.9900
C(4)-H(4A)	0.9900	C(19)-H(19A)	0.9900
C(4)-H(4B)	0.9900	C(19)-H(19B)	0.9900
C(5)-C(6)	1.530(2)	C(19)-C(20)	1.533(3)
C(6)-H(6)	1.0000	C(20)-H(20)	1.0000
C(6)-C(7)	1.546(2)	C(20)-C(21)	1.538(2)
C(6)-C(13)	1.557(2)	C(20)-C(22)	1.534(3)
C(7)-H(7A)	0.9900	C(21)-H(21A)	0.9900
C(7)-H(7B)	0.9900	C(21)-H(21B)	0.9900
C(7)-C(8)	1.498(3)	C(22)-H(22A)	0.9900
C(8)-H(8)	0.9500	C(22)-H(22B)	0.9900
C(8)-C(9)	1.324(2)	O(1')-C(1')	1.426(2)
C(9)-H(9)	0.9500	O(1')-C(3')	1.428(2)
C(9)-C(10)	1.475(3)	O(2')-C(5')	1.234(2)
C(11)-H(11A)	0.9900	O(3')-C(10')	1.345(2)
C(11)-H(11B)	0.9900	O(3')-C(11')	1.447(2)
C(11)-C(12)	1.505(3)	O(4')-C(10')	1.210(2)
C(12)-H(12A)	0.9800	N(1')-C(2')	1.463(2)
C(12)-H(12B)	0.9800	N(1')-C(4')	1.467(2)
C(12)-H(12C)	0.9800	N(1')-C(5')	1.360(2)

C(1')-H(1'A)	0.9900	C(16')-C(17')	1.531(3)
C(1')-H(1'B)	0.9900	C(17')-H(17')	1.0000
C(1')-C(2')	1.514(3)	C(17')-C(18')	1.536(3)
C(2')-H(2'A)	0.9900	C(17')-C(19')	1.531(3)
C(2')-H(2'B)	0.9900	C(18')-H(18C)	0.9900
C(3')-H(3'A)	0.9900	C(18')-H(18D)	0.9900
C(3')-H(3'B)	0.9900	C(19')-H(19C)	0.9900
C(3')-C(4')	1.512(3)	C(19')-H(19D)	0.9900
C(4')-H(4'A)	0.9900	C(19')-C(20')	1.527(3)
C(4')-H(4'B)	0.9900	C(20')-H(20')	1.0000
C(5')-C(6')	1.527(2)	C(20')-C(21')	1.534(2)
C(6')-H(6')	1.0000	C(20')-C(22')	1.530(2)
C(6')-C(7')	1.547(3)	C(21')-H(21C)	0.9900
C(6')-C(13')	1.559(2)	C(21')-H(21D)	0.9900
C(7')-H(7'A)	0.9900	C(22')-H(22C)	0.9900
C(7')-H(7'B)	0.9900	C(22')-H(22D)	0.9900
C(7')-C(8')	1.503(2)		
C(8')-H(8')	0.9500	C(3)-O(1)-C(1)	109.66(16)
C(8')-C(9')	1.323(3)	C(10)-O(3)-C(11)	116.63(14)
C(9')-H(9')	0.9500	C(4)-N(1)-C(2)	112.96(15)
C(9')-C(10')	1.475(2)	C(5)-N(1)-C(2)	118.28(16)
C(11')-H(11C)	0.9900	C(5)-N(1)-C(4)	127.15(15)
C(11')-H(11D)	0.9900	O(1)-C(1)-H(1A)	109.3
C(11')-C(12')	1.505(3)	O(1)-C(1)-H(1B)	109.3
C(12')-H(12D)	0.9800	O(1)-C(1)-C(2)	111.55(17)
C(12')-H(12E)	0.9800	H(1A)-C(1)-H(1B)	108.0
C(12')-H(12F)	0.9800	C(2)-C(1)-H(1A)	109.3
C(13')-C(14')	1.540(2)	C(2)-C(1)-H(1B)	109.3
C(13')-C(18')	1.541(3)	N(1)-C(2)-C(1)	109.84(16)
C(13')-C(21')	1.545(2)	N(1)-C(2)-H(2A)	109.7
C(14')-H(14C)	0.9900	N(1)-C(2)-H(2B)	109.7
C(14')-H(14D)	0.9900	C(1)-C(2)-H(2A)	109.7
C(14')-C(15')	1.537(3)	C(1)-C(2)-H(2B)	109.7
C(15')-H(15')	1.0000	H(2A)-C(2)-H(2B)	108.2
C(15')-C(16')	1.536(3)	O(1)-C(3)-H(3A)	109.2
C(15')-C(22')	1.537(3)	O(1)-C(3)-H(3B)	109.2
C(16')-H(16C)	0.9900	O(1)-C(3)-C(4)	112.03(16)
C(16')-H(16D)	0.9900	H(3A)-C(3)-H(3B)	107.9

