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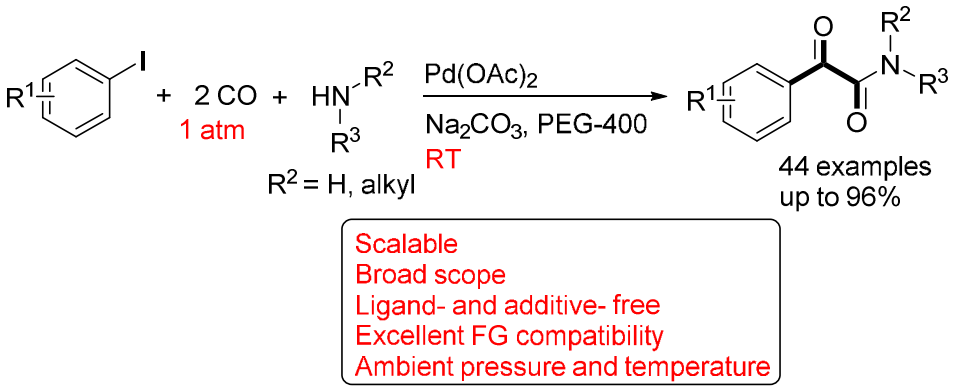
Ligand-Free Pd-Catalyzed Double Carbonylation of Aryl Iodides with Amines to α-Ketoamides under Atmospheric Pressure of Carbon Monoxide and at Room Temperature

Hongyan Du,[†] Qing Ruan,[†] Minghao Qi,[†] and Wei Han[*,†,‡]

[†]Jiangsu Key Laboratory of Biofunctional Materials, Key Laboratory of Applied Photochemistry, School of Chemistry and Materials Science, Nanjing Normal University, Wenyuan Road NO.1, Nanjing 210023, China

[‡]Jiangsu Collaborative Innovation Center of Biomedical Functional Materials, Nanjing 210023, China

[*]Corresponding author's email address: hanwei@njnu.edu.cn; whhanwei@gmail.com



ABSTRACT: A general Pd-catalyzed double carbonylation of aryl iodides with secondary or primary amines to produce α-ketoamides at atmospheric CO pressure has been developed. This transformation proceeds successfully even at room temperature and in the absence of any ligand and additive. A wide range of aryl iodides and amines can be coupled to the desired α-ketoamides in high yields with excellent chemoselectivities. Importantly, the current methodology has been demonstrated to be applied in the synthesis of bioactive molecules and chiral α-ketoamides.

α-Ketoamides are important fragments in biologically active molecules, synthetic

drugs, and pharmaceutically interesting compounds.[1] Moreover, they frequently serve as useful building blocks for an array of functional group transformations.[2] As a consequence, establishing a general, practical, and efficient approach to α-ketoamides having polyfunctional groups, is of significance.

Palladium-catalyzed double carbonylation of aryl halides with amines is well known as a direct and efficient protocol for the synthesis of α-ketoamides.[3,4] Generally, this transformation undergoes efficiently at a high pressure of carbon monoxide(≥10 bar) and/or an elevated temperature (≥80 ^{o}C).[4,5] Moreover, the palladium catalysts are required to be modified by cost of ligands (often with phosphine ligands).[2d,3b,5,6] These drawbacks have blocked the transfer of the advances to widespread applications, particularly in complex organic syntheses.

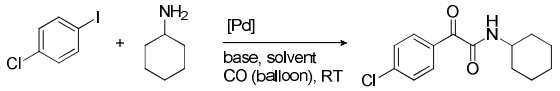
In contrast, double carbonylation for α-ketoamides under ambient pressure of CO gas has been scarcely reported, likely due to inertness of CO and poor chemoselectivity.[6,7] However, in these cases, the necessity to employ extra additives, such as a copper co-catalyst, a nucleophilic amine base, an air-sensitive phosphine, or Au-supported material. Most disadvantageous of all, aryl halide bearing a deactivating group such as halo, cyano, trifluoro, or an ester group in the aryl ring leads to a large amount of monocarbonylated side products.[6,7] To the best of our knowledge, there is no report of general, ligand- and additive-free double carbonylations of aryl iodides under ambient conditions thus far.

Recently, we demonstrated in situ generation of palladium nanoparticles in

polyethylene glycol (PEG) without any additional ligand and additive. And this catalytic system achieved outstanding performance in carbonylative Suzuki coupling[8] and hydrocarboxylation[9] of aryl halides with CO gas under ambient conditions. In continuation of our research to employ this in situ generation of palladium nanoparticles system for other carbonylation, herein we disclose a ligand-free palladium-catalyzed double carbonylation for the synthesis of α-ketoamides by direct three-component coupling of various aryl iodides (including electron-deprived aryl iodides) and amines with CO gas at ambient pressure and temperature. The generality of this protocol is demonstrated here by synthesizing a typical set of α-ketoamide compounds (44 examples) with high yields and excellent selectivities.

We commenced our studies by investigating the reaction between 1-chloro-4-iodobenzene **1a** and cyclohexylamine **2a** (1.0 equiv) employing $Pd(OAc)_2$ as a catalyst and Na_2CO_3 as a base in PEG-400 at room temperature and atmospheric pressure of CO gas (Table 1). The reaction resulted in double carbonylated product **3aa** in 74% yield with excellent selectivity (>95%) (entry 1). A screening of palladium sources revealed that $Pd(OAc)_2$ is much better than $PdCl_2$ (entry 2), and Pd/C is complete ineffective for the reaction (entry 3). Replacing PEG-400 with glycol, NHD-250 (polyethylene glycol dimethyl ether with an average molecular weight of 250 Da) , DMF, toluene, or 1,4-dioxane as the solvent resulted in poorer results (entries 4–8). Evaluation of several bases indicated that Na_2CO_3 was the optimal choice, albeit Na_3PO_4, and NEt_3 were also efficient bases for this

Table 1. Optimization of reaction conditions [a]



