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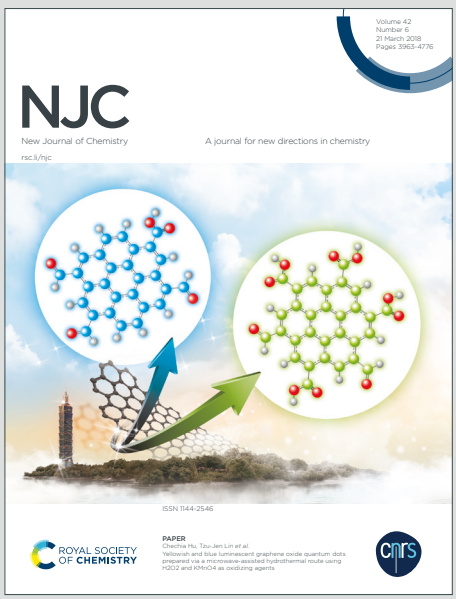

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PAPER

Copper-catalyzed oxidative cleavage of Passerini and Ugi adducts in basic medium yielding α-ketoamides

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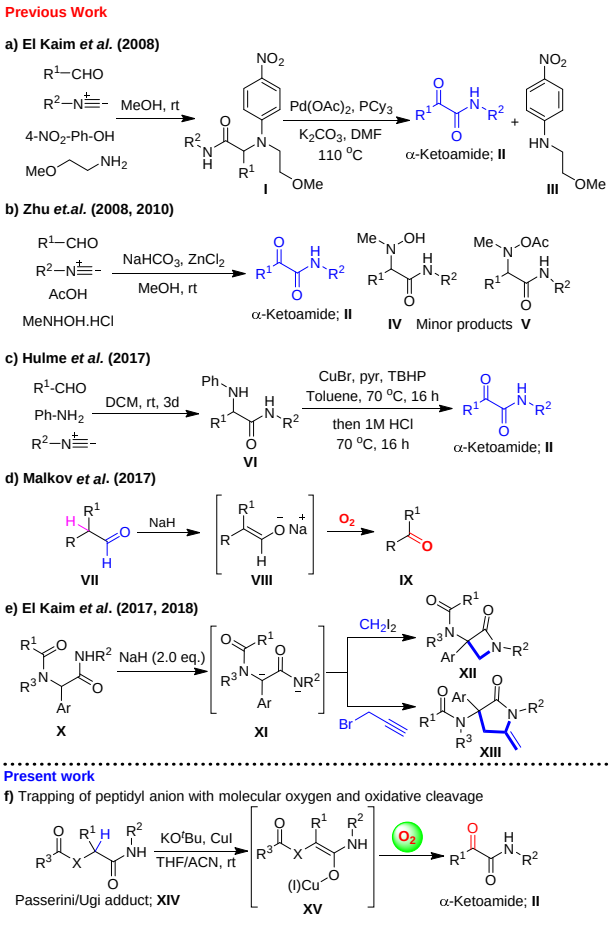
Anirban Ghoshal,[a,b,c] Mayur Ambule Diliprao,[a,b] Revoju Sravanthi,[c] Mohit Taneja[c] and Ajay Kumar Srivastava*[,a,b]

The aerobic oxidative cleavage of Passerini and Ugi adducts in presence of base and copper(I) iodide is studied in detail. The oxidative cleavage yields α-ketoamide along with acid and amide from Passerini and Ugi adducts respectively. Mechanistic investigations revealed that the reaction proceeds *via* a radical pathway involving molecular oxygen. Control experiments with ^{18}O-labeled Passerini adducts confirmed that the molecular oxygen is the source of oxygen in α-ketoamide. A variety of Passerini and Ugi adducts were studied to explore the effect of substitution. Overall, the present study provides an insight into the reactivity of Passerini and Ugi adducts in strong basic conditions along with a method to prepare α-ketoamides.

Introduction

The isocyanide-based multicomponent reactions (IMCRs) produce excellent building blocks to develop post-IMCR modifications.[1] These IMCRs and post-IMCR modifications are extremely helpful in constructing diverse small molecule libraries for drug discovery research.[2] Aldehyde-derived Passerini and Ugi adducts bear an acidic proton that can be abstracted to perform intermolecular and intramolecular addition and cyclization reactions in basic medium. Several groups have demonstrated that the alpha proton adjacent to amide carbonyl can be easily abstracted using base such as K_2CO_3, DBU, KO^{t}Bu and Cs_2CO_3 or under the microwave conditions for performing intramolecular cyclizations.[3] Efforts have been made to prepare α-ketoamides using Isocyanide based multi-component reactions (IMCRs).[4] El Kaim *et al*. reported the oxidative cleavage of Ugi-Smile adduct on treatment with $Pd(OAc)_2$ yielding α-ketoamide (Scheme 1a).[4a]

Zhu's protocol involves the use of hydroxylamine and acetic acid in the Ugi reaction that helps in the acid-catalyzed oxygen transfer to provide the α-ketoamide along with some side products.[4b] The method was further improved by the same group, wherein use of $ZnCl_2$ increases the formation of α-ketoamide (Scheme 1b).[4c]



Scheme 1. Base-mediated aerobic oxidative cleavage and trapping of Ugi-peptidyl anion.

[a] *Division of Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow-226031, UP, India.*
[b] *Chemical Sciences Division, Academy of Scientific and Innovative Research (AcSIR), New Delhi-110025, India.*
[c] *Organic Synthesis and Process Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India.*
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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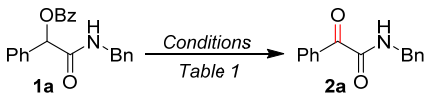
Hulme and co-workers reported a two-step MCR-oxidation methodology to access diverse α-ketoamides *via* a copper(I)-mediated C-N oxidation/acidic hydrolysis of Ugi three-component and Ugi-azide reaction products. The reaction proceeds through enolization followed by palladium-mediated oxidative cleavage (Scheme 1c).[4d] Recently, Malkov *et al.* reported dehomologation of aldehydes bearing α-hydrogen by using molecular oxygen as a terminal oxidant in presence of strong base such as NaH (Scheme 1d).[5] Currently, our research group is engaged in exploring novel post-Ugi transformations to identify medicinally important structural frameworks.[6] In this direction, recently we have utilized the Ugi adducts to perform intramolecular cyclo-isomerizations in basic medium leading to the formation of β-lactams and 2,5-pyrrolidinones. The reaction proceeds *via* formation of peptidyl anion followed by 4-*exo*-dig cyclization.[7] Recently, El Kaim *et al.* describe trapping of Ugi derived peptidyl anion with external electrophiles such as alkyl halides (Scheme 1e).[8] The results prompted us to investigate the fate of Passerini and Ugi adducts in presence of oxygen and base. We envisioned that the trapping of Passerini and Ugi adduct derived peptidyl anion with molecular oxygen might lead to the formation of α-ketoamides through oxidative cleavage. Herein, we present a general method for the oxidative cleavage of Passerini and Ugi adducts in basic medium yielding α-ketoamides (Scheme 1f).

Results and Discussion

At the outset of this investigation, benzoic acid derived Passerini adduct **1a** was treated with different bases such as NaH and KO^{t}Bu in THF under oxygen atmosphere (entries 1 and 5, Table 1). To our delight, the formation of desired α-ketoamide **2a** was observed albeit in low yields and poor rate of conversion (entries 1 and 5, Table 1). Next to improve the yield, CuI was added, as copper (I) helps the oxygen transfer in such reactions. Addition of 5 mol% CuI alongwith NaH however did not improve the yield of the product (entry 2, Table 1). Addition of 10 mol% CuI alongwith NaH in THF resulted the desired product **2a** in 15% yield, showing the expected role of copper in the transformation (entry 3, Table 1). Increasing the quantity of CuI to 20 mol% resulted in 22% yield of **2a** (entry 4, Table 1). Addition of 5 mol% CuI alongwith KO^{t}Bu resulted in 25% yield of corresponding α-ketoamide **2a** (entry 6, Table 1). Increasing the quantity of CuI to 10 mol% afforded **2a** in 41% yield (entry 7, Table 1). However, 20 mol% of CuI alongwith KO^{t}Bu yielded **2a** in 87% yield (entry 8, Table 1). With bases such as K_2CO_3 and Cs_2CO_3, no formation of **2a** was observed and the Passerini adduct **1a** remained unreacted even under reflux conditions (entries 9 and 10, Table 1). The oxidative cleavage with organic base such as DBU was also unsuccessful (entry 11, Table 1). After screening of bases with various solvents and 20 mol% of CuI (entries 12-17, Table 1), it was observed that KO^{t}Bu in THF gave the best result with complete conversion of **1a** and formation of **2a** in 87% yield (entry 8, Table 1). With other copper salts, corresponding α-ketoamide **2a** was obtained in low yields (entries 18-20, Table 1). It was observed that oxygen is essential for the conversion as the reaction did not proceed under argon atmosphere (entry 21, Table 1). The α-ketoamide **2a** was fully characterized by ^{1}H and ^{13}C NMR spectral analysis in which the characteristic peaks (deshielded ortho-protons of phenyl group) of **2a** were observed at δ 8.3 ppm (^{1}H NMR, 400 MHz, $CDCl_3$) and two carbonyls appeared at δ 187.5 and 161.5 ppm (^{13}C NMR, 100 MHz, $CDCl_3$) respectively.

Table 1. Optimization of the reaction conditions[a]



Entry	Base	Additive (mol %)	Solvent	Time	**2a**; yield (%)[c]
1.	NaH	-	THF	10 min	trace
2.	NaH	CuI (5)	THF	10 min	trace
3.	NaH	CuI (10)	THF	10 min	15
4.	NaH	CuI (20)	THF	10 min	22
5.	KO^{t}Bu	-	THF	10 min	12
6.	KO^{t}Bu	CuI (5)	THF	10 min	25
7.	KO^{t}Bu	CuI (10)	THF	10 min	41
8.	**KO^{t}Bu**	**CuI (20)**	**THF**	**10 min**	**87**
9.	K_2CO_3	CuI (20)	THF	12 h	0
10.	Cs_2CO_3	CuI (20)	THF	12 h	0
11.	DBU	CuI (20)	THF	12 h	0
12.	KO^{t}Bu	CuI (20)	CH_3CN	10 min	trace
13.	KO^{t}Bu	CuI (20)	Toluene	10 min	53
14.	KO^{t}Bu	CuI (20)	DMF	10 min	trace
15.	KO^{t}Bu	CuI (20)	Dioxane	10 min	0
16.	KO^{t}Bu	CuI (20)	DCM	10 min	38
17.	KO^{t}Bu	CuI (20)	DMSO	10 min	trace
18.	KO^{t}Bu	CuBr (20)	THF	10 min	27
19.	KO^{t}Bu	I_2 (20)	THF	10 min	24
20.	KO^{t}Bu	NIS (20)	THF	10 min	15
21[b]	KO^{t}Bu	CuI (20)	THF	10 min	trace

[a]Reaction Conditions: **1a** (0.1 mmol), base (0.3 mmol), CuI in solvent (2.0 mL) at rt under oxygen balloon. [b]Under argon. [c]Isolated yields.

In order to check the scope of the method for the oxidative cleavage of Passerini adducts, adducts **1a-l** were subjected to the standard reaction conditions (Table 2). All the Passerini

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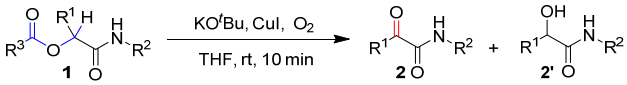
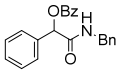
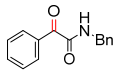
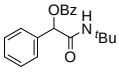
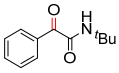
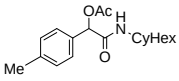
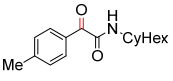
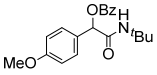
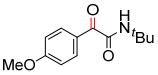
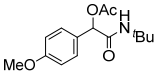
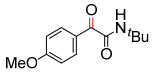
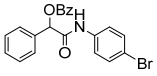
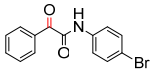
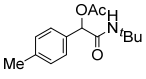
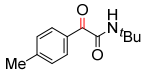
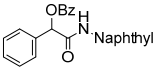
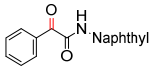
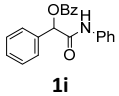
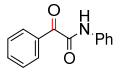
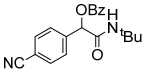
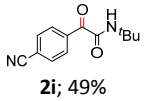
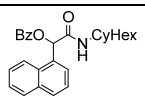
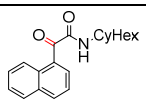
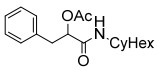
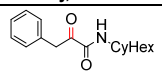
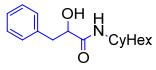
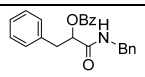
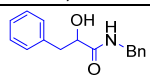
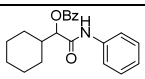
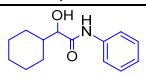
adducts **1a-k** reacted well and corresponding α-ketoamides **2** were isolated in good-to-excellent yields (Table 2). To further explore the robustness and scope of our methodology, we tried to perform the oxidative cleavage in aliphatic aldehyde derived Passerini adducts **1l-n**. Notably, the Passerini adduct **1l** with R^1 as benzyl was sluggish and the α-ketoamide **2k** was obtained in 28% yield along with the hydrolysis product **2k'** in 23% yield (entry 12, Table 2). To our disappointment, the other aliphatic aldehyde derived Passerini adducts **1m** and **1n** did not yield the desired α-ketoamide and only the hydrolysis products **2l'** and **2m'** were obtained in 53% and 72% yields respectively (entries 13 and 14, Table 2). This could be due to the poor enolizability of such adducts.