C(4)-C(3)-H(3A)	109.2	C(11)-C(12)-H(12A)	109.5
C(4)-C(3)-H(3B)	109.2	C(11)-C(12)-H(12B)	109.5
N(1)-C(4)-C(3)	109.95(16)	C(11)-C(12)-H(12C)	109.5
N(1)-C(4)-H(4A)	109.7	H(12A)-C(12)-H(12B)	109.5
N(1)-C(4)-H(4B)	109.7	H(12A)-C(12)-H(12C)	109.5
C(3)-C(4)-H(4A)	109.7	H(12B)-C(12)-H(12C)	109.5
C(3)-C(4)-H(4B)	109.7	C(14)-C(13)-C(6)	108.73(14)
H(4A)-C(4)-H(4B)	108.2	C(14)-C(13)-C(18)	107.67(13)
O(2)-C(5)-N(1)	120.59(16)	C(18)-C(13)-C(6)	108.54(14)
O(2)-C(5)-C(6)	119.56(17)	C(21)-C(13)-C(6)	114.60(14)
N(1)-C(5)-C(6)	119.84(16)	C(21)-C(13)-C(14)	108.25(15)
C(5)-C(6)-H(6)	107.6	C(21)-C(13)-C(18)	108.84(14)
C(5)-C(6)-C(7)	106.79(14)	C(13)-C(14)-H(14A)	109.4
C(5)-C(6)-C(13)	112.05(14)	C(13)-C(14)-H(14B)	109.4
C(7)-C(6)-H(6)	107.6	H(14A)-C(14)-H(14B)	108.0
C(7)-C(6)-C(13)	114.92(15)	C(15)-C(14)-C(13)	111.07(15)
C(13)-C(6)-H(6)	107.6	C(15)-C(14)-H(14A)	109.4
C(6)-C(7)-H(7A)	109.4	C(15)-C(14)-H(14B)	109.4
C(6)-C(7)-H(7B)	109.4	C(14)-C(15)-H(15)	109.5
H(7A)-C(7)-H(7B)	108.0	C(16)-C(15)-C(14)	109.30(15)
C(8)-C(7)-C(6)	111.18(15)	C(16)-C(15)-H(15)	109.5
C(8)-C(7)-H(7A)	109.4	C(16)-C(15)-C(22)	109.73(15)
C(8)-C(7)-H(7B)	109.4	C(22)-C(15)-C(14)	109.24(14)
C(7)-C(8)-H(8)	117.7	C(22)-C(15)-H(15)	109.5
C(9)-C(8)-C(7)	124.61(18)	C(15)-C(16)-H(16A)	109.8
C(9)-C(8)-H(8)	117.7	C(15)-C(16)-H(16B)	109.8
C(8)-C(9)-H(9)	118.8	C(15)-C(16)-C(17)	109.38(14)
C(8)-C(9)-C(10)	122.48(18)	H(16A)-C(16)-H(16B)	108.2
C(10)-C(9)-H(9)	118.8	C(17)-C(16)-H(16A)	109.8
O(3)-C(10)-C(9)	110.33(16)	C(17)-C(16)-H(16B)	109.8
O(4)-C(10)-O(3)	123.54(17)	C(16)-C(17)-H(17)	109.5
O(4)-C(10)-C(9)	126.12(16)	C(16)-C(17)-C(18)	109.58(15)
O(3)-C(11)-H(11A)	110.4	C(16)-C(17)-C(19)	109.62(17)
O(3)-C(11)-H(11B)	110.4	C(18)-C(17)-H(17)	109.5
O(3)-C(11)-C(12)	106.59(15)	C(19)-C(17)-H(17)	109.5
H(11A)-C(11)-H(11B)	108.6	C(19)-C(17)-C(18)	109.15(15)
C(12)-C(11)-H(11A)	110.4	C(13)-C(18)-H(18A)	109.5
C(12)-C(11)-H(11B)	110.4	C(13)-C(18)-H(18B)	109.5