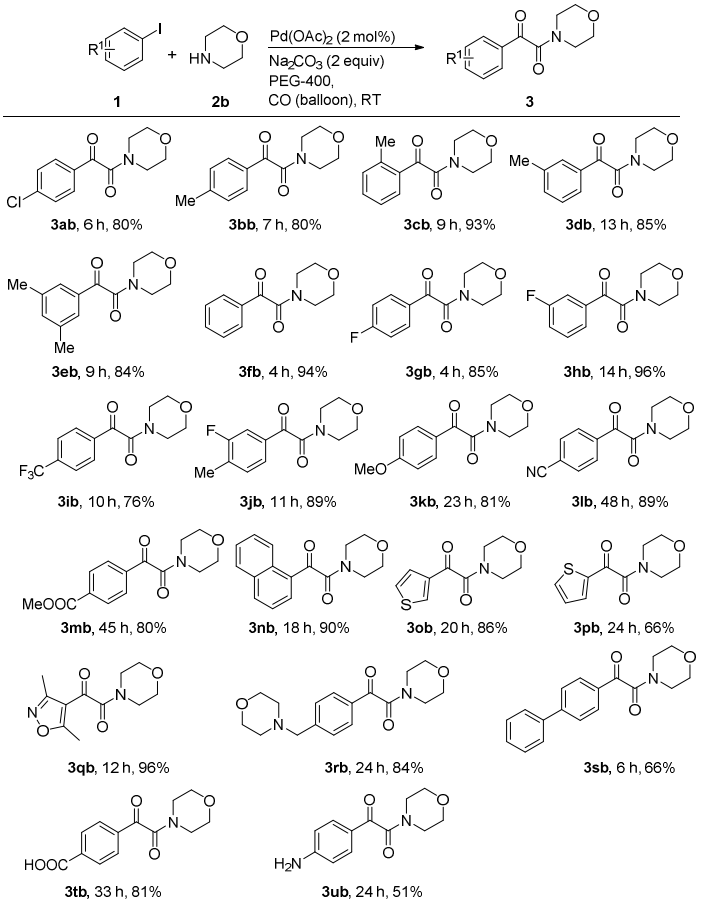
1a **2a** **3aa**

Entry	[Pd]	Base	Solvent	Yield of **3aa**/%
1	$Pd(OAc)_2$	Na_2CO_3	PEG-400	74
2	$PdCl_2$	Na_2CO_3	PEG-400	61
3	Pd/C	Na_2CO_3	PEG-400	-
4	$Pd(OAc)_2$	Na_2CO_3	Ethylene glycol	<5
5	$Pd(OAc)_2$	Na_2CO_3	NHD-250	40
6	$Pd(OAc)_2$	Na_2CO_3	DMF	7
7	$Pd(OAc)_2$	Na_2CO_3	Toluene	10
8	$Pd(OAc)_2$	Na_2CO_3	Dioxane	25
9	$Pd(OAc)_2$	$NaHCO_3$	PEG-400	59
10	$Pd(OAc)_2$	Na_3PO_4	PEG-400	72
11	$Pd(OAc)_2$	NaF	PEG-400	67
12	$Pd(OAc)_2$	DBU	PEG-400	<5
13	$Pd(OAc)_2$	Et_3N	PEG-400	73
14	$Pd(OAc)_2$	DIEA	PEG-400	52
15	$Pd(OAc)_2$	Bu_4NOH	PEG-400	Trace
16[b]	$Pd(OAc)_2$	Na_2CO_3	PEG-400	Trace
17	$Pd(OAc)_2$	DABCO	PEG-400	76
18[c]	Nano-Pd	Na_2CO_3	PEG-400	69

[a] *Reaction conditions* (unless otherwise stated): **1a** (0.5 mmol), **2a** (0.5 mmol), [Pd] (0.01 mmol), CO (balloon), base (1.0 mmol), solvent (2.0 mL), RT, and 6 h. [b] With addtion of Hg (1.0 mmol). [b] Pre-prepared nanopalladium.

transformation (entries 10 and 13); other bases, like $NaHCO_3$, NaF, and DIEA (*N,N*-Diisopropylethylamine), gave rise to lower yields (entries 9, 11, and 14), but DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) and Bu_4NOH were totally ineffective (entries 12 and 15). DABCO (1,4-Diazabicyclo[2.2.2]octane) known as a base

promoting double carbonylation[6b] was also effective and gave a comparable result to Na_2CO_3 (entry 17). Considering that DABCO is more expensive and can readily contaminate products, we chose Na_2CO_3 as the base. TEM (transmission electron microscopy) analyzed the reaction mixture and indicated palladium nanoparticles were formed (see ESI, Figure S1). And the size distribution of Pd nanoparticles was



Reaction conditions(unless otherwise stated): **1** (0.5 mmol), **2b** (0.5 mmol), CO (balloon), Na_2CO_3 (1.0 mmol), $Pd(OAc)_2$ (2 mol %), PEG-400 (2.0 mL), and RT.

Scheme 1. Pd-catalyzed double carbonylation of 2b with various aryl iodides

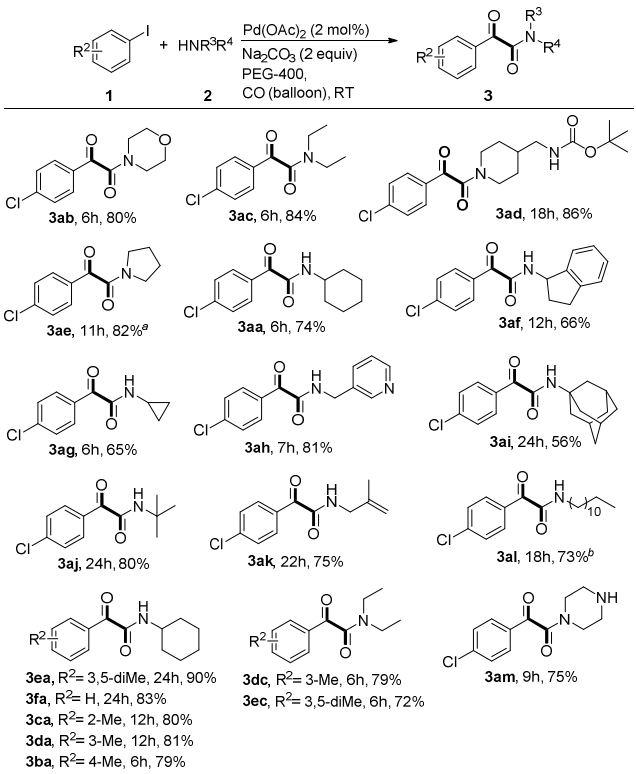
about 3.0 ± 0.6 nm. An enlarged TEM image indicated that the shape of nanoparticles was spherical [see ESI, Figure S1 (**b**)]. Furthermore, under the optimal conditions, Hg

(100 equiv to Pd) was added to the system and led to complelely inhibit the reaction (entry 16), suggesting that the real active catalyst is likely to be nanopalladium. Moreover, recently, we reported $Pd(OAc)_2$ readily formed palladium nanoparticles in PEG.[10] According to our previous study, pre-prepared palladium nanoparticles had an average size of 3.6 nm,[10b] bigger than that of the present *in situ* generated palladium nanoparticles (3.0 nm), and exhibited lower activity (entry 18).

Having the optimized conditions in hand, a series of aryl iodides **1** as coupling partners to morpholine **2b** were explored (Scheme 1). This protocol was efficient with diverse aryl iodides bearing electron-donating substitutes, such as methyl and methoxy, to give the corresponding coupling products in high yields. To our delight, the *ortho*-substituted substrate **1c** wasn't affected by the steric hindrance of methyl group and provided **3cb** in excellent yield. A free amino group (**1u**) proved to be compatible in the system, albeit a moderate conversion was obtained. The inductive electron-deprived chloro, fluoro, and trifluoro groups were also well tolerated, and the desired products **3ab** and **3gb–3jb** were generated in high yields. Electron-poor cyano- and ester-substituted iodides that readily directed the reactions towards monocarbonylation[6,7] reacted slowly but still afforded the desired double carbonylated products in 89% (**3lb**) and 80% (**3mb**) yields, along with yielding 8% and 6% of amides, respectively. Gratifyingly, a reactive and useful carboxyl group (**1t**) was intact under the present conditions, which had never been demonstrated in double carbonylation process. The new protocol was also applicable to 1-iodonaphthalene

(**1n**) and 4-iodo-1,1'-biphenyl (**1s**) as illustrated by the synthesis of **3nb** (90%) and **3sb** (66%), the latter accompanied by the formation of amide side product in 15% yield. In addition, heterocyclic iodides such as 3-iodothiophene (**1o**), 2-iodothiophene (**1p**), and 4-iodo-3,5-dimethylisoxazole (**1q**) were readily converted to the corresponding α-ketoamides in 86%, 66%, and 96% yields. It should also be noted that the reaction between 1-(bromomethyl)-4-iodobenzene (**1r**) and morpholine **2b** (2.0 equiv) under ambient conditions underwent one-pot amination/double carbonylation to yield **3rb** in 84%. However, bromobenzene and chlorobenzene derivatives when tested failed to give desired products even at 100 ^{o}C. And 1,4-diiodobenzene as aryl iodide resulted in a complex mixture.