Table 2. Oxidative cleavage of Passerini adducts[a]

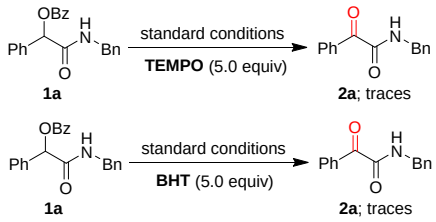


Entry	Passerini adduct	**2**; yield (%)[b]
1.	 **1a**	 **2a**; 87%
2.	 **1b**	 **2b**; 47%
3.	 **1c**	 **2c**; 58%
4.	 **1d**	 **2d**; 46%
5.	 **1e**	 **2d**; 48%
6.	 **1f**	 **2e**; 68%
7.	 **1g**	 **2f**; 50%
8.	 **1h**	 **2g**; 28%
9.	 **1i**	 **2h**; 45%
10.	 **1j**	 **2i**; 49%
11.	 **1k**	 **2j**; 55%
12.	 **1l**	 **2k**; 28%  **2k'**; 23%
13.	 **1m**	 **2l'**; 53%
14.	 **1l**	 **2m'**; 72%

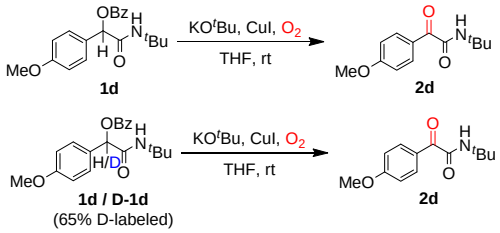
[a]Reaction Conditions: **1** (0.2 mmol), KO^{t}Bu (0.6 mmol), CuI (20 mol %) in THF (5.0 mL) for 30 min at rt under oxygen balloon. [b]Isolated yields.

In order to investigate the reaction mechanism, we subjected the Passerini adduct **1a** to standard reaction conditions in presence of radical quenchers (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) and butylated hydroxytoluene (BHT) respectively (Scheme 2a). In both the cases, α-ketoamide **2a** was obtained in traces with sluggish reaction indicating a radical pathway for the reaction (Scheme 2a).

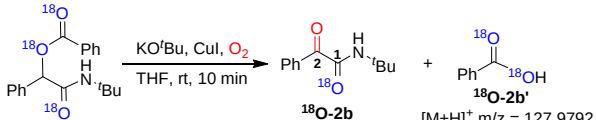
a) Oxidative cleavage of Passerini adduct 1a in presence of radical scavangers



b) KIE studies



c) Oxidative cleavage of ^{18}O-labeled Passerini adduct ^{18}O-1b



^{18}O-1b
$[M+H]^+$ m/z = 318.1717
70.92% ^{18}O/^{18}O/^{18}O
29.08% ^{18}O/^{18}O/^{16}O

^{18}O-2b
$[M+H]^+$ m/z = 208.1217
90.9% ^{18}O/^{16}O
9.09% ^{16}O/^{16}O

^{18}O-2b'
$[M+H]^+$ m/z = 127.9792
51.02% ^{18}O/^{18}O
23.98% ^{18}O/^{16}O
25% ^{16}O/^{16}O

Scheme 2. Control experiments.

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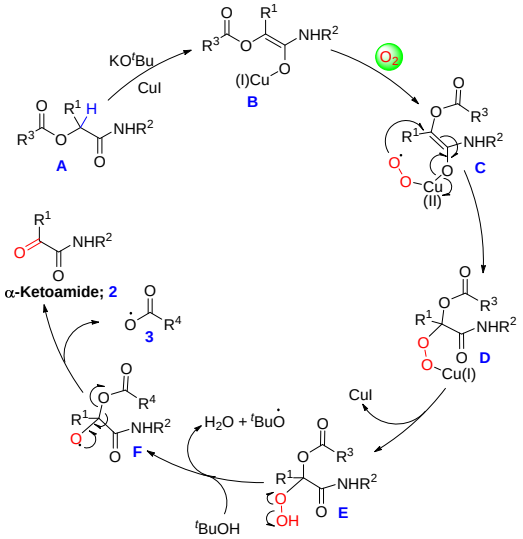
Next, the kinetic isotope effect was studied by performing the oxidative cleavage with deuterated Passerini adduct **D-1d** under the standard reaction conditions (Scheme 2b). K_H/K_D was found to be 3.14 for the formation of α-ketoamide **2d**, reflecting that the proton abstraction is the rate determining step in this reaction (See Supporting Information). Further, to rule out the possibility of ester hydrolysis and alcohol oxidation, we prepared the ^{18}O-labeled Passerini adduct **^{18}O-1b** (m/z = 318.1717) by reacting ^{18}O-labeled benzoic acid[9] and ^{18}O-labeled benzaldehyde.[10] When the Passerini adduct **^{18}O-1b** was subjected to the standard reaction conditions, it yielded predominantly the ^{18}O-labeled α-ketoamide **^{18}O-2b** and corresponding acid **^{18}O-2b'** in 27% and 38% yields respectively (Scheme 2c). HRMS analysis revealed that the α-ketoamide **^{18}O-2b** (having only C-1 oxygen labeled) has m/z = 208.1217, while the ^{18}O-labeled benzoic acid has m/z = 127.9792 (See Supporting Information). This confirms that the oxygen at C-2 position of the α-ketoamide **^{18}O-2b** is coming from molecular oxygen (Scheme 2c). Notably, this experiment also confirmed the incorporation of only one ^{16}O oxygen atom in the α-ketoamide as there was negligible formation of **2b** in the reaction.[11]

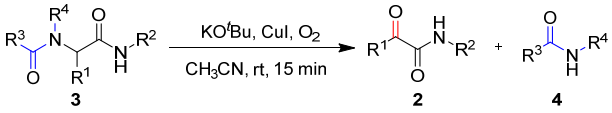
Considering the observations from above experiments and previous literature reports,[11,12] the oxidative cleavage of Passerini adducts can be explained by a putative reaction mechanism as depicted in Scheme 3. Passerini adduct **A** might undergo enolization in presence of base which might be trapped by Cu(I) to form intermediate **B**. Intermediate **B** could be oxidized to superoxide radical **C** through radical pathway in presence of molecular oxygen. Radical species rearranges to form intermediate **D**, which then forms peroxide intermediate **E** by regeneration of CuI. Peroxide intermediate **E** then undergoes homolytic cleavage with elimination of water and *tert*-butoxide radical to form intermediate **F**. Subsequent elimination of acetate radical **3** affords α-ketoamide **2** and corresponding acid.



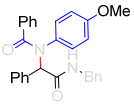
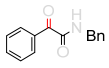
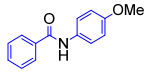
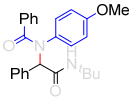
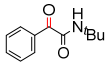
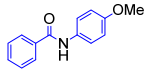
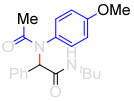
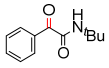
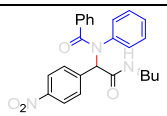
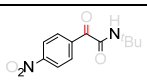
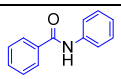
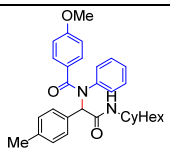
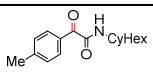
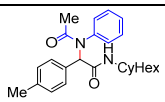
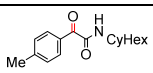
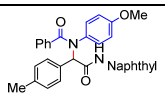
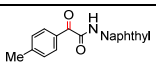
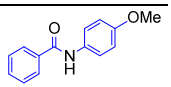
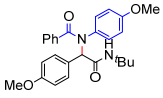
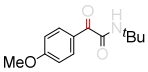
Scheme 3. Proposed reaction mechanism.

In order to extend the scope of this methodology, the Ugi adduct **3a** was reacted under the standard reaction conditions. Although formation of the α-ketoamide **2a** was observed on TLC, the conversion was very low. Subsequent screening of different reaction conditions revealed that KO^{t}Bu (3.0 equiv) and CuI (20 mol %) in CH_3CN provided the best condition for the formation of α-ketoamide and amide from the corresponding Ugi adduct (See Supporting Information for optimization table).

Table 3. Oxidative cleavage of Ugi adducts[a]



3 2 4

Entry	Ugi adduct	2; yield (%)[b]	4; yield (%)[b]
1.	 **3a**	 **2a**; 81%	 **4a**; 53%
2.	 **3b**	 **2b**; 60%	 **4a**; 75%
3.	 **3c**	 **2b**; 78%	----[#]
4.	 **3d**	 **2n**; 35%	 **4b**; 70%
5.	 **3e**	 **2c**; 50%	----[#]
6.	 **3f**	 **2c**; 74%	----[#]
7.	 **3g**	 **2o**; 45%	 **4a**; 44%
8.	 **3h**	 **2d**; 83%	 **4a**; 48%

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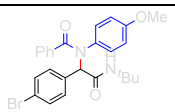
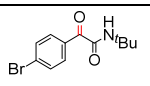
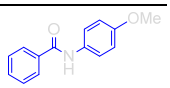
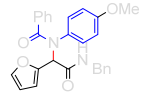
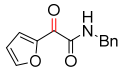
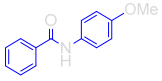
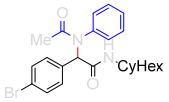
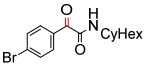
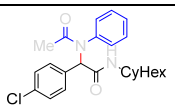
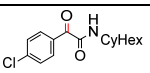
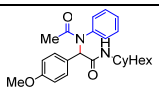
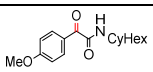
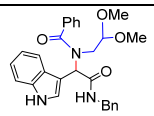
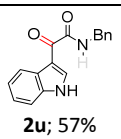
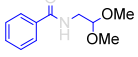
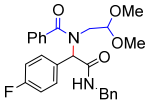
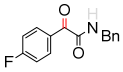
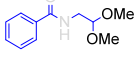
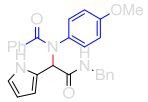
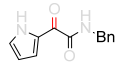
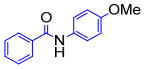
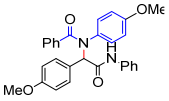
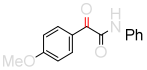
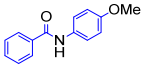
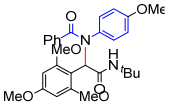
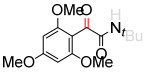
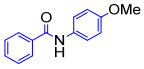
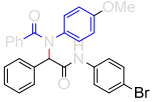
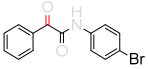
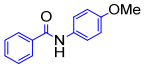
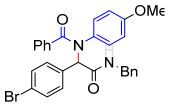
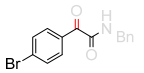
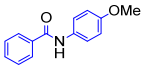
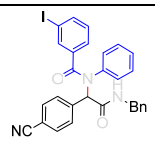
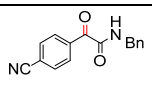
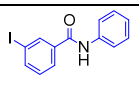
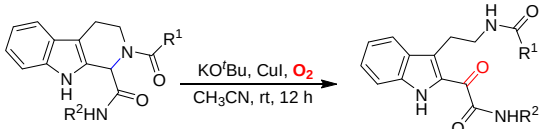
9.	 **3i**	 **2p**; 78%	 **4a**; 69%
10.	 **3j**	 **2q**; 75%	 **4a**; 49%
11.	 **3k**	 **2r**; 50%	----#
12.	 **3l**	 **2s**; 79%	----#
13.	 **3m**	 **2t**; 84%	----#
14.	 **3n**	 **2u**; 57%	 **4c**; 43%
15.	 **3o**	 **2v**; 65%	 **4c**; 60%
16.	 **3p**	 **2w**; 75%	 **4a**; 49%
17.	 **3q**	 **2x**; 87%	 **4a**; 65%
18.	 **3r**	 **2y**; 65%	 **4a**; 74%
19.	 **3s**	 **2e**; 76%	 **4a**; 45%
20.	 **3t**	 **2z**; 79%	 **4a**; 58%
21.	 **3u**	 **2aa**; 60%	 **4d**; 67%

[a]Reaction Conditions: **3** (0.2 mmol), KO^{t}Bu (0.6 mmol), CuI (20 mol %) in CH_3CN (5.0 mL) for 15 min at rt under oxygen balloon. [b]Isolated yields. [#]Complex mixture.

To explore the generality of the oxidative cleavage, a wide variety of Ugi adducts were reacted under the optimized reaction conditions (Table 3). It was observed that the reaction worked well with both the aromatic and heteroaromatic aldehyde derived Ugi adducts. The Ugi adducts with R^1 as electron rich aromatic groups (entries 5, 6, 8, 13, 17, 18; Table 3) reacted well in comparison to the electron deficient aromatic groups (entries 4, 9, 11, 12, 15, 20, 21; Table 3). It was interesting to note that the Ugi adducts with R^1 as heteroaromatic groups such as furyl, indolyl and pyrolyl underwent smooth transformation yielding the corresponding α-ketoamides in good yields (entries 10, 14, 16; Table 3). The Ugi adducts with R^2 as ^{t}Bu, CyHex, Bn, Ph and 4-Br-C_6H_4 reacted well except with the naphthyl group yielding the corresponding α-ketoamide **2o** in 45% yield (entry 7, Table 3). Notably, the Ugi adducts with R^3 as phenyl and methyl were found to be suitable for the oxidative cleavage. However, in the cases with R^3 as methyl, corresponding amides could not be isolated and formation of a complex mixture was observed (entries 3, 6, 11-13; Table 3). Both the aromatic and aliphatic groups at R^4 were well tolerated for the oxidative cleavage.

Next, the cyclic imine derived Ugi adducts **5a-c** were subjected to the standard reaction conditions (Scheme 4). Interestingly, the smooth ring cleavage was observed leading to the formation of corresponding α-ketoamides **6a-c** in reasonably good yields (Scheme 4). The complete conversion of **5** took longer reaction time of 12 h, with formation of corresponding α-ketoamide **6c** in 29% yield.



5a: R^1= Ph, R^2= ^{t}Bu
5b: R^1= Ph, R^2= CyHex
5c: R^1= Me, R^2= CyHex

6a; 63%
6b; 51%
6c; 29%

Scheme 4. Oxidative cleavage of cyclic U-3CR adducts. Reaction Conditions: **5** (0.2 mmol), KO^{t}Bu (0.6 mmol), CuI (20 mol %) in CH_3CN (5.0 mL) for 12 h at rt under oxygen balloon. Isolated yields.