C(17)-C(18)-C(13)	110.56(15)	C(2')-C(1')-H(1'B)	109.2
C(17)-C(18)-H(18A)	109.5	N(1')-C(2')-C(1')	109.84(16)
C(17)-C(18)-H(18B)	109.5	N(1')-C(2')-H(2'A)	109.7
H(18A)-C(18)-H(18B)	108.1	N(1')-C(2')-H(2'B)	109.7
C(17)-C(19)-H(19A)	109.7	C(1')-C(2')-H(2'A)	109.7
C(17)-C(19)-H(19B)	109.7	C(1')-C(2')-H(2'B)	109.7
H(19A)-C(19)-H(19B)	108.2	H(2'A)-C(2')-H(2'B)	108.2
C(20)-C(19)-C(17)	109.73(15)	O(1')-C(3')-H(3'A)	109.3
C(20)-C(19)-H(19A)	109.7	O(1')-C(3')-H(3'B)	109.3
C(20)-C(19)-H(19B)	109.7	O(1')-C(3')-C(4')	111.60(17)
C(19)-C(20)-H(20)	109.6	H(3'A)-C(3')-H(3'B)	108.0
C(19)-C(20)-C(21)	109.40(16)	C(4')-C(3')-H(3'A)	109.3
C(19)-C(20)-C(22)	109.36(15)	C(4')-C(3')-H(3'B)	109.3
C(21)-C(20)-H(20)	109.6	N(1')-C(4')-C(3')	109.87(17)
C(22)-C(20)-H(20)	109.6	N(1')-C(4')-H(4'A)	109.7
C(22)-C(20)-C(21)	109.39(15)	N(1')-C(4')-H(4'B)	109.7
C(13)-C(21)-H(21A)	109.5	C(3')-C(4')-H(4'A)	109.7
C(13)-C(21)-H(21B)	109.5	C(3')-C(4')-H(4'B)	109.7
C(20)-C(21)-C(13)	110.54(14)	H(4'A)-C(4')-H(4'B)	108.2
C(20)-C(21)-H(21A)	109.5	O(2')-C(5')-N(1')	120.46(16)
C(20)-C(21)-H(21B)	109.5	O(2')-C(5')-C(6')	119.63(15)
H(21A)-C(21)-H(21B)	108.1	N(1')-C(5')-C(6')	119.92(16)
C(15)-C(22)-C(20)	109.58(16)	C(5')-C(6')-H(6')	107.7
C(15)-C(22)-H(22A)	109.8	C(5')-C(6')-C(7')	106.94(15)
C(15)-C(22)-H(22B)	109.8	C(5')-C(6')-C(13')	111.83(14)
C(20)-C(22)-H(22A)	109.8	C(7')-C(6')-H(6')	107.7
C(20)-C(22)-H(22B)	109.8	C(7')-C(6')-C(13')	114.65(14)
H(22A)-C(22)-H(22B)	108.2	C(13')-C(6')-H(6')	107.7
C(1')-O(1')-C(3')	109.66(14)	C(6')-C(7')-H(7'A)	109.5
C(10')-O(3')-C(11')	117.02(14)	C(6')-C(7')-H(7'B)	109.5
C(2')-N(1')-C(4')	112.82(14)	H(7'A)-C(7')-H(7'B)	108.0
C(5')-N(1')-C(2')	127.07(15)	C(8')-C(7')-C(6')	110.94(14)
C(5')-N(1')-C(4')	118.45(15)	C(8')-C(7')-H(7'A)	109.5
O(1')-C(1')-H(1'A)	109.2	C(8')-C(7')-H(7'B)	109.5
O(1')-C(1')-H(1'B)	109.2	C(7')-C(8')-H(8')	117.8
O(1')-C(1')-C(2')	112.09(18)	C(9')-C(8')-C(7')	124.42(18)
H(1'A)-C(1')-H(1'B)	107.9	C(9')-C(8')-H(8')	117.8
C(2')-C(1')-H(1'A)	109.2	C(8')-C(9')-H(9')	118.4