Encouraged by the above results, various amines **2** were subjected to the double carbonylation conditions to further evaluate the scope of the transformation (Scheme 2). Generally, cyclic or acyclic primary and secondary amines (**2a**–**2l**) furnished the corresponding α-ketoamides in satisfactory yields with excellent selectivities (>95%). For instance, *N*-Boc-protected amine **2d** worked well to give the double carbonylated product **3ad** in 86% yield. Amines bearing a strain ring (**2g**), a pyridyl group (**2h**), and an allylic substituent (**2k**) were also applied succesfully to the double carbonylation protocol, affording the corresponding products in 65%, 81%, and 75% yields, respectively. Additionally, the double carbonylation of bulky amantadine (**3i**) or *t*-butyl amine (**3j**) with 1-chloro-4-iodobenzene (**1a**) proceeded smoothly. To our



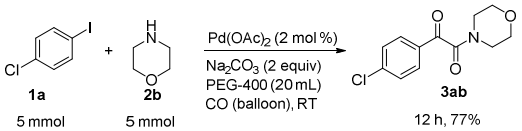
Reaction conditions (unless otherwise stated): **1** (0.5 mmol), **2** (0.5 mmol), CO (balloon), Na_2CO_3 (1.0 mmol), $Pd(OAc)_2$ (2 mol %), PEG-400 (2.0 mL), and RT. [a] Withou the use of a base. [b]50 °C.

Scheme 2. Pd-catalyzed double carbonylation of aryl iodides with various amines

delight, a long-alkyl-chain lauryl amine (**2l**) gave access to the desired α-ketoamide in 73% at an elevated temperature (50 °C). When piperazine (**2m**) bearing two identical reactive sites was subjected to the nomal conditions, mono α-ketoamide **3am**, a versatile intermediate for further synthetic manipulations, was obtained in 75% yield with high selectivity.

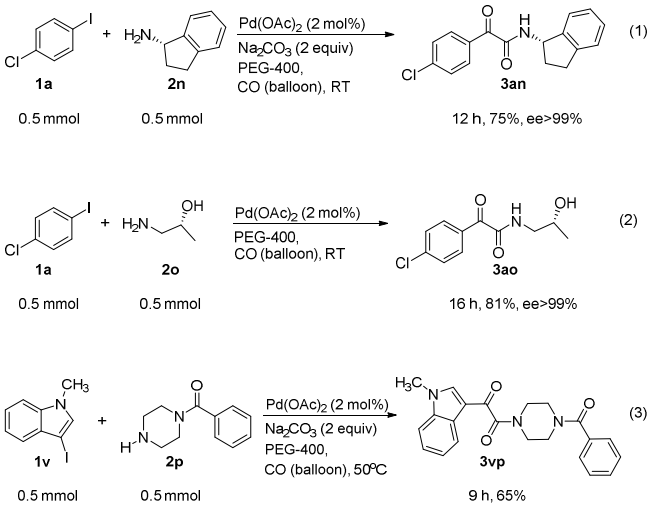
To demonstrate the transformation's practical utility, a gram-scale reaction was performed by using **1a** and **2b** under ambient conditions, which provided the α-ketoamide **3ab** in 77% yield (Scheme 3). Moreover, the same reaction was used to

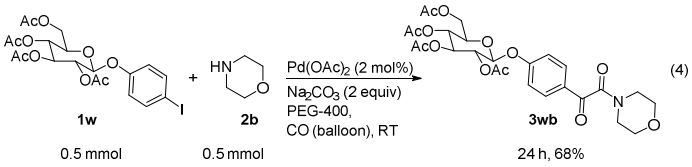
test the recycling uses of the catalytic system. Gratifyingly, the in situ nanocatalyst can be recycled up to five times to provide the corresponding product in 80, 80, 77, 77,



Scheme 3 A gram-scale synthesis of 3ab

and 72 % yield, respectively. To our delight, when optically active amines **2n** and **2o**, were treated with **1a**, the desired products **3an** and **3ao** were obtained in satisfactory yields without racemization (eq 1 and 2).[11] And the latter proceeded smoothly even in the absence of a base. To further test the applicability of this protocol to bioactive or drug-like molecules, a HIV-1 inhibitor **3vp**[12] and an acetylated gluco-ketoamine **3wb** could be directly synthesized via the present double carbonylation approach and were obtained in 65% (eq 3) and 68% (eq 4) yields, respectively.





In summary, we have developed the first general, ligandless, and non-additive palladium-catalyzed double carbonylation of aryl iodides and amines giving α-ketoamides in high yields. Notably, the in situ generated catalyst system devoid of a tedious process for the preparation of nanopalladium enables the transformation to proceed efficiently even at atmospheric pressure of carbon monoxide and room temperature with excellent chemoselectivities. Moreover, a series of reactive groups are compatible with the reaction conditions. This protocol has also been successfully demonstrated to be adaptable to chiral amines as substrates and to be applicable to the synthesis of a HIV-1 inhibitor and an acetylated gluco-ketoamine.

Experiment Section

General Information. PEG-400 was pre-dried (toluene azeotrope). ^{1}H and ^{13}C NMR spectra of solutions in $CDCl_3$ or DMSO-d_6 were recorded on a 400 MHz instrument. Chemical shifts were expressed in parts per million (ppm) downfield from tetramethylsilane and refer to the solvent signals ($CDCl_3$: H 7.24 and C 77.0 ppm; DMSO-d_6: H 2.50 and C 39.5 ppm). The signals of water were observed at about 1.58 ppm in $CDCl_3$ and 3.42 ppm in DMSO-d_6, respectively.

General Procedures for Pd-Catalyzed Double Carbonylation of Aryl Iodide with Amine:

General Procedure A: A 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), sodium carbonate (1.0 mmol, 106.5 mg), and PEG-400 (2.0 mL) before standard cycles of evacuation and back-filling with dry and pure carbon monoxide. Corresponding aryl iodide (0.5 mmol) and amine (0.5 mmol) were added successively. The mixture was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (petroleum ether: diethyl ether = 10 : 1–10 : 6).

In the recycling experiment, the residue was subjected to a second run of the double carbonylation by charging it with the same materials (**1a**, **2b**, and Na_2CO_3) without further addition of $Pd(OAc)_2$ except addition of another 0.5 mL PEG-400 to the reaction mixture.

General Procedure B: A 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), sodium carbonate (1.0 mmol, 106.5 mg), and PEG-400 (2.0 mL) before standard cycles of evacuation and back-filling with dry and pure carbon monoxide. Corresponding aryl iodide (0.5 mmol) and amine (0.5 mmol) were added successively. The mixture was stirred at 50 ^{o}C for the indicated time. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl solution (15 mL) and extracted with ethyl acetate (3

× 15 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (petroleum ether: diethyl ether = 10 : 1–10 : 6).

General Procedure C: A 25 mL Schlenk flask was charged with $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), and PEG-400 (2.0 mL) before standard cycles of evacuation and back-filling with dry and pure carbon monoxide. Corresponding aryl iodide (0.5 mmol) and amine (0.5 mmol) were added successively. The mixture was stirred at room temperature for the indicated time. At the end of the reaction, the reaction mixture was poured into a saturated aqueous NaCl solution (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic phases were combined, and the volatile components were evaporated in a rotary evaporator. The crude product was purified by column chromatography on silica gel (petroleum ether: diethyl ether = 10 : 1–10 : 6).