Surprisingly, the dihydroisoquinoline derived Ugi adduct **7** did not undergo the oxidative ring opening, rather a mixture of deacylated dihydroisoquinoline **8** and isoquinoline **9** were obtained (Scheme 5). This might have happened predominantly due to the thermodynamic stability of DHIQ **8** and isoquinoline **9**. A putative mechanism has been given wherein the hydroxyl group at C1 in intermediate **C** might have migrated to the amide carbonyl leading to the formation of

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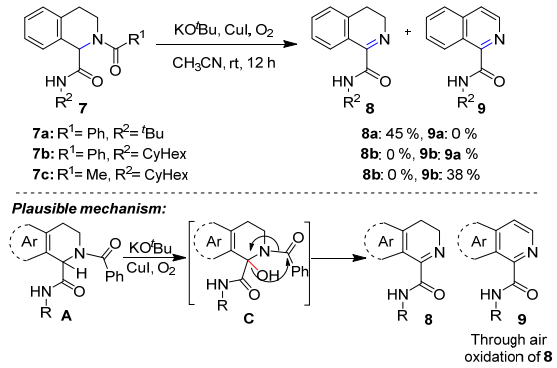
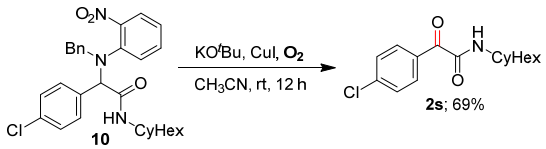
dihydroisoquinoline **8**. Air oxidation of **8** would have generated the isoquinoline **9** (Scheme 5).



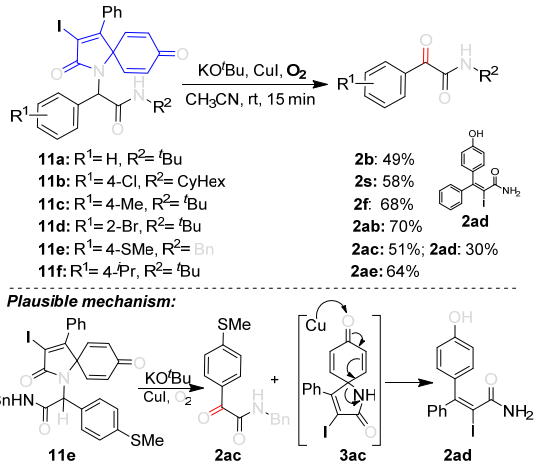
Scheme 5. Unexpected formation of deacylated dihydroisoquinoline and isoquinoline from THIQ-derived Ugi adducts. Reaction Conditions: **7** (0.2 mmol), KO^{t}Bu (0.6 mmol), CuI (20 mol %) in CH_3CN (5.0 mL) for 12 h at rt under oxygen balloon. Isolated yields.

In another effort to see the applicability of this oxidative cleavage, the Ugi-Smile adduct **10** was reacted under standard conditions (Scheme 6). Adduct **10** underwent smooth cleavage affording the α-ketoamide **2s** in 69% yield.



Scheme 6. Aerobic oxidative cleavage of Ugi-Smile adduct **10.** Reaction Conditions: **10** (0.2 mmol), KO^{t}Bu (0.6 mmol), CuI (20 mol %) in CH_3CN (5.0 mL) for 12 h at rt under oxygen balloon. Isolated yields.

We further investigated the scope of the oxidative cleavage in azaspirotrienone containing Ugi adducts **11a-f**, that were readily available in our lab through our reported one-pot procedure.[6b] The reaction proceeded well and clean formation of the corresponding α-ketoamides were observed in good yields (Scheme 7). Formation of a byproduct **2ad** was noticed with all the substrates, but the characterizable quantity of **2ad** could be isolated only with **11e**. Structure of **2ad** was established on the basis of ^{1}H-, ^{13}C-NMR and Mass data. It can be postulated that the ring cleavage of amide **3ac** might have happened in the presence of copper leading to the formation of **2ad** as shown in the plausible mechanism (Scheme 7).[13]



Scheme 7. Aerobic oxidative cleavage of azaspirotrienone containing Ugi-type adducts. Reaction Conditions: **11** (0.2 mmol), KO^{t}Bu (0.6 mmol), CuI (20 mol %) in CH_3CN (5.0 mL) for 15 min at rt under oxygen balloon. Isolated yields.

Conclusion

In conclusion, the present study provides an insight into the reactivity of Passerini and Ugi adducts in strong basic conditions resulting in the formation of α-ketoamides. A detailed mechanistic investigation established the role of copper and confirmed the incorporation of single oxygen atom in the product from molecular oxygen. This method is general and tolerates a variety of functionalities making it suitable for a diverse set of Passerini and Ugi adducts. The present study would be of great importance in designing novel post-functionalization of Passerini and Ugi adducts.

Experimental Section

A. General Information. All the reagents and solvents were used as received from commercial sources without further purification. All air and moisture sensitive reactions were conducted under inert atmosphere of nitrogen. Reactions were monitored by thin-layer chromatography carried out on silica plates (Silica gel 60 F_{254}, Merck) using uv-light, iodine, ninhydrin and *p*-anisaldehyde for visualization. Column chromatography was carried out using silica gel (100-200 and 230-400 mesh) packed in glass columns. Technical grade ethyl acetate and petroleum ether used for column chromatography were distilled prior to use. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 as solvent (300 and 75 MHz / 400 and 100 MHz / 500 and 125 MHz) at ambient temperature. The coupling constant *J* is given in Hz. The chemical shifts (δ) are reported in ppm on scale downfield from TMS and using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 ppm and C: δ = 77.00 ppm) or TMS (δ = 0.00) as internal standard and signal patterns are indicated as follows: s = singlet, d = doublet, dd = doublet of doublet, ddd = doublet of doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Exactive ORBITRAP

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spectrometer using H_2O/MeOH mixed with 0.1% formic acid as mobile phase. All the known compounds were in accordance with the data reported in the literatures.

B. Experimental Procedures

I. General Procedure for the synthesis of Passerini adducts 1a-l. Equimolar mixture of aldehyde (1.0 equiv, 0.8 mmol), acid (1.0 equiv, 0.8 mmol) and isocyanide (1.0 equiv, 0.8 mmol) in water was stirred at room temperature for 6 h. After completion of the reaction (based on TLC), reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. Aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate followed by evaporation of solvent *in vacuo*. The crude was purified by silica gel column chromatography to afford the desired product **1**.

2-(benzylamino)-2-oxo-1-phenylethyl benzoate (1a). White solid (200.0 mg, 72%); m.p: 84 °C, R_f = 0.35 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (dd, J = 1.8, 1.2 Hz, 1H), 8.07 (t, J = 1.7 Hz, 1H), 7.62 – 7.53 (m, 3H), 7.48 – 7.37 (m, 5H), 7.31 – 7.24 (m, 3H), 7.24 – 7.18 (m, 2H), 6.50 (s, 1H), 6.37 (s, 1H), 4.58 – 4.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 165.0, 137.7, 135.5, 133.6, 129.8, 129.2, 129.0, 128.8, 128.7, 128.6, 127.5, 127.5, 127.3, 75.9, 43.3; HRMS (ESI): calcd. for $C_{22}H_{20}NO_3$ $[M+H]^+$: 346.1443, found: 346.1431.

2-(tert-butylamino)-2-oxo-1-phenylethyl benzoate (1b). White solid (205.0 mg, 82%); m.p: 148 °C; R_f = 0.32 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.06 (m, 2H), 7.63 – 7.58 (m, 1H), 7.54 – 7.46 (m, 4H), 7.42 – 7.33 (m, 3H), 6.22 (s, 1H), 5.98 (s, 1H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.3, 164.9, 135.9, 133.6, 129.7, 129.4, 128.9, 128.8, 128.6, 127.4, 76.0, 51.6, 28.7; HRMS (ESI): calcd. for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1600, found: 312.1591.

2-(cyclohexylamino)-2-oxo-1-(p-tolyl)ethyl acetate (1c). White solid (256.0 mg, 81%); m.p: 153 °C; R_f = 0.36 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.96 (m, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.28 (s, 1H), 7.18 (d, J = 7.9 Hz, 1H), 6.26 (s, 1H), 6.10 – 5.97 (m, 1H), 3.87 – 3.77 (m, 1H), 2.42 (s, 3H), 2.34 (s, 3H), 1.97 – 1.86 (m, 2H), 1.68 (ddd, J = 17.2, 8.8, 4.7 Hz, 2H), 1.35 (m, 2H), 1.15 (tdd, J = 27.3, 11.7, 3.6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 164.9, 144.3, 138.7, 132.9, 129.8, 129.4, 129.3, 127.4, 126.7, 75.7, 48.1, 32.9, 32.8, 25.4, 24.7, 24.6, 21.7, 21.2; HRMS (ESI): calcd. for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1756, found: 290.1750.

2-(tert-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl benzoate (1d). White solid (212.0 mg, 77%); m.p: 145 °C; R_f = 0.30 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 – 8.01 (m, 2H), 7.62 – 7.57 (m, 1H), 7.45 (ddd, J = 9.4, 6.4, 2.2 Hz, 4H), 6.97 – 6.85 (m, 2H), 6.17 (s, 1H), 5.96 (s, 1H), 3.80 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 164.9, 160.0, 133.5, 129.7, 129.5, 129.0, 128.6, 128.1, 114.2, 75.7, 55.3, 51.5, 28.7; HRMS (ESI): calcd. for $C_{20}H_{23}NNaO_4$ $[M+Na]^+$: 364.1525, found: 364.1526.

2-(tert-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl acetate (1e). Yellow solid (156.0 mg, 69%); m.p: 129 °C; R_f = 0.32 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.32 (m, 2H), 6.90 – 6.87 (m, 2H), 6.00 (s, 1H), 5.91 (s, 1H), 3.79 (s, 3H), 2.15 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 167.6, 163.2, 160.7, 159.9, 128.9, 127.9, 114.0, 75.2, 55.2, 51.4, 28.7, 28.5, 20.9; HRMS (ESI): calcd. for $C_{15}H_{22}NO_4$ $[M+H]^+$: 280.1549, found: 280.1555.

2-((4-bromophenyl)amino)-2-oxo-1-phenylethyl benzoate (1f). Yellow solid (200.0 mg, 60%); m.p: 142 °C; R_f = 0.38 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 – 8.12 (m, 2H), 7.91 (s, 1H), 7.66 – 7.59 (m, 3H), 7.51 (t, J = 7.7 Hz, 2H), 7.45 – 7.40 (m, 7H), 6.43 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.4, 165.2, 136.0, 134.8, 133.9, 131.9, 129.9, 129.4, 129.0, 128.7, 127.5, 121.6, 117.5, 76.1; HRMS (ESI): calcd. for $C_{21}H_{17}BrNO_3$ $[M+H]^+$: 410.0392, found: 410.0385.

2-(tert-butylamino)-2-oxo-1-(p-tolyl)ethyl acetate (1g). White solid (176.0 mg, 82%); m.p: 138 °C; R_f = 0.35 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 5.92 (s, 1H), 5.89 (s, 1H), 2.34 (s, 3H), 2.15 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 167.5, 138.7, 132.9, 129.4, 127.4, 75.5, 51.5, 28.6, 21.2, 21.0; HRMS (ESI): calcd. for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1600, found: 264.1595.

2-(naphthalen-1-ylamino)-2-oxo-1-phenylethyl benzoate (1h). White solid (220.0 mg, 72%); m.p: 170 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.21 (d, J = 7.3 Hz, 2H), 7.98 (d, J = 7.1 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 6.5 Hz, 3H), 7.65 (t, J = 10.4 Hz, 2H), 7.52 (t, J = 7.2 Hz, 2H), 7.48 – 7.42 (m, 6H), 6.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 165.0, 135.3, 134.0, 133.8, 131.2, 129.9, 129.3, 129.1, 129.0, 128.81, 128.7, 127.5, 126.5, 126.2, 125.9, 125.7, 120.7, 120.0, 76.4; HRMS (ESI): calcd. for $C_{25}H_{20}NO_3$ $[M+H]^+$: 382.1443, found: 382.1444.

2-oxo-1-phenyl-2-(phenylamino)ethyl benzoate (1i). Yellow solid (200.0 mg, 75%); m.p: 177 °C; R_f = 0.30 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 – 8.15 (m, 1H), 8.14 (d, J = 1.4 Hz, 1H), 7.88 (s, 1H), 7.66 – 7.60 (m, 3H), 7.50 (dd, J = 10.8, 4.6 Hz, 4H), 7.45 – 7.38 (m, 3H), 7.33 – 7.28 (m, 2H), 7.12 (t, J = 7.4 Hz, 1H), 6.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 165.0, 136.9, 135.1, 133.8, 129.9, 129.2, 129.1, 129.0, 128.9, 128.7, 127.5, 124.9, 120.1, 76.1; HRMS (ESI): calcd. for $C_{21}H_{18}NO_3$ $[M+H]^+$: 332.1287, found: 332.1284.

2-(tert-butylamino)-1-(4-cyanophenyl)-2-oxoethyl benzoate (1j). White solid (216.0 mg, 80%); m.p: 150 °C; R_f = 0.45 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 8.07 (t, J = 1.7 Hz, 1H), 7.68 – 7.65 (m, 4H), 7.55 – 7.47 (m, 3H), 6.25 (s, 1H), 6.15 (s, 1H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 164.5, 140.9, 134.0, 133.6, 132.5, 130.1, 129.7, 128.8, 128.7, 128.4, 127.9, 118.4, 112.7, 75.1, 51.9, 28.6; HRMS (ESI): calcd. for $C_{20}H_{21}N_2O_3$ $[M+H]^+$: 337.1552, found: 337.1556.

2-(cyclohexylamino)-1-(naphthalen-1-yl)-2-oxoethyl benzoate (1k). White solid (275.0 mg, 70%); m.p: 140 °C; R_f = 0.30 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 8.3 Hz, 1H), 8.14 – 8.01 (m, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 7.0 Hz, 1H), 7.52 (ddt, J = 22.2, 15.1, 6.4 Hz, 6H), 6.97 (s, 1H), 5.89 (d, J = 8.0 Hz, 1H), 3.85 (dtt, J = 12.1, 8.1, 3.9 Hz, 1H), 1.94 (d, J = 9.2 Hz, 1H), 1.88 – 1.76 (m, 1H), 1.67 (d, J = 4.0 Hz, 1H), 1.56 (s, 2H), 1.39 – 1.21 (m, 2H), 1.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 165.3, 134.1, 133.5, 131.6, 131.4, 130.1, 129.9, 129.4, 128.8, 128.5, 127.3, 126.9, 126.1, 125.1, 123.9,

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74.2, 48.4, 32.8, 32.7, 25.4, 24.7, 24.6; HRMS (ESI): calcd. for $C_{25}H_{26}NO_3$ $[M+H]^+$: 388.1913, found: 388.1888.