C(8')-C(9')-C(10')	123.10(18)	C(17')-C(16')-C(15')	109.74(15)
C(10')-C(9')-H(9')	118.4	C(17')-C(16')-H(16C)	109.7
O(3')-C(10')-C(9')	110.03(15)	C(17')-C(16')-H(16D)	109.7
O(4')-C(10')-O(3')	123.80(17)	C(16')-C(17')-H(17')	109.6
O(4')-C(10')-C(9')	126.17(18)	C(16')-C(17')-C(18')	109.04(17)
O(3')-C(11')-H(11C)	110.4	C(18')-C(17')-H(17')	109.6
O(3')-C(11')-H(11D)	110.4	C(19')-C(17')-C(16')	109.49(15)
O(3')-C(11')-C(12')	106.81(14)	C(19')-C(17')-H(17')	109.6
H(11C)-C(11')-H(11D)	108.6	C(19')-C(17')-C(18')	109.58(16)
C(12')-C(11')-H(11C)	110.4	C(13')-C(18')-H(18C)	109.5
C(12')-C(11')-H(11D)	110.4	C(13')-C(18')-H(18D)	109.5
C(11')-C(12')-H(12D)	109.5	C(17')-C(18')-C(13')	110.85(15)
C(11')-C(12')-H(12E)	109.5	C(17')-C(18')-H(18C)	109.5
C(11')-C(12')-H(12F)	109.5	C(17')-C(18')-H(18D)	109.5
H(12D)-C(12')-H(12E)	109.5	H(18C)-C(18')-H(18D)	108.1
H(12D)-C(12')-H(12F)	109.5	C(17')-C(19')-H(19C)	109.8
H(12E)-C(12')-H(12F)	109.5	C(17')-C(19')-H(19D)	109.8
C(14')-C(13')-C(6')	114.26(15)	H(19C)-C(19')-H(19D)	108.2
C(14')-C(13')-C(18')	108.95(15)	C(20')-C(19')-C(17')	109.51(16)
C(14')-C(13')-C(21')	108.07(14)	C(20')-C(19')-H(19C)	109.8
C(18')-C(13')-C(6')	108.91(14)	C(20')-C(19')-H(19D)	109.8
C(18')-C(13')-C(21')	107.74(15)	C(19')-C(20')-H(20')	109.5
C(21')-C(13')-C(6')	108.71(14)	C(19')-C(20')-C(21')	109.48(14)
C(13')-C(14')-H(14C)	109.6	C(19')-C(20')-C(22')	109.82(15)
C(13')-C(14')-H(14D)	109.6	C(21')-C(20')-H(20')	109.5
H(14C)-C(14')-H(14D)	108.1	C(22')-C(20')-H(20')	109.5
C(15')-C(14')-C(13')	110.38(16)	C(22')-C(20')-C(21')	109.07(15)
C(15')-C(14')-H(14C)	109.6	C(13')-C(21')-H(21C)	109.4
C(15')-C(14')-H(14D)	109.6	C(13')-C(21')-H(21D)	109.4
C(14')-C(15')-H(15')	109.6	C(20')-C(21')-C(13')	111.05(14)
C(14')-C(15')-C(22')	109.38(15)	C(20')-C(21')-H(21C)	109.4
C(16')-C(15')-C(14')	109.66(15)	C(20')-C(21')-H(21D)	109.4
C(16')-C(15')-H(15')	109.6	H(21C)-C(21')-H(21D)	108.0
C(16')-C(15')-C(22')	109.11(17)	C(15')-C(22')-H(22C)	109.8
C(22')-C(15')-H(15')	109.6	C(15')-C(22')-H(22D)	109.8
C(15')-C(16')-H(16C)	109.7	C(20')-C(22')-C(15')	109.49(14)
C(15')-C(16')-H(16D)	109.7	C(20')-C(22')-H(22C)	109.8
H(16C)-C(16')-H(16D)	108.2	C(20')-C(22')-H(22D)	109.8

H(22C)-C(22')-H(22D)

108.2

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Yu108. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	25(1)	20(1)	55(1)	18(1)	2(1)	6(1)
O(2)	13(1)	21(1)	22(1)	7(1)	4(1)	7(1)
O(3)	20(1)	28(1)	12(1)	4(1)	2(1)	12(1)
O(4)	16(1)	23(1)	19(1)	5(1)	0(1)	6(1)
N(1)	14(1)	15(1)	20(1)	8(1)	3(1)	4(1)
C(1)	22(1)	20(1)	46(1)	12(1)	-1(1)	2(1)
C(2)	18(1)	19(1)	29(1)	12(1)	5(1)	3(1)
C(3)	25(1)	23(1)	46(1)	13(1)	4(1)	11(1)
C(4)	16(1)	20(1)	25(1)	10(1)	0(1)	6(1)
C(5)	14(1)	14(1)	9(1)	0(1)	-1(1)	4(1)
C(6)	12(1)	14(1)	14(1)	4(1)	1(1)	4(1)
C(7)	19(1)	13(1)	15(1)	3(1)	2(1)	3(1)
C(8)	15(1)	11(1)	18(1)	2(1)	-2(1)	1(1)
C(9)	14(1)	16(1)	16(1)	2(1)	-2(1)	3(1)
C(10)	15(1)	10(1)	18(1)	3(1)	1(1)	2(1)
C(11)	24(1)	24(1)	12(1)	3(1)	-1(1)	9(1)
C(12)	25(1)	30(1)	16(1)	5(1)	1(1)	10(1)
C(13)	12(1)	13(1)	13(1)	3(1)	2(1)	3(1)
C(14)	12(1)	14(1)	15(1)	3(1)	1(1)	3(1)
C(15)	14(1)	15(1)	16(1)	5(1)	3(1)	2(1)
C(16)	23(1)	20(1)	15(1)	4(1)	6(1)	5(1)
C(17)	25(1)	13(1)	16(1)	-2(1)	4(1)	1(1)
C(18)	16(1)	13(1)	17(1)	2(1)	2(1)	2(1)
C(19)	20(1)	29(1)	12(1)	3(1)	-1(1)	-4(1)
C(20)	14(1)	27(1)	16(1)	7(1)	-1(1)	5(1)
C(21)	13(1)	17(1)	18(1)	4(1)	1(1)	4(1)
C(22)	21(1)	22(1)	13(1)	6(1)	1(1)	6(1)
O(1')	25(1)	20(1)	48(1)	-12(1)	-1(1)	7(1)
O(2')	13(1)	21(1)	19(1)	-1(1)	-2(1)	7(1)
O(3')	18(1)	26(1)	11(1)	4(1)	0(1)	8(1)
O(4')	15(1)	24(1)	20(1)	4(1)	3(1)	6(1)
N(1')	13(1)	15(1)	20(1)	-3(1)	-2(1)	4(1)
C(1')	22(1)	24(1)	43(1)	-5(1)	-2(1)	11(1)