2-(4-Chlorophenyl)-*N*-cyclohexyl-2-oxoacetamide (3aa). *Following general procedure A*, **3aa** was isolated as a white solid (98 mg, 74%). Known compound (CAS: 24914-10-1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8 Hz, 2 H), 7.42 (d, J = 8 Hz, 2 H), 6.98 (s, 1 H), 3.86-3.76 (m, 1 H), 1.97–1.71 (m, 2 H), 1.65–1.23 (m, 4 H), 1.29–1.20 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.7, 160.4, 141.0, 132.7, 131.8, 128.8, 48.5, 32.7, 25.4, 24.7 ppm; mp 100.5–100.9 °C.

1-(4-Chlorophenyl)-2-morpholinoethane-1,2-dione(3ab).[13] Following *general procedure A*, **3ab** was isolated as a white solid (102 mg, 80%). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2 H), 7.48 (d, *J* = 8 Hz, 2 H), 3.79–3.73 (m, 4 H), 3.64 (t, *J* = 4 Hz, 2 H), 3.36 ppm (t, *J* = 4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 164.9, 141.6, 131.5, 131.1, 129.5, 66.7, 66.6, 46.3, 41.7 ppm; mp 116.0–116.5 °C.

1-Morpholino-2-(*p*-tolyl)ethane-1,2-dione (3bb).[13] *Following general procedure A*, **3bb** was isolated as a yellow oil (93 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8 Hz, 2 H), 7.30 (d, *J* = 8 Hz, 2 H), 3.79–3.74 (m, 4 H), 3.63 (t, *J* = 8 Hz, 2 H), 3.35 (t, *J* = 8 Hz, 2 H), 2.42 ppm (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 165.7, 146.3, 130.7, 129.8, 129.8, 66.8, 66.7, 46.3, 41.6, 21.9 ppm.

1-Morpholino-2-(*o*-tolyl)ethane-1,2-dione (3cb).[13] *Following general procedure A*, **3cb** was isolated as a yellow solid (108 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8 Hz, 1 H), 7.47 (td, *J* = 8, 1.2 Hz, 1 H), 7.33–7.28(m, 2 H), 3.78–3.74(m, 4 H), 3.65(t, *J* = 8 Hz, 2 H), 3.37(t, *J* = 8 Hz, 2 H), 2.64 ppm (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 166.2, 141.6, 133.9, 132.7, 132.7, 131.5, 126.2, 66.7, 66.6, 46.3, 41.6, 21.8 ppm; mp 80.5–81.2 °C.

1-Morpholino-2-(*m*-tolyl)ethane-1,2-dione (3db).[14] *Following general procedure A*, **3db** was isolated as a yellow oil (115 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1 H), 7.71 (d, *J* = 8 Hz, 1 H), 7.44 (d, *J* = 8 Hz, 1 H), 7.40–7.36 (m, 1 H) 3.79–3.75 (m, 4 H), 3.63 (t, *J* = 4 Hz, 2 H), 3.35 (t, *J* = 4 Hz, 2 H), 2.40 ppm (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 165.6, 139.1, 135.8, 133.0, 129.9, 129.0, 127.0, 66.7, 66.6, 46.2, 41.6, 21.2 ppm.

1-(3,5-Dimethylphenyl)-2-morpholinoethane-1,2-dione (3eb). *Following general procedure A*, **3eb** was isolated as a white solid (104 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 2 H), 7.26 (s, 1 H), 3.79–3.74 (m, 4 H), 3.63 (t, *J* = 4.8 Hz, 2 H), 3.34 (t, *J* = 4.8 Hz, 2 H), 2.35 ppm (d, *J* = 0.5 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 165.7, 138.9, 136.8, 133.1, 127.3, 66.7, 66.7, 46.2, 41.6, 21.1 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{17}NO_3Na$ 270.1100; found 270.1113; IR ν_{max} (KBr)/ cm^{-1} 3458,

2965, 2921,2893, 2850, 1755, 1675, 1653, 1592, 1444, 1289, 1179,1115, 843, 803,761, 746, 665; mp 93.0–93.7 °C.

1-Morpholino-2-phenylethane-1,2-dione (3fb).[13] *Following general procedure A*, **3fb** was isolated as a brown oil (103 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8 Hz, 2 H), 7.64 (tt, *J* = 4, 1.2 Hz, 1 H), 7.52–7.48 (m, 2 H), 3.79–3.76 (m, 4 H), 3.63 (t, *J* = 4.8 Hz, 2 H), 3.36 ppm (t, *J* = 4.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 165.4, 134.9, 133.0, 129.7, 129.1, 66.7, 66.7, 46.3, 41.6 ppm.

1-(4-Fluorophenyl)-2-morpholinoethane-1,2-dione (3gb).[15] *Following general procedure A*, **3gb** was isolated as a gray solid (101 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8, 4 Hz, 2 H), 7.17 (dd, *J* = 8, 4 Hz, 2 H), 3.79–3.73 (m, 4 H), 3.64 (t, *J* = 4 Hz, 2 H), 3.36 ppm (t, *J* = 4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.3, 165.1, 166.8 (d, *J* = 256 Hz), 132.5 (d, *J* = 10 Hz), 129.6 (d, *J* = 2.8 Hz),116.4 (d, *J* = 22 Hz), 66.7, 66.6, 46.3, 41.7 ppm; mp 86.1–86.3 °C.

1-(3-Fluorophenyl)-2-morpholinoethane-1,2-dione (3hb). *Following general procedure A*, **3hb** was isolated as a yellow liquid (114 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 8, 0.3 Hz, 1 H), 7.65–7.62 (m, 1 H), 7.48 (td, *J* = 7.6, 5.6 Hz, 1 H), 7.32 (tdd, *J* = 16.4, 2.4, 0.8 Hz, 1 H), 3.77–3.75 (m, 4 H), 3.64(t, *J* = 4 Hz, 2 H), 3.35 ppm (t, *J* = 8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 164.7, 162.9 (d, *J* = 248 Hz), 135.1 (d, *J* = 6 Hz), 130.8 (d, *J* = 7 Hz), 125.7 (d, *J* = 3 Hz), 122.0 (d, *J* = 21 Hz), 115.9 (d, *J* = 23 Hz), 66.7, 66.6, 46.2, 41.7 ppm. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{12}FNO_3Na$ 260.0693; found 260.0692; IR ν_{max} (KBr)/ cm^{-1} 3092, 2972, 2920, 2859, 1682, 1647, 1606, 1584, 1482, 1369, 1167, 1150, 1066, 797, 772, 762.

1-Morpholino-2-(4-(trifluoromethyl)phenyl)ethane-1,2-dione (3ib).[14] *Following general procedure A*, **3ib** was isolated as a violet solid (109 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8 Hz, 2H), 7.75 (d, *J* = 8 Hz, 2 H), 3.79–3.75 (m, 4 H), 3.64 (t, *J* = 4 Hz, 2 H), 3.37(t, *J* = 4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 164.5,

135.9(q, J = 31 Hz), 130.0, 126.1(q, J = 4 Hz), 123.3(q, J = 271 Hz), 66.7, 66.6, 46.3, 41.8 ppm; mp 127.3–127.5 °C.