1-(cyclohexylamino)-1-oxo-3-phenylpropan-2-yl acetate (1l). White solid (216.0 mg, 68%); m.p: 82 °C; R_f = 0.30 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.24 (m, 3H), 7.23 – 7.15 (m, 2H), 5.68 (d, *J* = 7.6 Hz, 1H), 5.34 (t, *J* = 5.8 Hz, 1H), 3.75 (ttd, *J* = 12.2, 8.2, 3.9 Hz, 1H), 3.27 – 3.11 (m, 2H), 2.10 (s, 3H), 1.86 – 1.75 (m, 2H), 1.64 (dd, *J* = 9.6, 3.7 Hz, 2H), 1.43 – 1.26 (m, 3H), 1.14 (ddd, *J* = 14.8, 8.1, 3.7 Hz, 1H), 1.02 (ddd, *J* = 15.1, 7.2, 3.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 167.7, 135.8, 129.6, 128.3, 126.8, 74.3, 47.8, 37.6, 32.8, 32.7, 25.4, 24.7, 24.6, 20.9; HRMS (ESI): calcd. for $C_{17}H_{24}NO_3$ $[M+H]^+$: 290.1756, found: 290.1745.

1-(benzylamino)-1-oxo-3-phenylpropan-2-yl benzoate (1m). White solid (200.0 mg, 70%), m.p: 122 °C; R_f = 0.30 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 – 7.92 (m, 2H), 7.62 – 7.53 (m, 1H), 7.48 – 7.38 (m, 2H), 7.30 – 7.21 (m, 8H), 7.14 – 6.97 (m, 2H), 6.21 (s, 1H), 5.70 (t, *J* = 5.6 Hz, 1H), 4.48 (dd, *J* = 15.0, 6.2 Hz, 1H), 4.35 (dd, *J* = 15.0, 5.6 Hz, 1H), 3.35 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 165.2, 137.5, 135.8, 133.6, 129.8, 129.7, 129.1, 128.6, 128.4, 127.4, 126.9, 74.8, 43.1, 37.8; HRMS (ESI): calcd. for $C_{23}H_{22}NO_3$ $[M+H]^+$: 360.1600, found: 360.1600.

1-cyclohexyl-2-oxo-2-(phenylamino)ethyl benzoate (1n). White solid (100.0 mg, 37%), m.p: 102 °C; R_f = 0.30 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (dd, *J* = 1.9, 1.2 Hz, 1H), 8.12 (t, *J* = 1.7 Hz, 1H), 7.74 (s, 1H), 7.68 – 7.62 (m, 1H), 7.56 – 7.48 (m, 4H), 7.35 – 7.27 (m, 2H), 7.12 (ddd, *J* = 8.5, 2.2, 1.1 Hz, 1H), 5.41 (d, *J* = 4.7 Hz, 1H), 2.29 – 2.15 (m, 1H), 1.90 – 1.75 (m, 4H), 1.69 (d, *J* = 12.1 Hz, 1H), 1.38 – 1.23 (m, 3H), 1.23 – 1.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 165.4, 136.8, 133.7, 129.8, 129.2, 128.9, 128.8, 124.8, 120.2, 78.4, 40.4, 29.3, 27.5, 26.0, 25.9, 25.9; HRMS (ESI): calcd. for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1756, found: 338.1747.

II. General procedure for the oxidative cleavage of Passerini adducts 1a-n. To the solution of **1** (1.0 equiv, 0.2 mmol) in dry THF was added KO^{t}Bu (3.0 equiv, 0.6 mmol) and CuI (0.2 equiv, 20 mol %) at room temperature and the reaction vessel was flushed with O_2. The resulting reaction mixture was stirred at room temperature. After completion of the reaction (based on TLC) in 10 minutes, the reaction mixture was quenched with water and the crude product was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo* and the crude was purified by silica gel column chromatography to afford the desired α-ketoamide **2**.

N-benzyl-2-oxo-2-phenylacetamide (2a)[4c]. White solid (39.0 mg, 81%); m.p: 96 °C; R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.66 – 7.60 (m, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.44 – 7.27 (m, 6H), 4.58 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.5, 161.5, 137.1, 134.4, 133.3, 131.2, 128.8, 128.5, 127.9, 127.8, 43.5; HRMS (ESI): calcd. for $C_{15}H_{14}NO_2$ $[M+H]^+$: 240.1025, found: 240.1017.

N-(tert-butyl)-2-oxo-2-phenylacetamide (2b)[4d]. Yellow solid (24.7 mg, 60%); m.p: 77 °C; R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.30 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 6.92 (s, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5, 161.1, 134.1, 133.4, 131.2, 128.3, 51.6, 28.3; HRMS (ESI): calcd. for $C_{12}H_{16}NO_2$ $[M+H]^+$: 206.1181, found: 206.1169.

N-cyclohexyl-2-oxo-2-(p-tolyl)acetamide (2c)[14]. Yellow sticky solid (24.6 mg, 50%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 – 8.19 (m, 2H), 7.29 (s, 1H), 7.26 (s, 1H), 6.95 (s, 1H), 3.92 – 3.78 (m, 1H), 2.42 (s, 3H), 2.04 – 1.92 (m, 2H), 1.82 – 1.71 (m, 2H), 1.70 – 1.61 (m, 1H), 1.50 – 1.38 (m, 2H), 1.38 – 1.27 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.6, 161.1, 145.5, 131.4, 130.9, 129.2, 48.4, 32.7, 25.4, 24.7, 21.9; HRMS (ESI): calcd. for $C_{15}H_{20}NO_2$ $[M+H]^+$: 246.1494, found: 246.1487.

N-(tert-butyl)-2-(4-methoxyphenyl)-2-oxoacetamide (2d)[14]. Yellow solid (39.1 mg, 83%); m.p: 61 °C; R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 – 8.35 (m, 2H), 6.97 (s, 1H), 6.96 – 6.91 (m, 2H), 3.88 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.6, 164.5, 161.7, 133.9, 126.4, 113.7, 55.5, 51.5; HRMS (ESI): calcd. for $C_{13}H_{18}NO_3$ $[M+H]^+$: 236.1287, found: 236.1278.

N-(4-bromophenyl)-2-oxo-2-phenylacetamide (2e)[15]. Yellow sticky solid (46.3 mg, 76%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (s, 1H), 8.44 – 8.38 (m, 2H), 7.69 – 7.65 (m, 1H), 7.63 – 7.59 (m, 2H), 7.55 – 7.49 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.0, 158.8, 135.7, 134.8, 132.9, 132.2, 131.5, 128.6, 121.4, 118.1; HRMS (ESI): calcd. for $C_{14}H_{11}BrNO_2$ $[M+H]^+$: 303.9973, found: 303.9964.

N-(tert-butyl)-2-oxo-2-(p-tolyl)acetamide (2f)[4c]. Yellow oil (29.9 mg, 68%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.3 Hz, 2H), 7.28 – 7.25 (m, 2H), 6.93 (s, 1H), 2.42 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 161.4, 145.3, 131.4, 130.9, 129.1, 51.6, 28.4, 28.2, 21.8; HRMS (ESI): calcd. for $C_{13}H_{18}NO_2$ $[M+H]^+$: 220.1338, found: 220.1331.

N-(naphthalen-1-yl)-2-oxo-2-phenylacetamide (2g)[16]. Yellow oil (15.5 mg, 28%); R_f = 0.69 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.55 (s, 1H), 8.50 (d, *J* = 7.6 Hz, 2H), 8.25 (d, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.69 (t, *J* = 7.3 Hz, 1H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 6.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.5, 159.3, 134.7, 134.1, 133.2, 131.6, 131.1, 128.9, 128.6, 126.7, 126.5, 126.3, 125.7, 120.2, 119.5; HRMS (ESI): calcd. for $C_{18}H_{14}NO_2$ $[M+H]^+$: 276.1025, found: 276.1023.

2-oxo-N,2-diphenylacetamide ***(2h)***[17]. Yellow oil (20.2 mg, 45%); R_f = 0.67 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 8.43 (d, *J* = 7.4 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.4, 158.9, 136.7, 134.6, 133.1, 131.5, 129.2, 128.6, 125.3, 119.9; HRMS (ESI): calcd. for $C_{14}H_{12}NO_2$ $[M+H]^+$: 226.0868, found: 226.0863.

N-(tert-butyl)-2-(4-cyanophenyl)-2-oxoacetamide (2i)[18]. Yellow solid (22.6 mg, 49%); m.p: 120 °C; R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (d, *J* = 1.8 Hz, 1H), 8.41 (d, *J* = 1.8 Hz, 1H), 7.77 (d, *J* = 1.8 Hz, 1H), 7.75 (d, *J* = 1.8 Hz, 1H), 6.96 (s, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.1, 159.9, 136.6, 132.0, 131.6, 117.9, 117.1, 51.9, 28.3; HRMS (ESI): calcd. for $C_{13}H_{15}N_2O_2$ $[M+H]^+$: 231.1134, found: 231.1127.

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***N*-cyclohexyl-2-(naphthalen-2-yl)-2-oxoacetamide (2j)**. White sticky solid (41.9 mg, 55%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, J = 8.5 Hz, 1H), 8.30 (dd, J = 7.3, 1.2 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.92 – 7.87 (m, 1H), 7.62 (ddd, J = 8.5, 6.9, 1.6 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.06 (s, 1H), 3.98 – 3.83 (m, 1H), 2.05 (dd, J = 9.4, 5.2 Hz, 2H), 1.85 – 1.75 (m, 2H), 1.49 – 1.41 (m, 2H), 1.40 – 1.33 (m, 3H), 1.31 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.9, 161.2, 134.4, 133.9, 133.0, 131.2, 129.9, 128.7, 128.3, 126.5, 125.3, 124.2, 48.7, 32.8, 25.4, 24.8; HRMS (ESI): calcd. for $C_{18}H_{20}NO_2$ $[M+H]^+$: 282.1494, found: 282.1482.

***N*-cyclohexyl-2-oxo-3-phenylpropanamide (2k)**. White sticky solid (13.5 mg, 28%); R_f = 0.75 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.30 (m, 2H), 7.29 – 7.24 (m, 3H), 6.81 (s, 1H), 4.22 (s, 2H), 3.74 (tdd, J = 8.6, 7.5, 4.2 Hz, 1H), 1.93 – 1.87 (m, 2H), 1.76 – 1.69 (m, 2H), 1.38 (dd, J = 10.0, 6.7 Hz, 2H), 1.23 – 1.13 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 158.9, 132.9, 129.8, 128.6, 127.2, 48.5, 43.1, 32.6, 25.3, 24.7; HRMS (ESI): calcd. for $C_{15}H_{19}NNaO_2$ $[M+Na]^+$: 268.1313, found: 268.1299.

***N*-cyclohexyl-2-hydroxy-3-phenylpropanamide (2k')**. White solid (11.5 mg, 23%), m.p: 82 °C; R_f = 0.30 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 – 7.23 (m, 5H), 6.24 (d, J = 6.8 Hz, 1H), 4.28 (dt, J = 7.9, 4.7 Hz, 1H), 3.77 (tdt, J = 12.3, 8.2, 3.9 Hz, 1H), 3.21 (dd, J = 13.9, 4.6 Hz, 1H), 2.95 (dd, J = 13.9, 7.8 Hz, 1H), 2.60 (d, J = 4.9 Hz, 1H), 1.85 (dd, J = 14.3, 6.3 Hz, 2H), 1.71 (d, J = 3.9 Hz, 1H), 1.60 (d, J = 3.8 Hz, 1H), 1.48 – 1.23 (m, 3H), 1.23 – 1.00 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 136.8, 129.6, 128.6, 126.9, 72.6, 47.8, 40.9, 32.9, 32.9, 25.4, 24.7, 24.6; HRMS (ESI): calcd. for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651, found: 248.1640.

***N*-benzyl-2-hydroxy-3-phenylpropanamide (2l')**[19]. White solid (27.0 mg, 53%), m.p: 104 °C; R_f = 0.30 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.14 (m, 10H), 6.82 (s, 1H), 4.49 – 4.29 (m, 3H), 3.23 (dd, J = 13.9, 4.1 Hz, 1H), 2.92 (dd, J = 13.9, 8.1 Hz, 1H), 2.78 (d, J = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 137.8, 136.7, 129.6, 128.7, 128.6, 127.7, 127.5, 126.9, 72.9, 43.1, 40.8; HRMS (ESI): calcd. for $C_{16}H_{18}NO_2$ $[M+H]^+$: 256.1338, found: 256.1333.

***2*-cyclohexyl-2-hydroxy-*N*-phenylacetamide (2m')**[20]. White solid (33.5 mg, 72%), m.p: 150 °C; R_f = 0.30 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.59 (dt, J = 8.7, 1.7 Hz, 2H), 7.40 – 7.31 (m, 2H), 7.19 – 7.09 (m, 1H), 4.10 (dd, J = 5.0, 3.2 Hz, 1H), 2.81 (d, J = 5.0 Hz, 1H), 1.97 (tt, J = 11.8, 3.3 Hz, 1H), 1.79 (dd, J = 12.0, 9.2 Hz, 3H), 1.62 (dd, J = 14.5, 9.9 Hz, 2H), 1.38 – 1.14 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 137.2, 129.0, 124.5, 119.8, 76.7, 41.8, 29.6, 26.3, 26.0, 25.9; HRMS (ESI): calcd. for $C_{14}H_{20}NO_2$ $[M+H]^+$: 234.1494, found: 234.1490.

***N*-(tert-butyl)-2-(4-nitrophenyl)-2-oxoacetamide (2n)**[21]. Yellow solid (17.6 mg, 35%); m.p: 88 °C; R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 – 8.47 (m, 2H), 8.32 – 8.27 (m, 2H), 6.98 (s, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.9, 159.8, 150.7, 138.1, 132.4, 123.3, 52.0, 28.3; HRMS (ESI): calcd. for $C_{12}H_{15}N_2O_4$ $[M+H]^+$: 251.1032, found: 251.1026.

***N*-(naphthalen-1-yl)-2-oxo-2-(p-tolyl)acetamide (2o)**. Yellow oil (26.2 mg, 45%); R_f = 0.75 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.43 (d, J = 8.3 Hz, 2H), 8.24 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.62 – 7.52 (m, 3H), 7.34 (d, J = 8.1 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.9, 159.5, 146.1, 134.1, 131.8, 131.2, 130.7, 129.4, 128.9, 126.7, 126.5, 126.3, 126.2, 125.7, 120.2, 119.4, 21.9; HRMS (ESI): calcd. for $C_{19}H_{16}NO_2$ $[M+H]^+$: 290.1181, found: 290.1175.