C(2')	16(1)	21(1)	25(1)	-4(1)	1(1)	5(1)
C(3')	24(1)	20(1)	41(1)	-5(1)	0(1)	4(1)
C(4')	17(1)	20(1)	25(1)	-6(1)	-5(1)	4(1)
C(5')	16(1)	16(1)	11(1)	5(1)	1(1)	5(1)
C(6')	13(1)	13(1)	15(1)	1(1)	0(1)	4(1)
C(7')	19(1)	14(1)	14(1)	2(1)	-2(1)	3(1)
C(8')	15(1)	14(1)	19(1)	4(1)	3(1)	3(1)
C(9')	14(1)	16(1)	17(1)	3(1)	1(1)	4(1)
C(10')	16(1)	9(1)	19(1)	2(1)	-2(1)	2(1)
C(11')	22(1)	24(1)	10(1)	4(1)	3(1)	5(1)
C(12')	21(1)	25(1)	14(1)	4(1)	0(1)	5(1)
C(13')	13(1)	13(1)	14(1)	1(1)	-1(1)	4(1)
C(14')	13(1)	24(1)	18(1)	1(1)	-1(1)	6(1)
C(15')	16(1)	35(1)	15(1)	-1(1)	2(1)	7(1)
C(16')	25(1)	35(1)	14(1)	4(1)	1(1)	-10(1)
C(17')	36(1)	13(1)	18(1)	6(1)	-4(1)	-2(1)
C(18')	24(1)	14(1)	16(1)	2(1)	-4(1)	2(1)
C(19')	29(1)	19(1)	15(1)	4(1)	-4(1)	7(1)
C(20')	14(1)	14(1)	14(1)	2(1)	-2(1)	2(1)
C(21')	13(1)	15(1)	16(1)	2(1)	0(1)	5(1)
C(22')	22(1)	22(1)	14(1)	0(1)	1(1)	8(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for Yu108.

	x	y	z	U(eq)
H(1A)	6170	6263	2177	36
H(1B)	6722	6589	1213	36
H(2A)	5999	4754	566	26
H(2B)	6867	4832	1459	26
H(3A)	3030	5630	1509	36
H(3B)	3976	5702	2355	36
H(4A)	3108	3859	1787	24
H(4B)	3543	4107	778	24
H(6)	3288	2569	2141	16
H(7A)	4861	1151	1741	19
H(7B)	3384	685	1928	19
H(8)	2909	1427	573	18
H(9)	5280	1185	164	19
H(11A)	4437	1828	-2528	23
H(11B)	4248	532	-2720	23
H(12A)	5987	1416	-3528	34
H(12B)	6507	914	-2717	34
H(12C)	6629	2193	-2624	34
H(14A)	2192	1766	3413	16
H(14B)	2846	798	3315	16
H(15)	2112	1004	4820	18
H(16A)	3000	2678	5789	23
H(16B)	2278	2908	4922	23
H(17)	4309	4238	5164	23
H(18A)	5041	4029	3654	19

H(18B)	3526	3732	3616	19
H(19A)	6177	3657	5006	27
H(19B)	5391	3137	5840	27
H(20)	6022	1752	4912	23
H(21A)	5232	1246	3365	19
H(21B)	6091	2498	3496	19
H(22A)	3982	430	4670	22
H(22B)	4045	1162	5634	22
H(1'A)	8958	5664	2800	35
H(1'B)	8031	5588	3637	35
H(2'A)	8564	4065	4057	26
H(2'B)	8102	3820	3002	26
H(3'A)	11732	6549	4104	36
H(3'B)	11162	6230	3078	36
H(4'A)	11871	4795	3498	26
H(4'B)	11017	4710	4379	26
H(6')	8282	2556	2355	16
H(7'A)	8362	663	2186	19
H(7'B)	9836	1120	2483	19
H(8')	7848	1343	3682	20
H(9')	10274	1243	4076	19
H(11C)	9316	581	6832	23
H(11D)	9441	1865	6885	23
H(12D)	11053	1487	7797	30
H(12E)	11626	2323	7074	30
H(12F)	11602	1067	6870	30
H(14C)	11083	2442	1014	22
H(14D)	10192	1201	888	22
H(15')	11014	1702	-549	27
H(16C)	11217	3618	-272	34

