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Photoredox catalyzed radical conjugate addition to Ugi-derived dehydroalanines toward the synthesis of β-heteroaryl α-amino acids

Alejandro Martínez-Zaldívar, Gustavo G. Flores-Bernal, Diego Alemán-Ponce de León, and Luis D. Miranda*

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, 04510 Ciudad de Mexico, Mexico

Email: lmiranda@unam.mx

This paper is dedicated to Professor Samir Z. Zard on the occasion of his retirement from teaching at the Ecole Polytechnique

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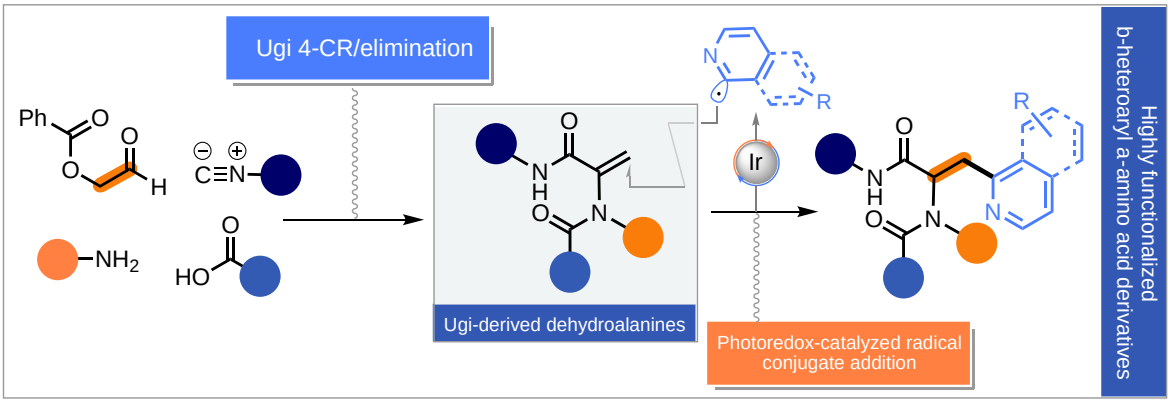
Abstract

A protocol was developed for reductive radical conjugate addition of 2-pyridyl radicals to Ugi-derived dehydroalanines (DHA). The conjugate addition of pyridyl radicals under reductive conditions allowed the formation of a C*sp*^{2}-C*sp*^{3} bond, yielding β-heteroaryl α-amino amides in good yields as important precursors of unnatural amino acid derivatives. Pyridine halides were activated as radical precursors by using Ir-photocatalysis and the Hantzsch ester as a reductant. The two-step synthetic strategy proposed in this work gave access to a series of highly functionalized non-natural β-heteroaryl α-amino acid derivatives.



Keywords: Multicomponent reaction, photocatalysis, radical conjugate addition, heteroaryl amino acids