***2*-(4-bromophenyl)-*N*-(tert-butyl)-2-oxoacetamide (2p)**[18]. Yellow oil (44.6 mg, 78%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 – 8.18 (m, 2H), 7.64 – 7.58 (m, 2H), 6.95 (s, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.4, 160.7, 132.8, 132.1, 131.8, 129.8, 51.7, 28.3; HRMS (ESI): calcd. for $C_{12}H_{15}BrNO_2$ $[M+H]^+$: 284.0286, found: 284.0282.

***N*-benzyl-2-(furan-2-yl)-2-oxoacetamide (2q)**[4d]. Light yellow solid (34.4 mg, 75%); m.p: 95 °C; R_f = 0.69 (20% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (d, J = 0.6 Hz, 1H), 7.54 (s, 1H), 7.46 (t, J = 1.4 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.33 – 7.30 (m, 3H), 6.90 (d, J = 1.9 Hz, 1H), 4.54 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.6, 160.3, 153.5, 143.6, 136.9, 128.9, 127.9, 127.8, 122.7, 109.2, 43.4; HRMS (ESI): calcd. for $C_{13}H_{12}NO_3$ $[M+H]^+$: 230.0817, found: 230.0810.

***2*-(4-bromophenyl)-*N*-cyclohexyl-2-oxoacetamide (2r)**. White solid (31.1 mg, 50%); m.p: 105 °C; R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 – 8.22 (m, 2H), 7.65 – 7.59 (m, 2H), 6.99 (s, 1H), 3.91 – 3.76 (m, 1H), 1.98 (dd, J = 12.2, 3.2 Hz, 2H), 1.82 – 1.72 (m, 2H), 1.71 – 1.62 (m, 1H), 1.46 – 1.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.9, 160.4, 132.7, 132.2, 131.8, 129.9, 48.5, 32.7, 25.4, 24.7; HRMS (ESI): calcd. for $C_{14}H_{17}BrNO_2$ $[M+H]^+$: 310.0443, found: 310.0436.

***2*-(4-chlorophenyl)-*N*-cyclohexyl-2-oxoacetamide (2s)**[21]. White solid (42.0 mg, 79%); m.p: 100 °C; R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 – 8.34 (m, 1H), 8.33 – 8.32 (m, 1H), 7.47 – 7.45 (m, 1H), 7.45 – 7.43 (m, 1H), 6.99 (s, 1H), 3.89 – 3.79 (m, 1H), 2.01 – 1.95 (m, 2H), 1.80 – 1.74 (m, 2H), 1.68 – 1.63 (m, 1H), 1.48 – 1.36 (m, 3H), 1.29 (d, J = 3.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.7, 160.4, 141.1, 132.7, 131.8, 128.8, 48.5, 32.7, 25.4, 24.7; HRMS (ESI): calcd. for $C_{14}H_{17}ClNO_2$ $[M+H]^+$: 266.0948, found: 266.0936.

***N*-cyclohexyl-2-(4-methoxyphenyl)-2-oxoacetamide (2t)**[22]. White sticky solid (44.0 mg, 84%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 – 8.41 (m, 1H), 8.41 – 8.39 (m, 1H), 7.02 (d, J = 5.5 Hz, 1H), 6.96 – 6.95 (m, 1H), 6.94 – 6.92 (m, 1H), 3.89 (s, 3H), 3.86 – 3.80 (m, 1H), 2.01 – 1.95 (m, 2H), 1.76 (ddd, J = 10.7, 7.3, 3.6 Hz, 3H), 1.68 – 1.61 (m, 2H), 1.47 – 1.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.0, 164.6, 161.3, 133.9, 126.5, 113.8, 55.5, 48.4, 32.7, 25.4, 24.7; HRMS (ESI): calcd. for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1443, found: 262.1437.

***N*-benzyl-2-(1H-indol-3-yl)-2-oxoacetamide (2u)**. Yellow oil (31.8 mg, 57%); R_f = 0.75 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (d, J = 3.2 Hz, 1H), 8.96 (s, 1H), 8.42 (dd, J = 6.7, 2.3 Hz, 1H), 7.86 (s, 1H), 7.43 (dt, J = 7.4, 3.2 Hz, 1H), 7.39 – 7.28 (m, 7H), 4.58 (d, J = 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.5, 162.3, 138.2, 137.4, 135.7, 128.8, 127.7, 127.7,

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126.6, 124.3, 123.4, 122.5, 113.5, 111.6, 43.4; HRMS (ESI): calcd. for $C_{17}H_{15}N_2O_2$ $[M+H]^+$: 279.1134, found: 279.1129.

N-benzyl-2-(4-fluorophenyl)-2-oxoacetamide (2v)[23]. White solid (33.5 mg, 65%); m.p: 65 °C; R_f = 0.68 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 – 8.42 (m, 2H), 7.46 (s, 1H), 7.39 – 7.29 (m, 5H), 7.18 – 7.12 (m, 2H), 4.56 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 167.9, 165.4, 161.3, 136.9, 134.3, 134.3, 129.8, 129.8, 128.9, 127.9, 115.9, 115.7, 43.5; HRMS (ESI): calcd. for $C_{15}H_{13}FNO_2$ $[M+H]^+$: 258.0930, found: 258.0905.

N-benzyl-2-oxo-2-(1H-pyrrol-2-yl)acetamide (2w). White sticky solid (34.3 mg, 75%); R_f = 0.70 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 – 7.84 (m, 2H), 7.79 (s, 1H), 7.54 (dt, J = 4.9, 2.8 Hz, 3H), 7.50 – 7.45 (m, 2H), 6.93 – 6.91 (m, 1H), 6.90 – 6.88 (m, 1H), 3.81 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 156.6, 135.0, 131.7, 131.0, 128.7, 126.9, 122.1, 114.2, 55.5; HRMS (ESI): calcd. for $C_{13}H_{13}N_2O_2$ $[M+H]^+$: 229.0977, found: 229.1043.

2-(4-methoxyphenyl)-2-oxo-N-phenylacetamide (2x)[17]. Yellow sticky solid (44.5 mg, 87%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.54 – 8.51 (m, 1H), 8.51 – 8.48 (m, 1H), 7.71 (t, J = 1.6 Hz, 1H), 7.68 (t, J = 1.6 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.19 (ddd, J = 8.6, 2.3, 1.1 Hz, 1H), 7.01 – 6.98 (m, 1H), 6.98 – 6.95 (m, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.2, 164.9, 159.5, 136.8, 134.3, 129.2, 126.1, 125.2, 119.9, 113.9, 55.6; HRMS (ESI): calcd. for $C_{15}H_{14}NO_3$ $[M+H]^+$: 256.0974, found: 256.0964.

N-(tert-butyl)-2-oxo-2-(2,4,6-trimethoxyphenyl)acetamide (2y). Yellow oil (38.5 mg, 65%); R_f = 0.67 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (s, 2H), 6.98 (s, 1H), 3.95 (s, 3H), 3.92 (s, 6H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.6, 161.3, 152.7, 143.9, 128.3, 108.9, 60.9, 56.3, 51.6, 28.4; HRMS (ESI): calcd. for $C_{15}H_{22}NO_5$ $[M+H]^+$: 296.1498, found: 296.1519.

N-benzyl-2-(4-bromophenyl)-2-oxoacetamide (2z)[24]. Light yellow solid (50.0 mg, 79%); m.p: 114 °C; R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 – 8.26 (m, 2H), 7.65 – 7.62 (m, 2H), 7.43 (s, J = 3.9 Hz, 1H), 7.39 – 7.31 (m, 5H), 4.57 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 161.1, 136.9, 132.8, 132.1, 131.9, 130.2, 128.9, 127.9, 127.9, 43.6; HRMS (ESI): calcd. for $C_{15}H_{13}BrNO_2$ $[M+H]^+$: 318.0130, found: 318.0114.

N-benzyl-2-(4-cyanophenyl)-2-oxoacetamide (2aa). Yellow sticky solid (31.8 mg, 60%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 – 8.44 (m, 2H), 7.81 – 7.78 (m, 1H), 7.77 (t, J = 1.7 Hz, 1H), 7.43 (s, 1H), 7.39 – 7.31 (m, 5H), 4.57 (d, J = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.1, 160.4, 136.7, 136.4, 132.2, 131.6, 128.9, 128.0, 127.9, 117.8, 117.4, 43.6; HRMS (ESI): calcd. for $C_{16}H_{13}N_2O_2$ $[M+H]^+$: 265.0977, found: 265.0999.

2-(2-bromophenyl)-N-(tert-butyl)-2-oxoacetamide (2ab). White solid (39.8 mg, 70%); m.p: 85 °C; R_f = 0.68 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 – 7.57 (m, 2H), 7.42 – 7.34 (m, 2H), 6.84 (s, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.9, 159.5, 136.4, 133.3, 132.7, 130.9, 127.0, 120.7, 51.8, 28.3; HRMS (ESI): calcd. for $C_{12}H_{15}BrNO_2$ $[M+H]^+$: 284.0286, found: 284.0279.

N-benzyl-2-(4-(methylthio)phenyl)-2-oxoacetamide (2ac). Yellow solid (29.2 mg, 51%); m.p: 100 °C; R_f = 0.68 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.37 – 8.29 (m, 2H), 7.44 (s, 1H), 7.39 – 7.29 (m, 5H), 7.28 (d, J = 1.9 Hz, 1H), 7.25 (t, J = 1.6 Hz, 1H), 4.56 (d, J = 6.1 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 186.0, 161.8, 148.3, 137.1, 131.6, 129.5, 128.8, 127.9, 127.8, 124.6, 43.4, 14.6; HRMS (ESI): calcd. for $C_{16}H_{16}NO_2S$ $[M+H]^+$: 286.0902, found: 286.0896.

(E)-3-(4-hydroxyphenyl)-2-iodo-3-phenylacrylamide (2ad). Yellow sticky solid (22.0 mg, 30%); R_f = 0.20 (50% EtOAc in hexane); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.60 (s, 1H), 7.55 (s, 1H), 7.42 – 7.36 (m, 2H), 7.34 – 7.28 (m, 1H), 7.17 (dd, J = 5.1, 3.2 Hz, 2H), 7.08 (s, 1H), 7.05 – 7.03 (m, 1H), 7.02 – 7.00 (m, 1H), 6.67 – 6.60 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.8, 157.3, 148.0, 144.7, 130.2, 130.1, 128.7, 128.3, 127.7, 114.8, 93.2; HRMS (ESI): calcd. for $C_{15}H_{13}INO_2$ $[M+H]^+$: 365.9991, found: 365.9961.

N-(tert-butyl)-2-(4-isopropylphenyl)-2-oxoacetamide (2ae)[4c]. Pale yellow solid (31.7 mg, 64%); m.p: 39 °C; R_f = 0.68 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 – 8.25 (m, 1H), 8.24 – 8.23 (m, 1H), 7.33 (d, J = 1.5 Hz, 1H), 7.31 – 7.29 (m, 1H), 6.92 (s, 1H), 3.04 – 2.89 (m, 1H), 1.45 (s, 9H), 1.28 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.2, 161.4, 155.9, 131.5, 131.2, 126.5, 51.6, 34.4, 28.4, 23.5; HRMS (ESI): calcd. for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651, found: 248.1645.

III. General Procedure for the synthesis of Ugi adducts 3a-u. Equimolar mixture of amine (1.0 equiv, 0.8 mmol), aldehyde (1.0 equiv, 0.8 mmol), acid (1.0 equiv, 0.8 mmol) and isocyanide (1.0 equiv, 0.8 mmol) in methanol (MeOH) was stirred at room temperature for 12 h. After completion of the reaction (based on TLC), MeOH was removed *in vacuo*, reaction mixture was diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. Aqueous layer was extracted with ethyl acetate and the combined organic layers were dried over anhydrous sodium sulfate followed by evaporation of solvent *in vacuo*. The crude was purified by silica gel column chromatography to afford the desired product **3**.

N-(2-(benzylamino)-2-oxo-1-phenylethyl)-N-(4-methoxyphenyl)benzamide (3a). White solid (310.0 mg, 85%); m.p: 155 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 – 7.31 (m, 1H), 7.31 – 7.29 (m, 2H), 7.27 (d, J = 2.4 Hz, 3H), 7.25 – 7.19 (m, 6H), 7.19 – 7.14 (m, 2H), 7.14 – 7.09 (m, 1H), 6.86 (d, J = 8.2 Hz, 2H), 6.50 (dd, J = 7.8, 1.4 Hz, 2H), 6.26 (t, J = 5.5 Hz, 1H), 6.21 (s, 1H), 4.53 (d, J = 5.8 Hz, 2H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 169.6, 158.2, 138.1, 136.1, 134.6, 133.8, 131.4, 130.3, 129.3, 128.6, 128.4, 128.4, 127.6, 127.3, 113.4, 66.5, 55.1, 43.7; HRMS (ESI): calcd. for $C_{29}H_{27}N_2O_3$ $[M+H]^+$: 451.2022, found: 451.1999.

N-(2-(tert-butylamino)-2-oxo-1-phenylethyl)-N-(4-methoxyphenyl)benzamide (3b). White solid (236.0 mg, 70%); m.p: 154 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.29 (m, 2H), 7.26 – 7.19 (m, 5H), 7.19 – 7.10 (m, 3H), 6.88 (d, J = 7.1 Hz, 2H), 6.50 (d, J = 9.1 Hz, 2H), 6.10 (s, 1H), 5.78 (s, 1H), 3.64 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 168.7, 158.1, 136.2, 135.0, 133.8, 131.3, 130.1, 129.1, 128.4, 128.3, 128.2, 127.5, 113.3, 66.7,

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55.1, 51.5, 28.6; HRMS (ESI): calcd. for $C_{26}H_{29}N_2O_3$ $[M+H]^+$: 417.2178, found: 417.2176.

N-(tert-butyl)-2-(N-(4-methoxyphenyl)acetamido)-2-phenylacetamide (3c). White solid (200.0 mg, 70%); m.p: 150 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.01 (m, 7H), 6.68 (s, 2H), 5.97 (s, 1H), 5.56 (s, 1H), 3.74 (s, 3H), 1.85 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 168.9, 158.8, 135.0, 133.3, 131.3, 130.3, 128.2, 128.2, 113.8, 65.1, 55.3, 51.5, 28.6, 23.2; HRMS (ESI): calcd. for $C_{21}H_{27}N_2O_3$ $[M+H]^+$: 355.2022, found: 355.2013.