H(16D)	10430	3109	-1214	34
H(17')	9381	4240	-332	29
H(18C)	8573	3738	1107	23
H(18D)	10084	4006	1142	23
H(19C)	7329	2941	-374	25
H(19D)	8053	2696	-1277	25
H(20')	7112	1031	-646	18
H(21C)	7821	801	824	18
H(21D)	7193	1785	912	18
H(22C)	9044	1149	-1408	23
H(22D)	8946	411	-588	23

3. References

1) Nakao, Y.; Idei, H.; Kanyiva, K. S.; Hiyama, T. Direct Alkenylation and Alkylation of Pyridone Derivatives by Ni/AlMe₃ Catalysis. *J. Am. Chem. Soc.* **2009**, *131*, 15996.

4. ^1H and ^{13}C NMR Spectra

N-isopropyl-*N*-methylisobutyramide (**1c**) (1:0.84 mixture of rotamers)

***N*-(2-methoxyethyl)-*N*-methylisobutyramide (1e) (1:0.65 mixture of rotamers)**

1-(azetidin-1-yl)-2-methylpropan-1-one (1f)

1-(azepan-1-yl)-2-methylpropan-1-one (1i)

2-methyl-1-(4-(2,2,2-trifluoroacetyl)piperazin-1-yl)propan-1-one (1k)

ethyl *N*-isobutyryl-*N*-methylglycinate (1m) (1:0.24 mixture of rotamers)

ethyl 1-isobutyrylpiperidine-4-carboxylate (1n)

N-octylisobutyramide (1p)

methyl pivaloylglycinate (1u)

***N*-(2,6-dimethylphenyl)-*N*-methylisobutyramide (1w)**

2-methyl-1-morpholinopentan-1-one (3b)

2-cyclohexyl-1-morpholinopropan-1-one (3c)

2-(adamantan-1-yl)-1-morpholinopropan-1-one (3d)

2-(5-methyl-6-morpholino-6-oxohexyl)isoindoline-1,3-dione (3e)

6-(benzyloxy)-2-methyl-1-morpholinohexan-1-one (3f)

6-fluoro-2-methyl-1-morpholinohexan-1-one (3g)

3-(2,6-difluorophenyl)-2-methyl-1-morpholinopropan-1-one (3i)

2-(2,6-difluorophenyl)-1-morpholinopropan-1-one (3j)

2,2-dimethyl-N-pentylbutanamide (3k)

2-ethyl-2-methyl-N-pentylbutanamide (3l)

5-(1,3-dioxoisindolin-2-yl)-2,2-dimethyl-N-pentylpentanamide (3m)

(1-methylcyclopropyl)(morpholino)methanone (3o)

(2,2-dimethylcyclopropyl)(morpholino)methanone (3p)

1-(1,3-dioxoisindolin-2-yl)-*N,N*-dimethylcyclopropane-1-carboxamide (3q)

1,3,3-trimethylpiperidin-2-one (3r)

1,3-dimethylpiperidin-2-one (3t)

5-methylpyridine-3-sulfonic acid (L4)

5-methoxypyridine-3-sulfonic acid (L5)

5-fluoropyridine-3-sulfonic acid (L6)

5-chloropyridine-3-sulfonic acid (L7)

5-(trifluoromethyl)pyridine-3-sulfonic acid (L8)

6-(trifluoromethyl)pyridine-3-sulfonic acid (L9)

4-(trifluoromethyl)pyridine-3-sulfonic acid (L10)

ethyl (*E*)-6-(dimethylamino)-5-methyl-6-oxohex-2-enoate (2a)

ethyl (*E*)-6-(isopropyl(methyl)amino)-5-methyl-6-oxohex-2-enoate (2b)

ethyl (*E*)-6-(isopropyl(methyl)amino)-5-methyl-6-oxohex-2-enoate (2c)

ethyl (*E*)-6-(diisopropylamino)-5-methyl-6-oxohex-2-enoate (2d)

ethyl (*E*)-6-((2-methoxyethyl)(methyl)amino)-5-methyl-6-oxohex-2-enoate (2e)

ethyl (*E*)-6-(azetidin-1-yl)-5-methyl-6-oxohex-2-enoate (2f)