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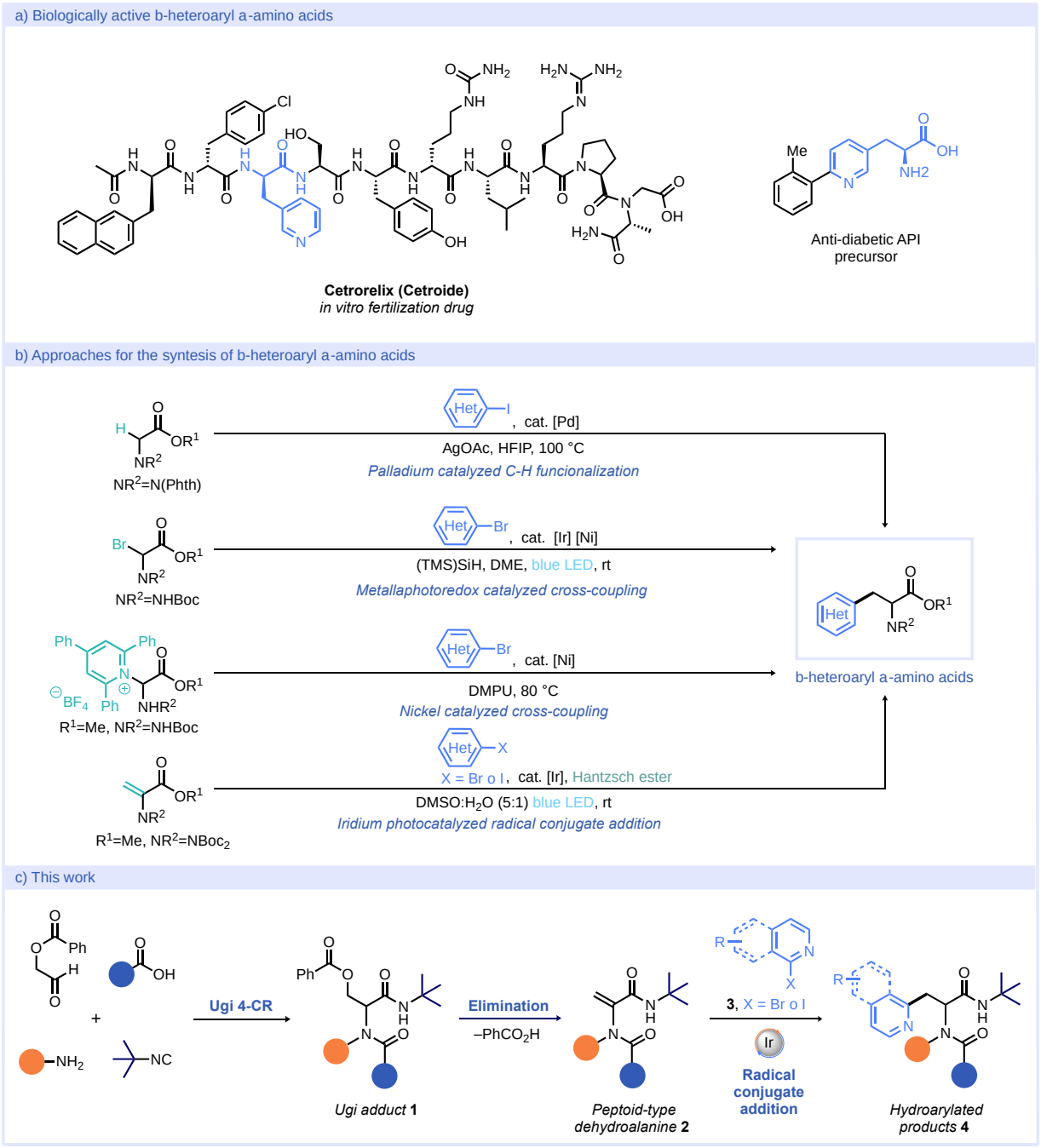
Introduction

The synthesis of unnatural amino acids has played a crucial role in drug development and protein engineering. Their incorporation allows bioactive molecules to increase their stability and activity.[1] From the synthetic point of view, preparation of modified peptide fragments in diversity-oriented synthesis requires efficient synthetic strategies for incorporating pharmacophores,[2] bioisosteres,[3,4] *N*-methylation,[5] or modification of the C- or N-terminal atoms.[6] Along this line, heteroaryl amino acids are an important class of unnatural amino acids in pharmaceutical chemistry as drug candidates,[7] such as, the *in vitro* fertilization drug Cetrorelix[8] and precursors of antidiabetic molecules[9] (Scheme 1a).