1-(3-Fluoro-4-methylphenyl)-2-morpholinoethane-1,2-dione (3jb). *Following general procedure A*, **3jb** was isolated as a white solid (112 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 2 H), 7.31 (t, J = 8 Hz, 1 H), 3.78–3.73 (m, 4 H), 3.62 (t, J = 4 Hz, 2 H), 3.34 (t, J = 4 Hz, 2 H), 2.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 165.0, 161.3 (d, J = 247 Hz), 133.3 (d, J = 18 Hz), 132.8 (d, J = 7 Hz), 132.1 (d, J = 5 Hz), 125.5 (d, J = 3 Hz), 115.5 (d, J = 25 Hz), 66.7, 66.6, 46.2, 41.6, 15.1 (d, J = 4 Hz); mp 84.0–84.5 °C; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{15}FNO_3$ 252.1030; found 252.1043; IR ν_{max} (KBr)/ cm^{-1} 3076, 2966, 2927, 2854, 2854, 1755, 1677, 1656, 1645, 1614, 1164, 1114, 1066, 1577, 1502, 880, 812, 764.

1-(4-Methoxyphenyl)-2-morpholinoethane-1,2-dione (3kb).[13] *Following general procedure A*, **3kb** was isolated as a white solid (101 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 2 H), 6.96 (d, J = 8 Hz, 2 H), 3.86 (s, 3 H), 3.78–3.73 (m, 4 H), 3.62 (t, J = 4 Hz, 2 H), 3.35 ppm (t, J = 4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.8, 165.8, 165.0, 132.1, 126.1, 114.4, 66.9, 66.7, 55.6, 46.3, 41.5 ppm; mp 113.1–113.3 °C.

4-(2-Morpholino-2-oxoacetyl)benzonitrile (3lb).[16] *Following general procedure A*, **3lb** was isolated as a white solid (109 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04(d, J = 8 Hz, 2 H), 7.79 (d, J = 8 Hz, 2 H), 3.79–3.74 (m, 4 H), 3.64 (t, J = 4.8 Hz, 2 H), 3.37 ppm (t, J = 4.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0, 164.1, 136.0, 132.7, 130.0, 117.8, 117.5, 66.7, 66.5, 46.3, 41.8 ppm; mp 118.3–118.5 °C.

Methyl 4-(2-morpholino-2-oxoacetyl)benzoate (3mb). *Following general procedure A*, **3mb** was isolated as a gray solid (111 mg, 80%). Known compound (CAS:1616527-07-1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.7 Hz, 2 H), 7.99 (d, J = 8.7 Hz, 2 H), 3.93 (s, 3 H), 3.79–3.75 (m, 4 H), 3.63 (t, J = 4 Hz, 2 H), 3.36 ppm (t, J =

4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2, 165.8, 164.7, 136.1, 135.3, 130.1, 129.6, 66.7, 66.6, 52.6, 46.2, 41.7 ppm ; mp 140.2–140.6 °C.

1-Morpholino-2-(naphthalen-1-yl)ethane-1,2-dione (3nb).[17] *Following general procedure A*, **3nb** was isolated as a white solid (121 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, *J* = 8.8 Hz, 1 H), 8.11 (d, *J* = 8 Hz, 1 H), 8.01 (dd, *J* = 8, 1.2 Hz, 1 H), 7.91 (d, *J* = 8 Hz, 1 H), 7.71–7.67 (m, 1 H), 7.61–7.52 (m, 2 H), 3.81 (m, 4 H), 3.65 (t, *J* = 4 Hz, 2 H), 3.42 ppm (t, *J* = 4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 166.0, 136.1, 134.5, 134.0, 130.9, 129.4, 128.8, 128.4, 127.1, 125.7, 124.5, 66.6, 46.4, 41.7 ppm; mp 123.8–124.1 °C.

1-Morpholino-2-(thiophen-3-yl)ethane-1,2-dione (3ob). *Following general procedure A*, **3ob** was isolated as a yellow liquid (97 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 4, 1.2 Hz, 1 H), 7.55 (dd, *J* = 4, 1.2Hz, 1 H), 7.34 (dd, *J* = 5.2, 3.2 Hz, 1 H), 3.75–3.69 (m, 4 H), 3.63 (t, *J* = 4 Hz, 2 H), 3.40 ppm (t, *J* = 4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 165.1, 138.4, 136.7, 127.2, 126.9, 66.7, 66.6, 46.3, 41.7 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{10}H_{11}NO_3SNa$ 248.0351; found 248.0354; IR ν_{max} (KBr)/ cm^{-1} 3103, 2974, 2923, 2853, 1643, 1508, 1467, 1444, 1414, 1182, 1117, 1071, 794, 754.

1-Morpholino-2-(thiophen-2-yl)ethane-1,2-dione (3pb).[15] *Following general procedure A*, **3pb** was isolated as a yellow liquid (74 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 4, 1.2 Hz, 1 H), 7.78 (dd, *J* = 8, 1.2 Hz, 1 H), 7.16 (dd, *J* = 5.2, 4 Hz, 1 H), 3.76–3.71 (m, 4 H), 3.64 (t, *J* = 4 Hz, 2 H), 3.46 ppm (t, *J* = 4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.7, 164.3, 140.2, 136.7, 136.2, 128.7, 66.8, 66.6, 46.4, 41.9 ppm.

1-(3,5-Dimethylisoxazol-4-yl)-2-morpholinoethane-1,2-dione (3qb): *Following general procedure A*, **3qb** was isolated as a white solid (114 mg, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (t, *J* = 4 Hz, 2 H), 3.70–3.64 (m, 4 H), 3.38 (t, *J* = 8 Hz, 2 H), 2.58 (s, 3 H), 2.38 ppm (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 176.6, 164.9, 159.3, 113.5,

66.6, 66.4, 46.2, 41.6, 13.3, 11.4 ppm; mp 88.6–88.8 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{14}N_2O_4Na$ 261.0845; found 261.0852; IR ν_{max} (KBr)/ cm^{-1} 2989, 2921, 2856, 1668, 1646, 1581, 1478, 1428, 1421, 1378, 1363, 1275, 1115, 1069, 974, 730.

1-Morpholino-2-(4-(morpholinomethyl)phenyl)ethane-1,2-dione (3rb): *Following general procedure A*, **3rb** was isolated as a white solid (134 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8 Hz, 2 H), 7.48 (d, *J* = 8 Hz, 2 H), 3.78–3.73 (m, 4 H), 3.68 (t, *J* = 4 Hz, 4 H), 3.63 (t, *J* = 4.8 Hz, 2 H), 3.55 (s, 2 H), 3.35 (t, *J* = 4.8 Hz, 2 H), 2.47–2.38 ppm (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 165.4, 132.1, 129.8, 129.6, 66.8, 66.7, 66.6, 62.8, 53.6, 46.2, 41.6 ppm; mp 127.2–127.9 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{22}N_2O_4Na$ 341.1471; found 341.1479; IR ν_{max} (KBr)/ cm^{-1} 3040, 2965, 2922, 2902, 2847, 1672, 1635, 1602, 1570, 1442, 1312, 1268, 1072, 823, 739.

1-([1,1'-Biphenyl]-4-yl)-2-morpholinoethane-1,2-dione (3sb): *Following general procedure B*, **3sb** was isolated as a yellow solid (97 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.8 Hz, 2 H), 7.71 (d, *J* = 8.4 Hz, 2 H), 7.60 (dd, *J* = 8, 4 Hz, 2 H), 7.47–7.42 (m, 2 H), 7.39 (tt, *J* = 8, 4 Hz, 1 H), 3.77 (s, 4 H), 3.63 (t, *J* = 4.4 Hz, 2 H), 3.38 ppm (t, *J* = 4.4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 165.4, 147.5, 139.3, 131.6, 130.1, 128.9, 128.6, 127.6, 127.2, 66.6, 66.5, 46.2, 41.5 pm; mp 138.7–139.5 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{18}H_{17}NO_3Na$ 318.1100; found 318.1112; IR ν_{max} (KBr)/ cm^{-1} 3059, 3024, 2995, 2981, 2916, 2851, 1676, 1637, 1599, 1557, 1442, 1175, 1311, 834, 745.