ethyl (*E*)-5-methyl-6-oxo-6-(pyrrolidin-1-yl)hex-2-enoate (2g)

ethyl (*E*)-5-methyl-6-oxo-6-(piperidin-1-yl)hex-2-enoate (2h)

ethyl (*E*)-6-(azepan-1-yl)-5-methyl-6-oxohex-2-enoate (2i)

ethyl (*E*)-5-methyl-6-morpholino-6-oxohex-2-enoate (2j)

ethyl (*E*)-5-methyl-6-oxo-6-(4-(2,2,2-trifluoroacetyl)piperazin-1-yl)hex-2-enoate (2k)

ethyl ((*E*)-6-ethoxy-2-methyl-6-oxohex-4-enoyl)-*L*-prolinate (2l)

ethyl (*E*)-6-((2-ethoxy-2-oxoethyl)(methyl)amino)-5-methyl-6-oxohex-2-enoate (2m)

ethyl (*E*)-1-(6-ethoxy-2-methyl-6-oxohex-4-enyl)piperidine-4-carboxylate (2n)

ethyl (*E*)-6-(methoxy(methyl)amino)-5-methyl-6-oxohex-2-enoate (2o)

ethyl (*E*)-5-methyl-6-(octylamino)-6-oxohex-2-enoate (2p)

diethyl (2*E*,4*E*)-3-(2-methyl-3-(octylamino)-3-oxopropyl)hexa-2,4-dienedioate (2*p'*-*E*)

diethyl (2Z,4E)-3-(2-methyl-3-(octylamino)-3-oxopropyl)hexa-2,4-dienedioate (2p'-Z)

ethyl (*E*)-5,5-dimethyl-6-(methylamino)-6-oxohex-2-enoate (2q)

diethyl (2*E*,7*E*)-5-methyl-5-(methylcarbamoyl)nona-2,7-dienedioate (2q-di)

ethyl (*E*)-6-(isopropylamino)-5,5-dimethyl-6-oxohex-2-enoate (2r)

ethyl (*E*)-6-(tert-butylamino)-5,5-dimethyl-6-oxohex-2-enoate (2s)

diethyl (2*E*,7*E*)-5-(tert-butylcarbamoyl)-5-methylnona-2,7-dienedioate (2*s-di*)

ethyl (*E*)-6-((2-methoxyethyl)amino)-5,5-dimethyl-6-oxohex-2-enoate (2t)

ethyl (*E*)-6-((2-methoxy-2-oxoethyl)amino)-5,5-dimethyl-6-oxohex-2-enoate (2u)

ethyl (*E*)-3-(2-(*N*-methylisobutyramido)phenyl)acrylate (2v')

ethyl (*E*)-6-((2,6-dimethylphenyl)(methyl)amino)-5-methyl-6-oxohex-2-enoate (2w)

ethyl (*E*)-5-(morpholine-4-carbonyl)hept-2-enoate (4a)

ethyl (*E*)-5-(morpholine-4-carbonyl)oct-2-enoate (4b)

ethyl (*E*)-5-cyclohexyl-6-morpholino-6-oxohex-2-enoate (4c)

ethyl (*E*)-5-(adamantan-1-yl)-6-morpholino-6-oxohex-2-enoate (4d)

ethyl (*E*)-9-(1,3-dioxisoindolin-2-yl)-5-(morpholine-4-carbonyl)non-2-enoate (4e)

ethyl (*E*)-9-(benzyloxy)-5-(morpholine-4-carbonyl)non-2-enoate (4f)

ethyl (*E*)-9-fluoro-5-(morpholine-4-carbonyl)non-2-enoate (4g)

diethyl (*E*)-5-(morpholine-4-carbonyl)non-2-enedioate (4h)

ethyl (*E*)-5-(2,6-difluorobenzyl)-6-morpholino-6-oxohex-2-enoate (4i)

(E)-2-(2,6-difluorophenyl)-1-morpholino-5-(phenylsulfonyl)pent-4-en-1-one (4j)

ethyl (*E*)-5-methyl-5-(pentylcarbamoyl)hept-2-enoate (4k-mono)

diethyl (2*E*,7*E*)-5-ethyl-5-(pentylcarbamoyl)nona-2,7-dienedioate (4k-di)

ethyl (*E*)-5-ethyl-5-(pentylcarbamoyl)hept-2-enoate (4l)

ethyl (*E*)-8-(1,3-dioxoisindolin-2-yl)-5-methyl-5-(pentylcarbamoyl)oct-2-enoate (4m)

ethyl (*E*)-3-(2-(morpholine-4-carbonyl)cyclopropyl)acrylate (4n)

ethyl (*E*)-3-(2-methyl-2-(morpholine-4-carbonyl)cyclopropyl)acrylate (4o)