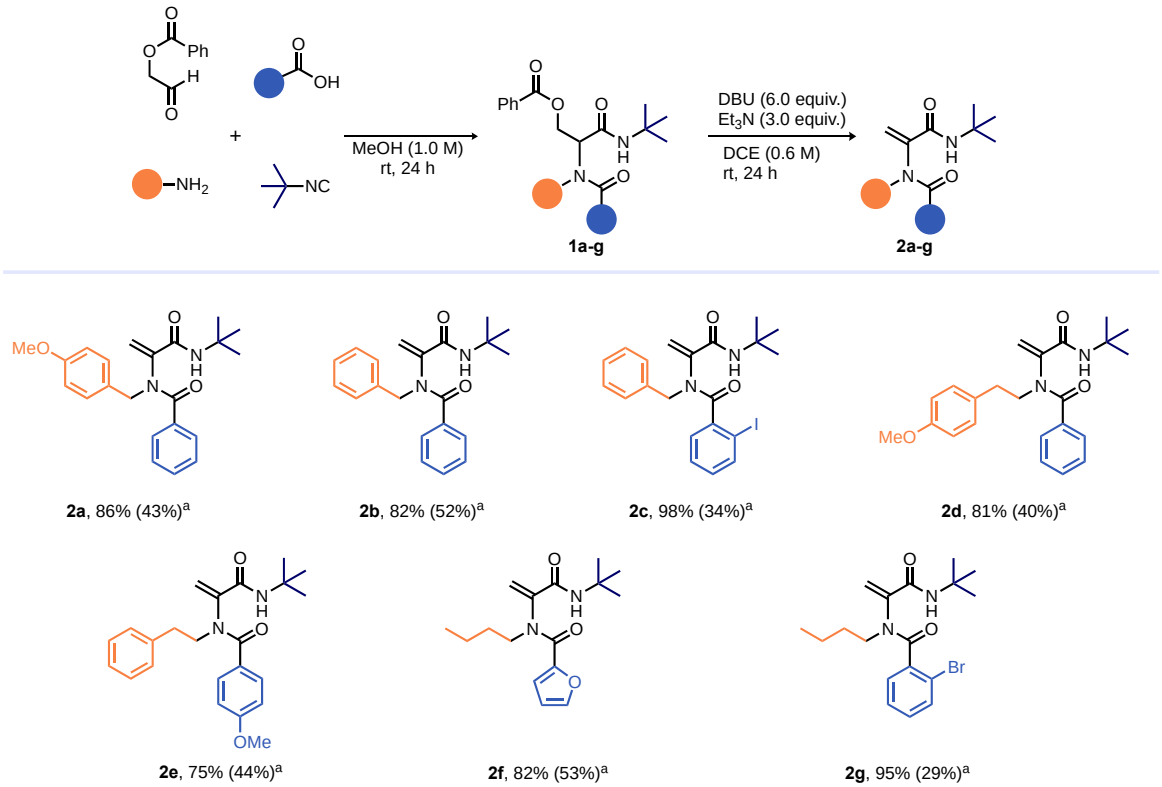
Scheme 1. State of the art in β-heteroaryl α-amino acids and homologated derivatives.

Despite the importance of heteroaryl moiety into the amino acid scaffold, methodologies for the preparation of heteroarylated derivatives are still scarce. The main approaches for the incorporation of aromatic groups in the synthesis of β-heteroaryl α-amino acids include the Pd-catalyzed C-H functionalization of alanine derivatives with aryl iodides,[10-13] reductive coupling of halogenated amino acids with aryl bromides by metallaphotoredox catalysis,[14] and deaminative reductive cross-coupling of amino acid pyridinium salts with aryl bromides[15] (Scheme 1b). However, the above strategies require harsh reaction conditions, use of unstable halogenated amino acids and prefunctionalized substrates. The radical approaches have emerged as a practical, mild, and expeditious synthetic alternative. In this context, Jui and co-workers synthetized β-heteroaryl α-amino acids through a reductive radical addition of heteroaryl halides to dehydroalanines as Michael acceptors by using iridium-based photoredox catalysis.[16] Although the use of dehydroalanines for amino acid diversification and late-stage functionalization of peptides has been widely studied through the conjugated addition of alkyl radicals,[17-20] to our knowledge, Jui's work is the only approach for the reductive addition of heteroaryl radicals. Recognizing the advantage of a photocatalytic system for the activation of heteroaryl halides and their subsequent radical conjugate addition on dehydroalanines, we have developed a protocol for the incorporation of heteroaryl groups into peptoid-type dehydroalanines constructed as Ugi 4-CR adducts (Scheme 1c). In contrast to previously reported approaches, the multicomponent Ugi reaction allows a broader exploration of the chemical space for access to the β-heteroaryl α-amino acid scaffold with greater structural diversity.