N-(2-(tert-butylamino)-1-(4-nitrophenyl)-2-oxoethyl)-N-(4-methoxyphenyl)benzamide (3d). Pale yellow oil (280.0 mg 80%); R_f = 0.65 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 8.06 (m, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.18 – 7.12 (m, 2H), 7.07 (dd, *J* = 6.9, 3.0 Hz, 3H), 7.03 – 6.94 (m, 2H), 6.20 (d, *J* = 6.1 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 167.6, 147.6, 142.1, 140.9, 135.2, 130.7, 129.9, 129.7, 128.9, 128.5, 127.8, 127.7, 123.4, 66.4, 51.9, 28.7; HRMS (ESI): calcd. for $C_{25}H_{26}N_3O_4$ $[M+H]^+$: 432.1923, found: 432.1896.

N-(2-(cyclohexylamino)-2-oxo-1-(p-tolyl)ethyl)-4-methoxy-N-phenylbenzamide (3e). White solid (300.0 mg, 81%); m.p: 210 °C; R_f = 0.52 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 7H), 6.62 (d, *J* = 8.8 Hz, 2H), 6.06 (s, 1H), 5.90 (d, *J* = 7.7 Hz, 1H), 3.91 – 3.81 (m, 1H), 3.71 (s, 3H), 2.29 (s, 3H), 2.00 – 1.87 (m, 2H), 1.72 (s, 2H), 1.60 (ddd, *J* = 17.1, 8.9, 4.1 Hz, 1H), 1.42 – 1.29 (m, 2H), 1.20 – 1.02 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 168.9, 160.5, 142.2, 138.1, 132.1, 130.8, 129.9, 129.8, 129.1, 128.4, 128.2, 126.8, 112.8, 67.1, 55.1, 48.6, 32.8, 25.5, 24.8, 24.7, 21.1; HRMS (ESI): calcd. for $C_{29}H_{33}N_2O_3$ $[M+H]^+$: 457.2491, found: 457.2458.

N-cyclohexyl-2-(N-phenylacetamido)-2-(p-tolyl)acetamide (3f). White solid (212.0 mg, 72%); m.p: 181 °C; R_f = 0.52 (40% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 2.7 Hz, 4H), 6.99 (q, *J* = 8.3 Hz, 5H), 5.97 (s, 1H), 5.57 (d, *J* = 7.8 Hz, 1H), 3.81 (tdt, *J* = 11.8, 8.0, 3.9 Hz, 1H), 2.26 (s, 3H), 1.94 (d, *J* = 10.5 Hz, 1H), 1.85 (s, 3H), 1.67 – 1.52 (m, 3H), 1.43 – 1.27 (m, 3H), 1.23 – 0.92 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.1, 168.9, 140.9, 138.1, 131.8, 130.3, 130.2, 129.0, 128.8, 127.9, 64.9, 48.7, 32.8, 32.8, 25.5, 24.8, 24.7, 23.2, 21.1; HRMS (ESI): calcd. for $C_{23}H_{29}N_2O_2$ $[M+H]^+$: 365.2229, found: 365.2216.

N-(4-methoxyphenyl)-N-(2-(naphthalen-1-ylamino)-2-oxo-1-(p-tolyl)ethyl)benzamide (3g). Brown solid (348.0 mg, 85%); m.p: 140 °C; R_f = 0.50 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.81 (ddd, *J* = 9.7, 5.8, 3.3 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.50 – 7.44 (m, 3H), 7.39 – 7.32 (m, 4H), 7.21 – 7.11 (m, 5H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 6.38 (s, 1H), 3.67 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 168.8, 158.4, 138.6, 135.9, 134.2, 134.1, 132.4, 131.5, 131.2, 129.9, 129.5, 129.4, 128.5, 127.6, 127.3, 126.3, 125.9, 125.7, 125.6, 121.0, 120.6, 116.4, 114.8, 113.7, 67.9, 55.2, 21.2; HRMS (ESI): calcd. for $C_{33}H_{29}N_2O_3$ $[M+H]^+$: 501.2178, found: 501.2163.

N-(2-(tert-butylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-N-(4-methoxyphenyl) benzamide (3h). Yellow sticky solid (296.0 mg, 81%); R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.16 (dd, *J* = 4.7, 2.3 Hz, 2H), 7.15 – 7.12 (m, 3H), 6.87 (d, *J* = 4.6 Hz, 2H), 6.76 (d, *J* = 2.9 Hz, 1H), 6.75 – 6.73 (m, 1H), 6.51 (d, *J* = 9.0 Hz, 2H), 6.09 (s, 1H), 5.76 (s, 1H), 3.76 (s, 3H), 3.65 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 169.0, 159.4, 158.2, 136.4, 133.7, 131.6, 131.5, 129.1, 128.4, 127.6, 127.0, 116.5, 114.8, 113.7, 113.3, 65.8, 55.2, 55.1, 51.5, 28.7; HRMS (ESI): calcd. for $C_{27}H_{31}N_2O_4$ $[M+H]^+$: 447.2284, found: 447.2264.

N-(1-(4-bromophenyl)-2-(tert-butylamino)-2-oxoethyl)-N-(4-methoxyphenyl)benzamide (3i). Yellow sticky solid (350.0 mg, 85%); R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.30 – 7.27 (m, 2H), 7.22 – 7.17 (m, 1H), 7.16 – 7.13 (m, 3H), 6.86 (d, *J* = 7.7 Hz, 2H), 6.78 – 6.64 (m, 1H), 6.54 (d, *J* = 9.0 Hz, 2H), 6.08 (s, 1H), 5.91 (s, 1H), 3.67 (s, 3H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 168.4, 158.4, 135.9, 133.9, 133.4, 131.9, 131.5, 131.3, 129.4, 128.4, 127.7, 122.6, 116.7, 114.8, 113.6, 65.8, 55.2, 51.7, 28.7.; HRMS (ESI): calcd. for $C_{26}H_{28}BrN_2O_3$ $[M+H]^+$: 495.1283, found: 495.1274.

N-(2-(benzylamino)-1-(furan-2-yl)-2-oxoethyl)-N-(4-methoxyphenyl)benzamide (3j). Brown sticky solid (230.0 mg, 64%); R_f = 0.52 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.34 – 7.25 (m, 8H), 7.21 – 7.10 (m, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.66 (s, 1H), 6.58 (d, *J* = 9.1 Hz, 2H), 6.25 (d, *J* = 1.1 Hz, 1H), 6.16 (s, 1H), 4.60 – 4.44 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 168.9, 158.5, 143.2, 142.9, 138.1, 135.8, 133.6, 130.9, 129.5, 128.6, 128.4, 127.7, 127.6, 127.4, 119.1, 113.7, 111.4, 57.9, 55.2, 43.7; HRMS (ESI): calcd. for $C_{27}H_{25}N_2O_4$ $[M+H]^+$: 441.1814, found: 441.1794.

2-(4-bromophenyl)-N-cyclohexyl-2-(N-phenylacetamido)acetamide (3k). White solid (270.0 mg, 78%); m.p: 230 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.15 (m, 4H), 7.08 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 5.97 (s, 1H), 5.72 (d, *J* = 7.5 Hz, 1H), 3.85 – 3.77 (m, 1H), 1.96 (d, *J* = 9.5 Hz, 1H), 1.86 (s, 3H), 1.72 – 1.63 (m, 4H), 1.61 – 1.55 (m, 1H), 1.42 – 1.28 (m, 2H), 1.20 – 1.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 168.3, 140.4, 133.8, 131.9, 131.4, 130.2, 129.1, 128.3, 122.6, 64.2, 48.8, 32.8, 32.8, 25.5, 24.8, 24.7, 23.2; HRMS (ESI): calcd. for $C_{22}H_{26}BrN_2O_2$ $[M+H]^+$: 429.1178, found: 429.1132.

2-(4-chlorophenyl)-N-cyclohexyl-2-(N-phenyl acetamido) acetamide (3l). White solid (212.0 mg, 68%); m.p: 220 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, *J* = 1.6 Hz, 1H), 7.23 (d, *J* = 2.2 Hz, 1H), 7.21 (s, 2H), 7.11 (d, *J* = 1.7 Hz, 1H), 7.09 (d, *J* = 1.7 Hz, 1H), 7.07 – 7.05 (m, 2H), 6.98 (s, 1H), 6.10 (s, 1H), 5.75 (d, *J* = 8.0 Hz, 1H), 3.91 – 3.81 (m, 1H), 1.97 (d, *J* = 12.7 Hz, 1H), 1.89 (d, *J* = 12.4 Hz, 1H), 1.74 – 1.60 (m, 3H), 1.59 (s, 3H), 1.36 (ddd, *J* = 13.1, 8.1, 3.5 Hz, 2H), 1.19 – 1.05 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 168.4, 140.4, 134.4, 133.2, 131.7, 130.2, 129.1, 128.5, 128.3, 64.1, 48.8, 32.8, 25.5, 24.8, 24.7, 23.2; HRMS (ESI): calcd. for $C_{22}H_{26}ClN_2O_2$ $[M+H]^+$: 385.1683, found: 385.0380.

N-cyclohexyl-2-(4-methoxyphenyl)-2-(N-phenyl acetamido) acetamide (3m). White solid (230.0 mg, 75%); m.p: 160 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 2.6 Hz, 4H), 7.11 – 6.89 (m, 3H), 6.75 – 6.62 (m, 2H), 6.00 (s, 1H), 5.59 (d, *J* = 7.8 Hz, 1H), 3.85 – 3.77 (m, 1H), 3.75 (d, *J* =

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8.8 Hz, 3H), 1.95 (d, *J* = 8.8 Hz, 1H), 1.85 (s, 3H), 1.71 – 1.54 (m, 4H), 1.39 – 1.27 (m, 2H), 1.18 – 1.00 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 171.2, 168.9, 159.5, 140.7, 131.6, 130.4, 128.8, 127.9, 126.8, 113.7, 64.3, 55.2, 48.7, 32.8, 32.8, 25.5, 24.8, 24.7, 23.2; HRMS (ESI): calcd. for $C_{23}H_{29}N_2O_3$ $[M+H]^+$: 381.2178, found: 381.2168.

N-(2-(benzylamino)-1-(1H-indol-3-yl)-2-oxoethyl)-N-(2,2-dimethoxyethyl)benzamide (3n). Light yellow solid (243.0 mg, 63%); m.p: 100 °C, R_f = 0.45 (40% EtOAc in hexane); *the product may contain rotamers*; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.99 (s, 1H), 8.47 (s, 1H), 7.57 (s, 2H), 7.42 (d, *J* = 15.5 Hz, 8H), 7.34 (s, 2H), 7.21 (s, 1H), 7.17 (s, 1H), 7.10 (s, 1H), 5.87 (s, 1H), 5.04 (s, 1H), 4.54 (s, 1H), 4.45 (s, 1H), 3.36 (d, *J* = 30.1 Hz, 6H), 3.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 174.6, 169.9, 138.1, 136.2, 130.8, 128.9, 128.7, 127.5, 127.1, 126.3, 125.1, 122.3, 120.2, 117.9, 111.6, 109.5, 102.7, 62.6, 55.8, 47.6, 43.9; HRMS (ESI): calcd. for $C_{28}H_{29}N_3NaO_4$ $[M+Na]^+$: 494.2056, found: 494.2022.

N-(2-(benzylamino)-1-(4-fluorophenyl)-2-oxoethyl)-N-(2,2-dimethoxyethyl)benzamide (3o). White sticky solid (280.0 mg, 76%); R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 9.05 (s, 1H), 7.46 (d, *J* = 7.2 Hz, 4H), 7.44 – 7.40 (m, 6H), 7.34 (d, *J* = 6.0 Hz, 1H), 7.02 (t, *J* = 8.2 Hz, 3H), 5.68 (s, 1H), 5.01 (s, 1H), 4.83 (s, 1H), 4.42 (d, *J* = 12.4 Hz, 1H), 3.32 (s, 2H), 3.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.6, 163.7, 161.2, 138.1, 131.2, 130.8, 128.9, 128.8, 128.3, 127.7, 127.1, 115.9, 115.7, 102.5, 67.6, 55.8, 48.9, 43.9; HRMS (ESI): calcd. for $C_{26}H_{28}FN_2O_4$ $[M+H]^+$: 451.2033, found: 451.2038.

N-(2-(benzylamino)-2-oxo-1-(1H-pyrrol-2-yl)ethyl)-N-(4-methoxyphenyl)benzamide (3p). White solid (259.0 mg, 72%); m.p: 161 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 9.80 (s, 1H), 7.33 (dd, *J* = 2.9, 1.9 Hz, 1H), 7.30 (d, *J* = 1.4 Hz, 4H), 7.28 (t, *J* = 1.9 Hz, 2H), 7.22 – 7.18 (m, 1H), 7.17 (d, *J* = 1.3 Hz, 1H), 7.14 (t, *J* = 1.8 Hz, 1H), 6.88 (s, 1H), 6.84 (d, *J* = 3.3 Hz, 1H), 6.75 (dd, *J* = 4.1, 2.6 Hz, 1H), 6.65 – 6.63 (m, 1H), 6.62 – 6.59 (m, 1H), 6.43 (s, 1H), 6.22 (dd, *J* = 4.3, 3.0 Hz, 1H), 6.14 (dd, *J* = 6.0, 2.7 Hz, 1H), 5.67 (s, 1H), 4.50 (d, *J* = 6.0 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 171.8, 168.7, 158.5, 138.1, 135.7, 135.5, 129.7, 128.6, 128.6, 127.7, 127.5, 127.3, 125.1, 119.5, 114.0, 111.1, 107.9, 62.5, 55.3, 43.7; HRMS (ESI): calcd. for $C_{27}H_{26}N_3O_3$ $[M+H]^+$: 440.1974, found: 440.1964.

N-(4-methoxyphenyl)-N-(1-(4-methoxyphenyl)-2-oxo-2-(phenylamino)ethyl)benzamide (3q). Red solid (256.0 mg, 67%); m.p: 110 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.94 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.34 – 7.28 (m, 4H), 7.20 (dd, *J* = 9.5, 5.7 Hz, 3H), 7.17 (dd, *J* = 3.9, 2.1 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.80 (s, 1H), 6.77 (s, 1H), 6.54 (d, *J* = 9.1 Hz, 2H), 6.35 (s, 1H), 3.77 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.7, 168.2, 159.8, 158.4, 137.8, 135.9, 133.5, 131.8, 131.6, 129.4, 128.9, 128.5, 127.6, 126.1, 124.3, 120.0, 113.9, 113.5, 66.3, 55.2, 55.2; HRMS (ESI): calcd. for $C_{29}H_{27}N_2O_4$ $[M+H]^+$: 467.1971, found: 467.1963.