4-(2-Morpholino-2-oxoacetyl)benzoic acid (3tb): *Following general procedure B*, **3tb** was isolated as a white solid (106 mg, 81%). ^{1}H NMR (400 MHz, DMSO) δ 8.14 (d, *J* = 8 Hz, 2 H), 8.02 (d, *J* = 8 Hz, 2 H), 3.72 (t, *J* = 4 Hz, 2 H), 3.65 (t, *J* = 4 Hz, 2 H), 3.54 (t, *J* = 4 Hz, 2 H), 3.31 ppm (t, *J* = 4 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 191.4, 164.9,137.1, 135.8, 130.5, 129.9, 66.5, 66.2, 46.1, 41.5 ppm; mp 203.8–204.7 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{13}H_{13}NO_5Na$ 286.0685; found 286.0686; IR ν_{max}

(KBr)/ cm^{-1} 3429, 3055, 2983, 2915, 2865, 1702, 1676, 1630, 1570, 1505, 1465, 1317, 1114, 1288, 816, 735.

1-(4-Aminophenyl)-2-morpholinoethane-1,2-dione (3ub): *Following general procedure B*, **3ub** was isolated as a yellow solid (60 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8 Hz, 2 H), 6.63 (d, *J* = 8 Hz, 2 H), 3.77–3.71 (m, 4 H), 3.61 (t, *J* = 4.8 Hz, 2 H), 3.35 ppm (t, *J* = 4.8 Hz, 2 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 189.3,166.4, 152.9, 132.4, 123.2, 114.0, 66.8, 66.7, 46.3, 41.5 ppm; mp 172.9–173.2 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{12}H_{14}N_2O_3Na$ 257.0896; found 257.0899; IR ν_{max} (KBr)/ cm^{-1} 3434, 3344, 3042, 2976, 2915, 2846, 1644, 1613, 1583, 1445,1311, 1266, 1066, 845, 742.

2-(4-Chlorophenyl)-*N,N*-diethyl-2-oxoacetamide (3ac).[6d] *Following general procedure A*, **3ac** was isolated as a white liquid (103 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8 Hz, 2 H), 7.44(d, *J* = 8 Hz, 2 H), 3.53 (q, *J* = 8 Hz, 2 H), 3.21 (q, *J* = 8 Hz, 2 H), 1.25 (d, *J* = 8 Hz, 3 H), 1.13 (t, *J* = 8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 166.2, 141.1,131.7, 130.9, 129.3, 42.1, 38.9, 14.1, 12.8 ppm.

***Tert*-butyl((1-(2-(4-chlorophenyl)-2-oxoacetyl)piperidin-4-yl)methyl)carbamate (3ad).** *Following general procedure A*, **3ad** was isolated as a white solid (164 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8 Hz, 2 H), 7.45 (d, *J* = 8 Hz, 2 H), 4.65–4.61 (m, 2 H), 3.57–3.48(m, 1 H), 3.03–2.76 (m, 4 H), 1.85–1.60 (m, 2 H), 1.40 (s, 9 H), 1.24–1.11 ppm (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 164.9, 156.0, 141.3, 131.5, 130.9, 129.4, 45.9, 41.2, 36.8, 30.0, 29.2, 28.3 ppm; mp 108.4–108.6 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{25}ClN_2O_4Na$ 403.1395; found 403.139863; IR ν_{max} (KBr)/ cm^{-1} 3365, 2987, 2947, 2925, 2865, 1765, 1685, 1646, 1588, 1525, 1458, 1363, 1316, 1268, 1244, 1207, 1115, 1093, 1072, 841, 726.

1-(4-Chlorophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (3ae).[14] *Following general procedure C,* **3ae** was isolated as a brown liquid (96 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8 Hz, 2 H), 7.42 (d, *J* = 8 Hz, 2 H), 3.59 (t, *J* = 8 Hz, 2 H), 3.38 (t, *J*

= 8 Hz, 2 H), 1.93–1.88 ppm (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 164.2, 141.1, 131.3, 131.2, 129.2, 46.7, 45.3, 25.8, 23.9 ppm;

2-(4-Chlorophenyl)-*N*-(2,3-dihydro-1H-inden-1-yl)-2-oxoacetamide (3af). *Following general procedure A*, **3af** was isolated as a yellow solid (76 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8 Hz, 2 H), 7.44 (d, *J* = 8 Hz, 2 H), 7.35 (d, *J* = 8 Hz, 1 H), 7.29 (d, *J* = 4 Hz, 1 H), 7.27–7.26 (m, 2 H), 7.23–7.20 (m, 1 H), 5.52 (dd, *J* =15.7, 7.7, 1 H), 3.04 (ddd, *J* = 16, 12, 4 Hz, 1 H), 2.92 (dt, *J* = 16, 8 Hz, 1 H), 2.68–2.58 (m, 1 H), 1.97–1.87 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 161.0, 143.4, 142.0, 141.2, 132.7, 131.7, 128.8, 128.3, 126.9, 124.9, 124.1, 54.7, 33.6, 30.3 ppm; mp 81.6–82.0 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{14}ClNO_2Na$ 322.0605; found 322.0603; IR ν_{max} (KBr)/ cm^{-1} 3275, 3035, 2967, 2856, 1687, 1639, 1587, 1531, 1478, 1450, 1010, 817, 761, 751.

2-(4-Chlorophenyl)-*N*-cyclopropyl-2-oxoacetamide (3ag). *Following general procedure A*, **3ag** was isolated as a yellow solid (73 mg, 65%). Known compound (CAS: 1267006-97-2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.2 Hz, 2 H), 7.42 (d, *J* = 8.4 Hz, 2 H), 7.15 (d, *J* = 2.4 Hz, 1 H), 2.87–2.79 (m, 1 H), 0.87 (dt, *J* = 12, 4 Hz, 2 H), 0.63 ppm (dt, *J* = 8,4 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 162.6, 141.2, 132.7, 131.6, 128.9, 22.6, 6.5 ppm; mp 79.6–80.0 °C.

2-(4-Chlorophenyl)-2-oxo-*N*-(pyridin-3-ylmethyl)acetamide (3ah). *Following general procedure A*, **3ah** was isolated as a yellow solid (111 mg, 81%). Known compound (CAS: 1267254-48-7). ^{1}H NMR (400 MHz, CDCl3) δ 8.60 (s, 1 H), 8.55 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.33 (d, *J* = 8.8 Hz, 2 H), 7.69 (d, *J* = 8 HZ, 1 H), 7.60 (s, 1 H), 7.44 (d, *J* = 8 Hz, 2 H), 7.30 (dd, *J* = 8, 4.8 Hz 1 H), 4.57 (d, *J* = 4 Hz, 2 H); ^{13}C NMR (100 MHz, CDCl3) δ 185.6, 161.3, 148.1, 147.9,141.1, 137.0, 132.7, 131.1, 129.0, 124.3, 123.9, 40.9 ppm; mp 105.3–105.6 °C.