ethyl (*E*)-3-(2,2-dimethyl-3-(morpholine-4-carbonyl)cyclopropyl)acrylate (4p)

ethyl (*E*)-3-(2-(dimethylcarbamoyl)-2-(1,3-dioxisoindolin-2-yl)cyclopropyl)acrylate (4q)

diethyl (4E)-3-(2-(dimethylcarbamoyl)-2-(1,3-dioxisoindolin-2-yl)cyclopropyl)hexa-2,4-dienedioate (4q')

ethyl (*E*)-4-(1,3-dimethyl-2-oxopiperidin-3-yl)but-2-enoate (4r)

ethyl (*E*)-4-(1,3-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl)but-2-enoate (**4s**)

ethyl (*E*)-4-(1-methyl-2-oxopiperidin-3-yl)but-2-enoate (4t)

diethyl (2*E*,4*E*)-3-((1-methyl-2-oxopiperidin-3-yl)methyl)hexa-2,4-dienedioate (4*t'*-*E*)

diethyl (2Z,4E)-3-((1-methyl-2-oxopiperidin-3-yl)methyl)hexa-2,4-dienedioate (4t'-Z)

ethyl (*E*)-4-(1-methyl-2-oxazepan-3-yl)but-2-enoate (4u)

ethyl (*E*)-4-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)but-2-enoate (4v)

phenyl (*E*)-5-methyl-6-morpholino-6-oxohex-2-enoate (5a)

(E)-2-methyl-1-morpholinoct-4-ene-1,6-dione (5b)

diethyl (*E*)-(4-methyl-5-morpholino-5-oxopent-1-en-1-yl)phosphonate (5c)

(E)-2-methyl-1-morpholino-5-(phenylsulfonyl)pent-4-en-1-one (5d)

(E)-2-methyl-5-(methylsulfonyl)-1-morpholinopent-4-en-1-one (5e)

phenyl (*E*)-4-methyl-5-morpholino-5-oxopent-1-ene-1-sulfonate (5f)

(E)-4-methyl-5-morpholino-5-oxopent-1-ene-1-sulfonyl fluoride (5g)

(E)-2,5-dimethyl-6-morpholino-6-oxohex-2-enal (5h-endo)

5-methyl-2-methylene-6-morpholino-6-oxohexanal (5h-*exo*)

dimethyl (*E*)-2-(3-methyl-4-morpholino-4-oxobutylidene)succinate (**5i**)

dimethyl 2-(2-methyl-3-morpholino-3-oxopropyl)maleate (5j)

dimethyl 2-(2-methyl-3-morpholino-3-oxopropyl)fumarate (5k)

(*E*)-2-methyl-1-morpholino-5-(perfluorophenyl)pent-4-en-1-one (5l)

Chemical structure of ethyl 2-methyl-2-((4-morpholin-4-yl)-2-oxoethyl)-3-oxopropionate is shown. The structure features a morpholine ring attached to a 2-oxoethyl group, which is further substituted with a methyl group and an ethyl ester group.

The ^1H NMR spectrum (CDCl₃) displays the following peaks and integrations:

- 7.2 ppm (s, 1H, integration 1.00)
- 5.4 ppm (s, 1H, integration 1.00)
- 4.1 ppm (d, 2H, integration 2.00)
- 3.5 ppm (m, 2H, integration 7.00)
- 2.4 ppm (m, 2H, integration 1.00)
- 1.8 ppm (m, 2H, integration 1.43)
- 1.5 ppm (d, 3H, integration 0.55)
- 1.2 ppm (t, 3H, integration 0.95)

ethyl 5-methyl-6-morpholino-3-(nitromethyl)-6-oxohexanoate (6b)

ethyl 5-methyl-6-morpholino-6-oxo-3-(phenylthio)hexanoate (6c)

ethyl 5-methyl-6-morpholino-6-oxohexanoate (3h)

4-methyl-5-morpholino-5-oxopentane-1-sulfonyl fluoride (6d)

3-(1,1-dioxido-2-pentyl-1,2-thiazetidin-3-yl)-2-methyl-1-morpholinopropan-1-one (6e)

diethyl 2,2'-(4,4-dimethyl-5-oxopyrrolidine-1,2-diyl)diacetate (6f)

4-fluorophenyl 4-methyl-5-morpholino-5-oxopentane-1-sulfonate (7a)

4-methoxyphenyl 4-methyl-5-morpholino-5-oxopentane-1-sulfonate (7b)

methyl (2S)-2-((tert-butoxycarbonyl)amino)-3-(4-(((4-methyl-5-morpholino-5-oxopentyl)sulfonyl)oxy)phenyl)propanoate (7c)

(8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl 4-methyl-5-morpholino-5-oxopentane-1-sulfonate (7d)

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