Results and Discussion

As the first synthetic stage, dehydroalanines **2** as radical acceptors were synthesized by a two-step protocol involving a Ugi four-component reaction (Ugi 4-CR) followed by an elimination reaction (Table 1).[21-24] Ugi 4-CR was performed with several aliphatic and aromatic carboxylic acids, primary amines, *tert*-butyl isocyanide, and 2-(benzoyloxy)acetaldehyde, with the latter as a precursor to the 1,1-disubstituted alkene. Ugi 4-CR adducts **1a**-**g** were obtained in 29-53% yields. Subsequently, elimination of the benzoate group by treating **1a**-**g** with DBU and Et_3N in 1,2-dichloroethane as solvent[25] afforded the peptoid-type dehydroalanines **2** in 75-95% yields.

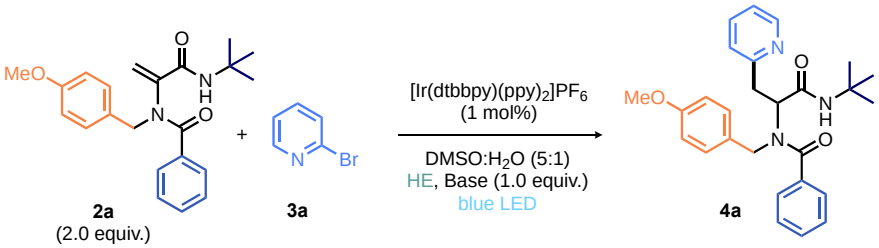
Table 1. Synthesis of dehydroalanines **1** from Ugi 4-CR adducts.



[a]Yields of the corresponding Ugi adducts are shown in parentheses.

Following previous findings,[16] the study of the photocatalyzed reductive radical conjugate addition onto dehydroalanines **2** started with the use of [Ir(dtbbpy)(ppy)$_2$]PF$_6$ as the photocatalyst and the Hantzsch ester (HE) as a stoichiometric reductant in aqueous DMSO. Dehydroalanine **2a** and 2-bromopyridine (**3a**) were selected as model substrates (Table 2). After irradiation of the reaction mixture for 24 h with blue LED, the hydroarylated product **4a** was obtained in 72% yield (Table 2, entry 1). The yield improvement of product **4a** was evaluated by using an inorganic base and increasing the number of equivalents of added Hantzsch ester (Table 2, entries 2-7). Thus, the employment of 1.0 equiv. of K_2HPO_4 and 1.5 equiv. of Hantzsch ester increased the yield of product **4a** to 92%.

Table 2. Evaluation of base and number of equivalents of Hantzsch ester.[a]



Entry	HE (equiv.)	Base (1.0 equiv.)	Yield (%)[b]
1	1.0	-	72
2	1.0	$NaHCO_3$	75
3	1.0	KH_2PO_4	77

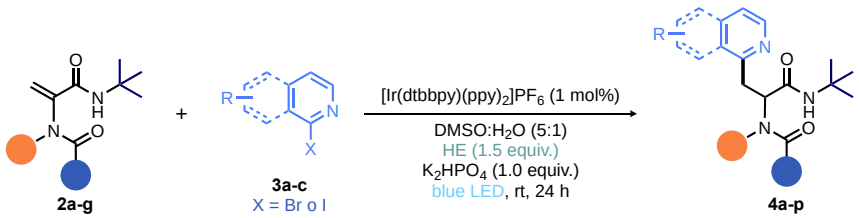
4	1.0	K_2HPO_4	78
5	1.5	$NaHCO_3$	76
6	1.5	KH_2PO_4	80
7	**1.5**	**K_2HPO_4**	**92**

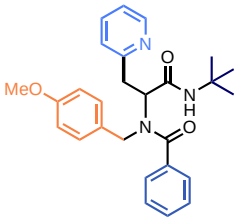
[a]Conditions: **2a** (0.11 mmol, 2.0 equiv), **3a** (0.22 mmol, 1.0 equiv), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol %), Base (1.0 equiv) and Hantzsch ester (HE) in DMSO:H_2O (5:1, 0.2 M), rt, 24 h. [b]Isolated yield after column chromatography.