***N*-((1S,3S)-adamantan-1-yl)-2-(4-chlorophenyl)-2-oxoacetamide (3ai).** *Following general procedure A*, **3ai** was isolated as a white solid (88 mg, 56%). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.28 (d, *J* = 8 Hz, 2 H), 7.41 (d, *J* = 8 Hz, 2 H), 6.80 (s, 1 H), 2.11 (m, 3H), 2.07 (d, *J* = 2.8 Hz, 6 H), 1.70 ppm (t, *J* = 4 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 160.4, 140.9, 132.8, 131.8, 128.7, 52.5, 41.1, 36.2, 29.3 ppm; mp 114.9–117.6 °C; HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{19}ClNO_2$ 316.1098; found 316.1123; IR ν_{max} (KBr)/ cm^{-1} 3370, 2960, 2928, 2906, 2849, 1665, 1586, 1517, 1445, 1360, 1345, 1314, 1091, 1022, 1016, 845, 800.

***N*-(*tert*-butyl)-2-(4-chlorophenyl)-2-oxoacetamide (3aj).**[18] *Following general procedure A*, **3aj** was isolated as a yellow solid (96 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8 Hz, 2 H), 7.42 (d, J = 8 Hz, 2 H), 6.94 (s, 1 H), 1.43 ppm (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.1, 160.9, 140.9, 132.7, 131.7, 128.7, 51.7, 28.3 ppm; mp 49–51 °C

2-(4-Chlorophenyl)-*N*-(2-methylallyl)-2-oxoacetamide (3ak). *Following general procedure A*, **3ak** was isolated as a yellow solid (89 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8 Hz, 2 H), 7.42 (d, *J* =8 Hz, 2 H), 7.24 (s, 1 H), 4.884 (d, *J* = 1.2 Hz, 1 H), 4.878 (d, *J* = 1.2 Hz, 1 H), 3.90 (d, *J* = 6.4 Hz, 2 H), 1.76 ppm (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 161.2, 141.2, 140.7, 132.7, 131.6, 128.9, 111.8, 44.9, 20.3 ppm; mp 33.6–34.2 °C; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{12}H_{12}ClNO_2Na$ 260.0448; found 260.0445; IR ν_{max} (KBr)/ cm^{-1} 3379, 3080, 2980, 2914, 2844, 1669, 1589, 1525, 1484, 1456, 1090, 895.

2-(4-Chlorophenyl)-N-dodecyl-2-oxoacetamide (3al). *Following general procedure B*, **3al** was isolated as a white solid (129 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.8 Hz, 2 H), 7.42 (d, *J* = 8.8 Hz, 2 H), 7.11 (s, 1 H), 3.35 (q, *J* = 4 Hz, 2 H), 1.61–1.54 (m, 2 H), 1.35–1.23 (m, 20 H), 0.85 ppm (t, *J* = 8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 161.3, 141.1, 132.7, 131.7, 128.8, 39.5, 31.9, 29.6, 29.5, 29.3, 29.2, 29.2, 26.9, 22.7, 14.1 ppm; mp 57.0–57.5 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{30}ClNO_2Na$ 374.1857; found 374.1849; IR ν_{max} (KBr)/ cm^{-1} 3346, 2962, 2916, 2845, 1672, 1651, 1589, 1524, 1477, 1469, 1389, 1098, 723.

***N*-cyclohexyl-2-(3,5-dimethylphenyl)-2-oxoacetamide (3ea).** *Following general procedure A*, **3ea** was isolated as a white solid (117 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 2 H), 7.22 (s, 1 H), 6.90 (s, 1 H), 3.88–3.77 (m, 1H), 2.34 (s, 6 H), 1.98–1.72 (m, 4 H), 1.65–1.29 (m, 4 H), 1.27–1.21 ppm (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 161.1, 138.1, 136.1, 133.4, 128.8, 48.5, 32.7, 25.4, 24.7, 21.2 ppm; mp 87.5–88.0 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{16}H_{21}NO_2Na$ 282.1464; found 282.1465; IR ν_{max} (KBr)/ cm^{-1} 3425, 3285, 3061. 2936, 2912, 2851, 1678, 1643, 1592, 1532, 1446, 1383, 808,687.

***N*-cyclohexyl-2-oxo-2-phenylacetamide (3fa).[19]** *Following general procedure A*, **3fa** was isolated as a white solid (96 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 8, 1.6 Hz, 2 H), 7.58 (tt, *J* = 8, 1.2 Hz, 1 H), 7.47–7.42 (m, 2 H), 6.96 (d, *J* = 8 Hz, 1 H), 3.87–3.78 (m, 1 H), 1.98–1.71 (m, 4 H), 1.65–1.29 (m, 4 H), 1.26–1.20 ppm (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 160.9, 134.2, 133.4, 131.2, 128.4, 48.4, 32.7, 25.4, 24.7 ppm; mp 112.7–112.9 °C.

***N*-cyclohexyl-2-oxo-2-(o-tolyl)acetamide (3ca).** *Following general procedure A*, **3ca** was isolated as a yellow solid (102 mg, 80%). Known compound (CAS: 1029542-43-5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8 Hz, 1 H), 7.43–7.38 (m, 1 H), 7.28–7.24 (m, 1 H), 7.23 (d, *J* = 4 Hz, 1 H), 6.91 (d, *J* = 4 Hz, 1 H), 3.87–3.77 (m, 1 H), 2.46 (s, 3 H), 1.99–1.71 (m, 4 H), 1.65–1.29 (m, 4 H), 1.27–1.21 ppm (m, 2 H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 161.1, 140.0, 132.9, 132.6, 131.9, 131.6, 125.3, 48.5, 32.7, 25.4, 24.7, 20.8 ppm; mp 100.1–100.4 °C.

***N*-cyclohexyl-2-oxo-2-(*m*-tolyl)acetamide (3da).** *Following general procedure A*, **3da** was isolated as a white solid (99 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 4 Hz, 1 H), 8.09 (s, 1 H), 7.40 (d, *J* = 8 Hz, 1 H), 7.35–7.31 (m, 1 H), 6.93 (d, *J* = 4 Hz, 1 H), 3.87–3.78 (m, 1 H), 2.38 (s, 3 H), 1.98–1.71 (m, 4 H), 1.66–1.29 (m, 4 H), 1.27–1.20 ppm (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.3, 161.0, 138.2, 135.1, 133.4, 131.5, 128.4, 128.3, 48.4, 32.7, 25.4, 24.7, 21.3 ppm; mp 107.2–107.6 °C; HRMS (ESI) *m/z*:

$[M+Na]^+$ calcd for $C_{15}H_{19}NO_2Na$ 268.1308, found 268.1307; IR ν_{max} (KBr)/ cm^{-1} 3420, 3288, 3058, 3055, 2933, 2849, 1652, 1584, 1540, 1446, 1378, 783, 694.

***N*-cyclohexyl-2-oxo-2-(*p*-tolyl)acetamide (3ba).** *Following general procedure A*, **3ba** was isolated as a yellow solid (97 mg, 79%). Known compound (CAS: 1266998-34-8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8 Hz, 2 H), 7.24 (d, *J* = 8 Hz, 2 H), 6.95 (d, *J* = 8 Hz, 1 H), 3.84–3.78 (m, 1 H), 2.39 (s, 3 H), 1.97–1.71 (m, 4 H), 1.65–1.28 (m, 4 H), 1.26–1.19 ppm (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6, 161.1, 145.4, 131.3, 130.9, 129.2, 48.4, 32.7, 25.4, 24.7, 21.8 ppm; mp 105.9–106.5 °C.