N-(2-(tert-butylamino)-2-oxo-1-(2,4,6-trimethoxyphenyl)ethyl)-N-(4-methoxyphenyl) benzamide (3r). Light yellow solid (326.0 mg, 79%); m.p: 120 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.33 – 7.28 (m, 2H), 7.20 – 7.09 (m, 3H), 6.88 (d, *J* = 6.8 Hz, 2H), 6.52 (dd, *J* = 7.8, 1.3 Hz, 2H), 6.45 (s, 2H), 6.09 (s, 1H), 5.85 (s, 1H), 3.80 (s, 3H), 3.70 (s, 6H), 3.65 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 171.4, 168.7, 158.3, 152.8, 137.9, 136.2, 133.5, 131.6, 130.2, 129.2, 128.3, 127.6, 113.3, 107.8, 65.9, 60.8, 56.1, 55.2, 51.6, 28.7; HRMS (ESI): calcd. for $C_{29}H_{35}N_2O_6$ $[M+H]^+$: 507.2495, found: 507.2486.

N-(2-((4-bromophenyl)amino)-2-oxo-1-phenylethyl)-N-(4-methoxyphenyl)benzamide (3s). Light brown solid (320.0 mg, 76%); m.p: 156 °C; R_f = 0.55 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.33 (s, 1H), 7.42 – 7.34 (m, 4H), 7.32 – 7.26 (m, 6H), 7.23 – 7.11 (m, 4H), 6.88 (d, *J* = 6.8 Hz, 2H), 6.53 (d, *J* = 9.1 Hz, 2H), 6.34 (s, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.8, 168.4, 158.4, 137.1, 135.8, 133.9, 133.4, 131.7, 131.5, 130.3, 129.6, 128.7, 128.6, 128.5, 128.1, 127.7, 121.4, 116.7, 113.5, 67.3, 55.2; HRMS (ESI): calcd. for $C_{28}H_{24}BrN_2O_3$ $[M+H]^+$: 515.0970, found: 515.0969.

N-(2-(benzylamino)-1-(4-bromophenyl)-2-oxoethyl)-N-(4-methoxyphenyl)benzamide (3t). White solid (320.0 mg, 74%); m.p: 160 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.39 – 7.23 (m, 9H), 7.16 (t, *J* = 10.2 Hz, 5H), 6.82 (d, *J* = 7.7 Hz, 2H), 6.53 (d, *J* = 8.6 Hz, 2H), 6.42 (s, 1H), 6.17 (s, 1H), 4.52 (d, *J* = 3.1 Hz, 2H), 3.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 171.5, 169.2, 158.5, 137.9, 135.8, 133.6, 133.4, 131.9, 131.6, 131.4, 129.5, 128.7, 128.4, 127.7, 127.4, 122.8, 113.6, 65.5, 55.2, 43.8; HRMS (ESI): calcd. for $C_{29}H_{26}BrN_2O_3$ $[M+H]^+$: 529.1127, found: 529.1122.

N-(2-(benzylamino)-1-(4-cyanophenyl)-2-oxoethyl)-3-iodo-N-phenylbenzamide (3u). Light brown solid (390.0 mg, 84%); m.p: 187 °C; R_f = 0.45 (40% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.66 (t, *J* = 1.6 Hz, 1H), 7.57 – 7.46 (m, 3H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.30 (m, 2H), 7.27 (dd, *J* = 6.4, 2.8 Hz, 3H), 7.19 – 7.15 (m, 1H), 7.13 – 7.03 (m, 3H), 6.92 (d, *J* = 6.0 Hz, 2H), 6.84 (t, *J* = 7.9 Hz, 1H), 6.59 (t, *J* = 5.6 Hz, 1H), 6.22 (s, 1H), 4.53 (qd, *J* = 14.8, 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.6, 168.4, 140.0, 139.3, 138.8, 137.7, 137.4, 137.0, 132.0, 130.8, 130.0, 129.3, 128.9, 128.7, 128.0, 127.6, 127.6, 127.5, 118.2, 112.4, 93.3, 65.8, 43.9; HRMS (ESI): calcd. for $C_{29}H_{23}IN_3O_2$ $[M+H]^+$: 572.0835, found: 572.0813.

IV. General procedure for the oxidative cleavage of Ugi adducts 3a-u. To the solution of **3** (1.0 equiv, 0.2 mmol) in dry CH_3CN was added KO^{t}Bu (3.0 equiv, 0.6 mmol) and CuI (0.2 equiv, 20 mol %) at room temperature and the reaction vessel was flushed with O_2. The resulting reaction mixture was stirred at room temperature. After completion of the reaction (based on TLC) in 15-30 minutes, the reaction mixture was quenched with water and the crude product was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo* and the crude was purified by silica gel column chromatography to afford the desired products **2** and **4** respectively.

N-(4-methoxyphenyl)benzamide (4a)[25]. Yellow solid (34.1 mg, 75%); m.p: 152 °C; R_f = 0.52 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.88 – 7.83 (m, 2H), 7.80 (s, 1H), 7.56 – 7.51 (m, 3H), 7.49 – 7.44 (m, 2H), 6.92 – 6.87 (m, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.8, 156.8, 135.2, 131.8,

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131.2, 128.9, 127.1, 122.3, 114.4, 55.6; HRMS (ESI): calcd. for $C_{14}H_{14}NO_2$ $[M+H]^+$: 228.1025, found: 228.1011.

***N*-phenylbenzamide (4b)**[26]. White solid (27.7 mg, 70%); m.p: 160 °C; R_f = 0.53 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, *J* = 5.2, 3.3 Hz, 3H), 7.68 – 7.61 (m, 2H), 7.58 – 7.46 (m, 3H), 7.40 – 7.34 (m, 2H), 7.19 – 7.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 137.9, 134.9, 131.8, 129.1, 128.8, 127.0, 124.6, 120.2; HRMS (ESI): calcd. for $C_{13}H_{12}NO$ $[M+H]^+$: 198.0919, found: 198.0900.

***N*-(2,2-dimethoxyethyl)benzamide (4c)**[27]. White solid (25.2 mg, 60%); m.p: 114 °C; R_f = 0.35 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.5 Hz, 2H), 7.54 – 7.48 (m, 1H), 7.43 (t, *J* = 7.4 Hz, 2H), 6.39 (s, 1H), 4.49 (t, *J* = 5.2 Hz, 1H), 3.61 (t, *J* = 5.5 Hz, 2H), 3.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 134.3, 131.5, 128.5, 126.9, 102.7, 54.6, 41.5; HRMS (ESI): calcd. for $C_{11}H_{16}NO_3$ $[M+H]^+$: 210.1130, found: 210.1114.

***3*-iodo-*N*-phenylbenzamide (4d)**. *White* sticky solid (43.4 mg, 67%); R_f = 0.59 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (t, *J* = 1.7 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.81 (ddd, *J* = 5.8, 3.5, 2.2 Hz, 2H), 7.66 – 7.58 (m, 2H), 7.42 – 7.33 (m, 2H), 7.25 – 7.13 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.2, 140.7, 137.6, 136.9, 136.0, 130.4, 129.1, 126.2, 124.9, 120.3, 94.4; HRMS (ESI): calcd. for $C_{13}H_{11}INO$ $[M+H]^+$: 323.9885, found: 323.9876.

V. General Procedure for the synthesis of Ugi adducts 5a-c. Ugi adducts **5a-c** were prepared by performing U-3CR using 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole that was prepared in two steps from tryptamine.

a) Preparation of 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole. Tryptamine (1.0 g, 6.24 mmol) and ethyl formate (0.6 ml, 7.49 mmol) were added in a round bottom flask and refluxed at 60 °C for 12 h. Excess ethyl formate in reaction mixture was removed *in vacuo* and crude reaction mixture was used for the next step. Crude was dissolved in dichloromethane, $POCl_3$ (0.9 ml, 9.36 mmol) was added to it at 0 °C and refluxed for 1 h. After completion of reaction (based on TLC), the reaction mixture was cooled to room temperature. Excess $POCl_3$ was removed *in vacuo*. The crude mixture was dissolved in 10% K_2CO_3 solution and the aqueous phase was extracted with dichloromethane. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and crude was purified by silica gel column chromatography to afford **4,9-dihydro-3*H*-pyrido[3,4-*b*]indole** as a brown solid (810.0 mg, 76%). The spectral data matched with literature reports.[28]

b) Preparation of Ugi adduct 5. To a solution of 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (1.0 equiv, 0.6 mmol) in dry DCM, acid (1.3 equiv, 0.8 mmol) and isocyanide (1.3 equiv, 0.8 mmol) were added and stirred at room temperature for 12 h. On completion of the reaction (based on TLC), the reaction mixture was diluted with dichloromethane and washed with saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over anhydrous sodium sulfate followed by evaporation of solvent *in vacuo*. The crude product was purified by silica gel column chromatography to afford the desired product **5**.

***2*-benzoyl-*N*-(tert-butyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxamide (5a)**. Yellow solid (136.0 mg, 60%); m.p: 243 °C; R_f = 0.45 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.68 (s, 1H), 7.81 (s, 1H), 7.50 (dd, *J* = 12.6, 4.8 Hz, 5H), 7.46 – 7.42 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 7.2 Hz, 1H), 5.93 (s, 1H), 3.89 (dd, *J* = 15.3, 8.6 Hz, 2H), 2.77 (dd, *J* = 21.0, 10.9 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.5, 167.7, 136.1, 136.0, 129.8, 129.3, 128.5, 126.8, 126.1, 121.3, 118.7, 117.7, 111.5, 53.5, 50.8, 44.1, 28.4, 21.0; HRMS (ESI): calcd. for $C_{23}H_{26}N_3O_2$ $[M+H]^+$: 376.2025, found: 376.2010.

***2*-benzoyl-*N*-cyclohexyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxamide (5b)**. Yellow solid (169.0 mg, 70 %); m.p: 249 °C; R_f = 0.45 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.66 (s, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 2.8 Hz, 3H), 7.43 – 7.37 (m, 3H), 7.33 (s, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.96 (t, *J* = 7.3 Hz, 1H), 5.91 (s, 1H), 3.87 – 3.75 (m, 2H), 3.56 (s, 1H), 2.75 (dd, *J* = 8.9, 5.4 Hz, 1H), 2.66 (d, *J* = 15.1 Hz, 1H), 1.80 (d, *J* = 9.2 Hz, 1H), 1.69 (d, *J* = 15.3 Hz, 3H), 1.54 (d, *J* = 11.4 Hz, 1H), 1.26 (dd, *J* = 17.8, 9.2 Hz, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.6, 167.2, 136.1, 135.9, 129.9, 129.1, 128.6, 126.9, 126.3, 126.0, 121.4, 118.8, 117.8, 111.5, 107.9, 53.3, 48.2, 44.2, 32.3, 32.1, 25.2, 24.6, 24.5, 21.1; HRMS (ESI): calcd. for $C_{25}H_{28}N_3O_2$ $[M+H]^+$: 402.2182, found: 402.2178.

***2*-acetyl-*N*-cyclohexyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-1-carboxamide (5c)**. Yellow solid (138.0 mg, 68%); m.p: 220 °C; R_f = 0.47 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (s, 1H), 7.47 (dd, *J* = 19.0, 7.6 Hz, 1H), 7.34 (dd, *J* = 14.6, 8.2 Hz, 1H), 7.21 – 7.14 (m, 1H), 7.13 – 7.06 (m, 1H), 6.40 (d, *J* = 7.0 Hz, 1H), 6.11 (s, 1H), 4.14 (d, *J* = 13.7 Hz, 1H), 3.72 (dd, *J* = 22.1, 18.6 Hz, 1H), 3.65 – 3.56 (m, 1H), 2.85 (s, 2H), 2.32 (s, 3H), 1.90 (d, *J* = 12.5 Hz, 1H), 1.78 (d, *J* = 11.6 Hz, 1H), 1.61 (dd, *J* = 32.6, 15.3 Hz, 3H), 1.32 (d, *J* = 11.1 Hz, 2H), 1.14 (dd, *J* = 22.3, 10.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 167.9, 136.5, 128.6, 126.2, 122.1, 119.4, 117.9, 111.3, 108.6, 53.5, 48.5, 43.6, 32.7, 32.6, 25.4, 24.6, 24.6, 21.9; HRMS (ESI): calcd. for $C_{20}H_{26}N_3O_2$ $[M+H]^+$: 340.2025, found: 340.2018.

VI. General Procedure for the oxidative cleavage of Ugi adducts 5a-c. To the solution of **5** (1.0 equiv, 0.2 mmol) in dry CH_3CN was added KO^tBu (3.0 equiv, 0.6 mmol) and CuI (0.2 equiv, 20 mol %) at room temperature and the reaction vessel was flushed with O_2. The resulting reaction mixture was stirred at room temperature. After completion of the reaction (based on TLC) in 12 h, the reaction mixture was filtered through a short pad of celite, quenched with water and the crude product was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo* and the crude was purified by silica gel column chromatography to afford the desired product **6**.

***N*-(2-(2-(2-(tert-butylamino)-2-oxoacetyl)-1*H*-indol-3-yl)ethyl)benzamide (6a)**. Yellow oil (49.0 mg, 63%); R_f = 0.52 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.37 (s, 1H), 7.75 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.63 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.44 (ddd, *J* = 6.7, 3.8, 1.3 Hz, 2H), 7.41 – 7.31 (m, 4H), 7.12 (ddd, *J* = 8.1, 4.8, 3.0 Hz, 1H), 6.63 (s, 1H), 3.86 – 3.76 (m, 2H), 3.53 (t, *J* = 6.5 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.6, 167.6, 162.2, 137.5, 134.6, 131.2, 129.3, 128.5,

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128.3, 128.2, 127.2, 126.9, 121.2, 121.1, 112.9, 51.7, 40.9, 29.7, 28.3; HRMS (ESI): calcd. for $C_{23}H_{26}N_3O_3$ $[M+H]^+$: 392.1974, found: 392.1972.