***N,N*-diethyl-2-oxo-2-(m-tolyl)acetamide (3dc).** *Following general procedure A*, **3dc** was isolated as a yellow liquid (87 mg, 79%). Known compound (CAS: 99821-90-6); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1 H), 7.74 (d, *J* = 8 Hz, 1 H), 7.46 (d, *J* = 8 Hz, 1 H), 7.40 (m, 1 H), 3.60–3.55 (m, 2 H), 3.28–3.22 (m, 2 H), 2.43 (s, 3 H), 1.30 (t, *J* = 8 Hz, 3 H), 1.16 ppm (t, *J* = 8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 166.8, 138.8, 135.4, 133.2, 129.8, 128.8, 126.9, 42.1, 38.7, 21.3, 14.0, 12.8 ppm.

2-(3,5-dimethylphenyl)-*N,N*-diethyl-2-oxoacetamide (3ec). *Following general procedure A*, **3ec** was isolated as a yellow liquid (84 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 2 H), 7.28 (s, 1 H), 3.58 (m, 2 H), 3.25 (m, 2 H), 2.39 (s, 6 H), 1.30 (t, *J* = 7.2 Hz, 4 H), 1.17 ppm (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 167.0, 138.7, 136.3, 133.3, 127.3, 42.1, 38.7, 21.2, 14.1, 12.8 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{14}H_{19}NO_2Na$ 256.1308, found 256.1311; IR ν_{max} (KBr)/ cm^{-1} 2973, 2935, 2869, 1678, 1640, 1603, 1440, 1382, 1306, 808, 680.

1-(4-Chlorophenyl)-2-(piperazin-1-yl)ethane-1,2-dione (3am). *Following general procedure A*, **3am** was isolated as a yellow liquid (95 mg, 75%). Known compound (CAS: 1225832-82-5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8 Hz, 2 H), 7.44 (d, *J* = 8 Hz, 2 H), 3.70 (t, *J* = 5.2 Hz, 2 H), 3.30 (t, *J* = 5.2 Hz, 2 H), 2.93 (t, *J* = 5.2 Hz, 2 H), 2.80 (t, *J* = 5.2 Hz, 2 H), 2.62 ppm (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 164.9, 141.4, 131.4, 130.9, 129.4, 46.5, 45.9, 45.4, 41.9 ppm.

(S)-2-(4-chlorophenyl)-N-(2,3-dihydro-1H-inden-1-yl)-2-oxoacetamide (3an). *Following general procedure A*, **3an** was isolated as a brown solid (86 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 9.6 Hz, 2 H), 7.45 (d, *J* = 9.6 Hz, 2 H), 7.30 (d, *J* = 0.8 Hz, 1 H), 7.29 (s, 1 H), 7.27–7.26 (m, 2 H), 7.23–7.20 (m, 1 H), 5.52 (dd, *J* = 16, 8 Hz, 1 H), 3.04 (ddd, *J* = 16, 8, 4 Hz, 1 H), 2.92 (dt, *J* = 16, 8 Hz, 1 H), 2.69–2.61 (m, 1 H), 1.96–1.89 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.1, 161.0, 143.4, 142.0, 141.2, 132.8, 131.8, 128.9, 128.4, 126.9, 125.0, 124.1, 54.8, 33.6, 30.3 ppm; mp 104.6–105.2 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{17}H_{14}ClNO_2Na$ 322.0605; found 322.0610; IR ν_{max} (KBr)/ cm^{-1} 3458, 3262, 3065, 2971, 2911, 2844, 1687, 1641, 1585, 1546, 1480, 1454, 1014, 817, 762, 750; chiral HPLC conditions: Chiralcel OD-H, (n-hexane/isopropanol, 80:20), flow rate = 1.0 mL/min, Rt = 5.7, and 8.6 min, respectively. Enantiomeric excess was determined to be >99% ee using the HPLC conditions.

(R)-2-(4-chlorophenyl)-N-(2-hydroxypropyl)-2-oxoacetamide (3ao). *Following general procedure C*, **3ao** was isolated as a gray solid (98 mg, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2 H), 7.56 (s, 1 H), 7.40 (d, *J* = 8.8 Hz, 2 H), 4.01–3.97 (m, 1 H), 3.52 (dd, *J*=12, 8 Hz, 1 H), 3.23 (dd, *J* = 12, 8 Hz, 1 H), 2.50 (s, 1 H), 1.22 ppm (d, *J* = 8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 162.1, 141.2, 132.6, 131.5, 128.9, 66.9, 46.6, 20.9 ppm; mp 87.0–87.5 °C; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{11}H_{12}ClNO_3Na$ 264.0397; found 264.0399; IR ν_{max} (KBr)/ cm^{-1} 3401, 3246, 3100, 2966, 2933, 2875, 1682, 1653, 1636, 1584, 1447, 1376, 813, 737; chiral HPLC conditions: Chiralcel OD-H, (*n*-hexane/isopropanol, 80:20), flow rate = 1.0 mL/min, R_t = 23.0, and 24.1 min, respectively. Enantiomeric excess was determined to be >99% ee using the HPLC conditions.

1-(4-Benzoylpiperazin-1-yl)-2-(1-methyl-1H-indol-3-yl)ethane-1,2-dione (3vp).[20] *Following general procedure B*, **3vp** was isolated as a white solid (122 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 7.87 (s, 1 H), 7.36 (d, *J* = 22.4 Hz, 8 H),

3.87–3.44 ppm (m, 11 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 170.6, 166.1, 139.6, 137.6, 134.9, 130.1, 128.6, 127.0, 126.0, 124.1, 123.4, 122.2, 113.2, 110.0, 45.9, 41.6, 33.8 ppm; mp 237.6–238.3 °C.

(2S,3S,5S,6R)-2-(acetoxymethyl)-6-(4-(2-morpholino-2-oxoacetyl)phenoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (3wb). *Following general procedure A*, **3wb** was isolated as a white oil (192 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 2 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 5.27 (t, *J* = 6.4 Hz, 2 H), 5.19 (d, *J* = 7.6 Hz, 1 H), 5.14 (t, *J* = 9.6 Hz, 1 H), 4.24 (dd, *J*=12.4, 5.2 Hz, 1 H), 4.13 (dd, *J*=12.4, 2 Hz, 1 H), 3.89 (ddd, *J*=10, 5.2, 2.4 Hz, 1 H), 3.76–3.69 (m, 4H), 3.61 (t, *J* =4 Hz, 2 H), 3.33 (t, *J* =4 Hz, 2 H), 2.02 (s, 3 H), 2.01 (s, 6 H), 2.00 ppm (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6, 170.4, 170.1, 169.3, 169.2, 165.3, 161.5, 132.0, 128.1, 116.7, 97.8, 72.3, 72.2, 70.8, 67.9, 66.7, 66.6, 61.7, 46.2, 41.5, 20.6, 20.5 ppm; HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{26}H_{31}NO_{13}Na$ 588.1687; found 588.1668; IR ν_{max} (KBr)/cm^{-1} 2967, 2931, 2859, 1726, 1641, 1596, 1575, 1506, 1447, 1436, 1373, 1227, 1113, 1067, 1033, 847, 700.

Hg(0) Poisoning Test. As *general procedure A*, a reaction of 1-chloro-4-iodobenzene **1a** (0.5 mmol, 122.9 mg), cyclohexylamine **2a** (0.75 mmol, 58 μL), $Pd(OAc)_2$ (0.01 mmol, 2.3 mg), sodium carbonate (1.0 mmol, 106.5 mg), and PEG-400 (2.0 mL), with the addition of Elemental mercury (1.0 mmol, 100equiv., 201 mg) (relative to palladium) was conducted. Following the reaction for 6 h at room temperature, the desired product **3aa** was formed in a trace amount, suggesting that the reaction is completely inhibited by the introduction of Hg(0).

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Supporting Information.

^{1}H NMR and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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