N-(2-(2-(2-(cyclohexylamino)-2-oxoacetyl)-1H-indol-3-yl)ethyl)benzamide (6b). Yellow oil (43.0 mg, 51%); R_f = 0.52 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.36 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.65 – 7.62 (m, 2H), 7.48 (s, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.39 (m, 2H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.13 (ddd, *J* = 8.0, 5.2, 2.5 Hz, 1H), 6.67 (s, 1H), 3.85 – 3.78 (m, 3H), 3.54 (t, *J* = 6.5 Hz, 2H), 1.88 (dd, *J* = 13.3, 3.9 Hz, 2H), 1.82 – 1.76 (m, 3H), 1.56 (d, *J* = 15.6 Hz, 3H), 1.47 – 1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.2, 167.6, 161.9, 137.5, 134.6, 131.2, 129.4, 128.5, 128.37, 128.2, 127.3, 126.8, 121.2, 121.1, 112.9, 48.6, 40.9, 34.3, 33.1, 32.5, 29.7; HRMS (ESI): calcd. for $C_{25}H_{28}N_3O_3$ $[M+H]^+$: 418.2131, found: 418.2105.

2-(3-(2-acetamidoethyl)-1H-indol-2-yl)-N-cyclohexyl-2-oxoacetamide (6c). Yellow oil (21.0 mg, 29%); R_f = 0.55 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.35 (s, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.15 (ddd, *J* = 8.1, 5.2, 2.6 Hz, 1H), 5.87 (s, 1H), 3.89 – 3.79 (m, 1H), 3.58 (dd, *J* = 12.4, 6.3 Hz, 2H), 3.39 (dd, *J* = 11.1, 4.7 Hz, 2H), 2.01 – 1.96 (m, 2H), 1.87 (s, 3H), 1.82 – 1.76 (m, 4H), 1.67 (m, 3H), 1.61 – 1.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 170.3, 161.9, 137.4, 129.3, 128.3, 128.1, 127.4, 121.2, 121.0, 112.9, 48.6, 40.2, 32.5, 25.3, 25.1, 24.6, 23.2; HRMS (ESI): calcd. for $C_{20}H_{26}N_3O_3$ $[M+H]^+$: 356.1974, found: 356.1966.

VII. General Procedure for the synthesis of THIQ-derived Ugi adducts 7. Substrate **7** was prepared according to reported procedure.[29] Compounds **7a-c** were in accordance with the data reported in the literature.

VIII. General Procedure for the oxidative cleavage of Ugi adducts 7. To the solution of **7** (1.0 equiv, 0.2 mmol) in dry CH_3CN was added KO^{t}Bu (3.0 equiv, 0.6 mmol) and CuI (0.2 equiv, 20 mol %) at room temperature and the reaction vessel was flushed with O_2. The resulting reaction mixture was stirred at room temperature. After completion of the reaction (based on TLC) in 12 h, the reaction mixture was quenched with water and the crude product was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, concentrated *in vacuo* and the crude was purified by silica gel column chromatography to afford the product **8** or **9**.

N-(tert-butyl)-3,4-dihydroisoquinoline-1-carboxamide (8a)[30]. Yellow oil (18.0 mg, 39%); R_f = 0.5 (20% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.41 – 7.26 (m, 3H), 7.20 – 7.14 (m, 1H), 3.79 – 3.70 (m, 2H), 2.74 – 2.66 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 160.5, 138.1, 131.1, 128.6, 127.0, 126.8, 126.3, 51.0, 47.1, 28.6, 25.9; HRMS (ESI): calcd. for $C_{14}H_{19}N_2O$ $[M+H]^+$: 231.1497, found: 231.1494.

N-cyclohexylisoquinoline-1-carboxamide (9b)[31]. White solid (13.0 mg, 26%); m.p: 118 °C; R_f = 0.7 (10% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.61 (d, *J* = 8.5 Hz, 1H), 8.46 (d, *J* = 5.5 Hz, 1H), 8.10 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 5.5 Hz, 1H), 7.69 (dtd, *J* = 16.8, 6.8, 1.3 Hz, 2H), 4.07 – 3.99 (m, 1H), 2.08 (dd, *J* = 12.3, 3.3 Hz, 2H), 1.83 – 1.78 (m, 2H), 1.71 – 1.64 (m, 1H), 1.50 – 1.45 (m, 2H), 1.38 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 148.7, 140.1, 137.4, 130.4, 128.5, 128.0, 127.1, 126.7, 124.1, 48.3, 33.1, 25.7, 24.9; HRMS (ESI): calcd. for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1497, found: 255.1491.

IX. Procedure for the synthesis of Substrate 10. Substrate **10** was prepared according to reported procedure.[32]

2-(benzyl(2-nitrophenyl)amino)-2-(4-chlorophenyl)-N-cyclohexylacetamide (10). Yellow solid (180.0 mg, 27%); m.p: 201 °C; R_f = 0.40 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 3H), 7.21 (q, *J* = 7.9 Hz, 3H), 7.16 (t, *J* = 7.4 Hz, 2H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.70 (d, *J* = 7.2 Hz, 2H), 4.82 (s, 1H), 4.03 – 3.95 (m, 2H), 3.57 – 3.49 (m, 1H), 1.71 – 1.60 (m, 2H), 1.52 (d, *J* = 6.5 Hz, 2H), 1.40 (d, *J* = 11.2 Hz, 1H), 1.34 – 1.18 (m, 3H), 1.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8, 147.4, 141.8, 134.9, 134.3, 133.9, 132.5, 129.9, 129.5, 128.9, 128.2, 127.9, 127.1, 125.6, 124.4, 70.8, 57.6, 47.8, 32.4, 32.3, 25.3, 24.6, 24.5; HRMS (ESI): calcd. for $C_{27}H_{29}ClN_3O_3$ $[M+H]^+$: 478.1897, found: 478.1891.

X. General Procedure for the synthesis of substrate 11. Substrate **11** was prepared according to the procedure previously reported by our research group.[6b] To a solution of *p*-anisidine (1.0 equiv, 0.4 mmol) in CH_3CN (3.0 mL) and water (0.1 mL), aldehyde (1.0 equiv, 0.4 mmol) was added with continuous stirring at rt and allowed to stir for 4-5 minutes To that mixture, phenyl propiolic acid (1.0 equiv, 0.4 mmol), followed by isocyanide (1.0 equiv, 0.4 mmol), was added and stirred for 12-18 h. After consumption of all the substrates (based on TLC), acetonitrile was added (3.0 mL) to dilute the reaction mixture. To this, iodine (2.0 equiv, 0.8 mmol) was added, and the mixture was allowed to stir for 5-6 h at rt. After completion of the reaction, reaction mixture was diluted with ethyl acetate and washed with sodium thiosulfate solution (10% w/v). Aqueous layer was extracted with ethyl acetate and the combined organic layers was dried over anhydrous sodium sulfate. After evaporation of ethyl acetate *in vacuo*, crude was dissolved in dichloromethane and distilled hexane was added to precipitate the product. Solid portion was filtered and dried in high vacuum to afford the desired product **11**.

N-(tert-butyl)-2-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)-2-phenylacetamide (11a). Pale yellow solid (184.0 mg, 82%); m.p: 170 °C; R_f = 0.45 (30% EtOAc in hexane); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.70 (s, 1H), 7.38 – 7.33 (m, 3H), 7.32 – 7.28 (m, 2H), 7.28 – 7.25 (m, 1H), 7.25 – 7.23 (m, 1H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.11 (dd, *J* = 6.5, 3.2 Hz, 2H), 6.49 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.12 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.52 (dd, *J* = 9.9, 1.9 Hz, 2H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 183.6, 167.7, 166.9, 159.1, 145.3, 144.9, 134.2, 132.2, 130.5, 130.4, 129.1, 128.7, 128.5, 128.3, 127.9, 127.5, 99.8, 71.2, 61.1, 50.5, 28.3; HRMS (ESI): calcd. for $C_{27}H_{26}IN_2O_3$ $[M+H]^+$: 553.0988, found: 553.0984.

2-(4-chlorophenyl)-N-cyclohexyl-2-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)acetamide (11b). White solid (217.0 mg, 87%); m.p: 182 °C; R_f = 0.45 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 7.93 (s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 5H), 7.21 (s, 1H), 7.15 – 7.04 (m, 3H), 6.50 (dd, *J* = 10.0, 2.8 Hz, 1H), 6.17 (d, *J* = 10.0 Hz, 1H), 5.82 (d, *J* = 10.0 Hz, 1H), 5.42 (s, 1H), 3.77 – 3.62 (m, 1H), 1.80 (s, 2H), 1.63 (d, *J* = 34.5 Hz, 3H), 1.34 – 1.23 (m,

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2H), 1.14 (dd, *J* = 24.1, 12.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 182.3, 170.1, 165.7, 157.9, 143.4, 142.9, 130.7, 130.0, 129.2, 128.2, 126.9, 126.8, 120.2, 97.5, 70.2, 59.4, 47.5, 43.8, 31.1, 28.1, 24.0, 23.4; HRMS (ESI): calcd. for $C_{29}H_{27}ClIN_2O_3$ $[M+H]^+$: 613.0755, found: 613.0740.

N-(tert-butyl)-2-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)-2-(p-tolyl)acetamide (11c). White solid (180.0 mg, 78%); m.p: 178 °C; R_f = 0.45 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.40 – 7.31 (m, 5H), 7.15 (t, *J* = 7.9 Hz, 4H), 6.73 (dd, *J* = 9.9, 3.0 Hz, 1H), 6.53 (dd, *J* = 9.9, 3.0 Hz, 1H), 6.26 – 6.16 (m, 2H), 5.52 (s, 1H), 4.80 (s, 1H), 2.35 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 183.9, 167.1, 166.8, 158.8, 144.3, 144.2, 139.2, 132.2, 132.1, 131.9, 131.9, 129.8, 129.6, 129.4, 128.4, 127.7, 98.6, 71.6, 62.6, 51.8, 28.5, 21.1; HRMS (ESI): calcd. for $C_{28}H_{28}IN_2O_3$ $[M+H]^+$: 567.1145, found: 567.1138.

2-(2-bromophenyl)-N-(tert-butyl)-2-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)acetamide (11d). White solid (244.0 mg, 95%); m.p: 187 °C; R_f = 0.45 (30% EtOAc in hexane); ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.67 (d, *J* = 7.4 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.35 (ddd, *J* = 22.2, 12.2, 7.2 Hz, 3H), 7.23 (dt, *J* = 7.3, 6.7 Hz, 2H), 7.17 – 7.11 (m, 2H), 6.71 (dd, *J* = 10.0, 2.9 Hz, 1H), 6.64 (dd, *J* = 9.8, 2.3 Hz, 1H), 6.14 (dd, *J* = 10.1, 1.3 Hz, 1H), 6.06 (dd, *J* = 9.9, 2.0 Hz, 1H), 5.59 (s, 1H), 5.30 (t, *J* = 5.2 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 183.9, 167.5, 165.9, 159.5, 144.0, 143.9, 134.4, 133.0, 131.8, 131.6, 131.1, 130.8, 129.9, 128.4, 128.1, 127.8, 126.1, 97.8, 71.4, 61.6, 52.1, 28.4; HRMS (ESI): calcd. for $C_{27}H_{25}BrIN_2O_3$ $[M+H]^+$: 631.0093, found: 631.0089.

N-benzyl-2-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)-2-(4-(methylthio)phenyl)acetamide (11e). White solid (226.0 mg, 88%); m.p: 230 °C; R_f = 0.42 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, DMSO-d_6): *δ* 8.36 (t, *J* = 5.9 Hz, 1H), 7.30 – 7.25 (m, 3H), 7.25 – 7.14 (m, 7H), 7.07 – 6.99 (m, 4H), 6.95 (dd, *J* = 10.1, 3.0 Hz, 1H), 6.56 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.06 (dd, *J* = 10.1, 1.9 Hz, 1H), 5.65 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.34 (s, 1H), 4.33 – 4.18 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): *δ* 183.8, 168.3, 167.2, 159.2, 145.22, 144.7, 139.2, 132.3, 131.4, 130.9, 130.9, 129.8, 129.4, 128.3, 128.2, 127.2, 126.9, 125.2, 99.8, 71.3, 60.7, 42.6, 14.7; HRMS (ESI): calcd. for $C_{31}H_{26}IN_2O_3S$ $[M+H]^+$: 633.0709, found: 633.0648.

N-(tert-butyl)-2-(3-iodo-2,8-dioxo-4-phenyl-1-azaspiro[4.5]deca-3,6,9-trien-1-yl)-2-(4-isopropylphenyl)acetamide (11f). Pale yellow solid (172.0 mg, 71%); m.p: 210 °C; R_f = 0.47 (30% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.37 – 7.29 (m, 5H), 7.18 (s, 1H), 7.16 – 7.11 (m, 3H), 6.63 (ddd, *J* = 9.7, 7.4, 2.9 Hz, 2H), 6.24 – 6.18 (m, 1H), 6.13 – 6.07 (m, 1H), 5.53 (s, 1H), 4.93 (s, 1H), 2.98 – 2.82 (m, 1H), 1.32 (s, 9H), 1.25 (d, *J* = 0.5 Hz, 3H), 1.22 (d, *J* = 0.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 184.1, 167.3, 167.1, 159.1, 150.4, 144.2, 144.2, 132.2, 131.9, 131.9, 131.6, 129.8, 128.5, 127.9, 126.9, 98.5, 71.7, 62.6, 51.9, 33.8, 28.6, 23.9, 23.7; HRMS (ESI): calcd. for $C_{30}H_{32}IN_2O_3$ $[M+H]^+$: 595.1458, found: 595.1457.

Conflicts of interest

The authors declare no competing financial interests.

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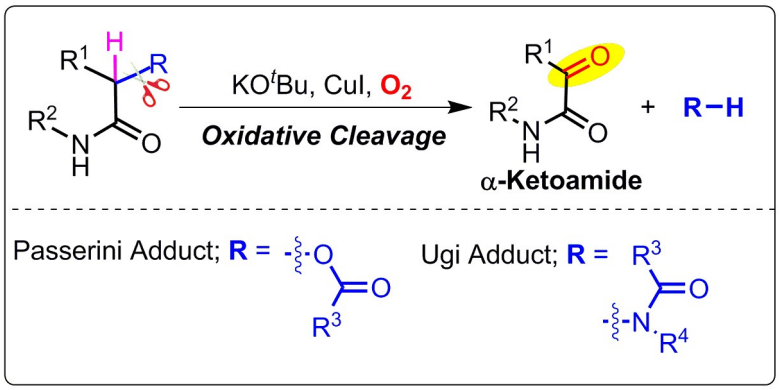

The present study provides an insight into the reactivity of Passerini and Ugi adducts in basic medium leading to α-ketoamides.