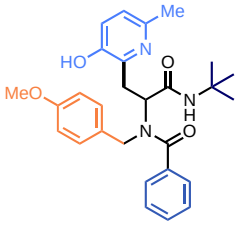
Under the defined reaction conditions, we next evaluated the reaction scope using the previously prepared dehydroalanines **2** as heteroaryl radical acceptors and 2-bromopyridine (**3a**), 3-hydroxy-2-iodo-6-methylpyridine (**3b**), and 1-iodoisoquinoline (**3c**) as radical precursors. The results are showcased in Table 3. The reductive radical conjugate addition on dehydroalanine **2a** worked efficiently with heteroaryl halides **3b** and **3c** to afford the hydroarylated products **4b** (89%) and **4c** (69%), respectively; however, the yields were relatively lower than the addition of pyridyl radical derived from **3a**. The same trend was observed when dehydroalanine **2b** reacted with heteroaryl halides **3a**-**c**, providing products **4d** (87%), **4e** (85%) and **4f** (67%), respectively. According to the observation that the yield depends on the heteroaryl halide (**3a**>**3b**>**3c**), it is feasible to propose that the efficiency of the radical conjugate addition depends mainly on the stereoelectronic nature of the heteroaryl halide rather than the structural characteristics of dehydroalanine. The above conjecture was confirmed again when the dehydroalanine **2c** was reacted with **3a**-**c**, giving the products **4g** (83%), **4h** (82%) and **4i** (61%), respectively. In this sense, the structural diversification of Ugi-derived dehydroalanines **2** was well tolerated during the radical conjugate addition, achieving the synthesis of sixteen highly functionalized peptoid-type hydroarylation products **4a**-**m**.

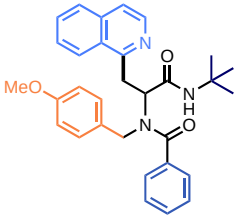
Based on the present experimental observations and the previous literature,[26] a plausible reaction mechanism for the photoredox catalyzed reductive radical conjugate addition of pyridyl radicals onto the dehydroalanines **2** is proposed (Scheme 2).

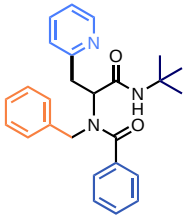
Table 3. Scope for the iridium-catalyzed reductive radical conjugate addition onto dehydroalanines **2**.[a]

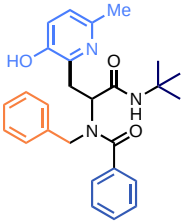


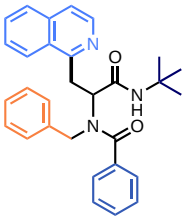

4a, (92%)

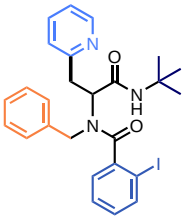

4b, (89%)

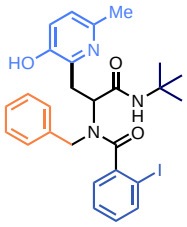

4c, (69%)

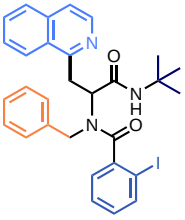

4d, (87%)

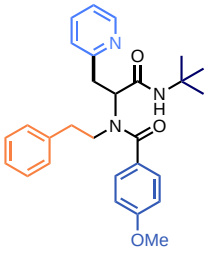

4e, (85%)

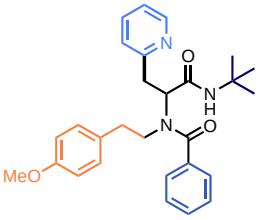

4f, (67%)

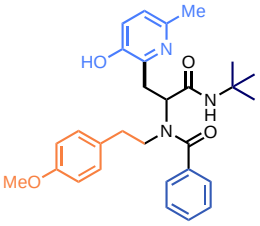

4g, (83%)

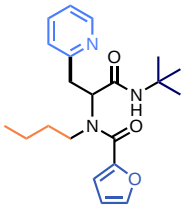

4h, (82%)

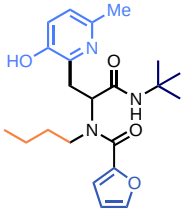

4i, (61%)

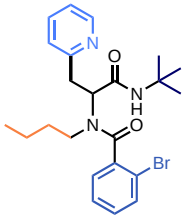

4j, (95%)

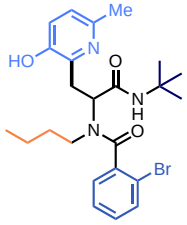

4k, (93%)


4l, (90%)


4m, (82%)

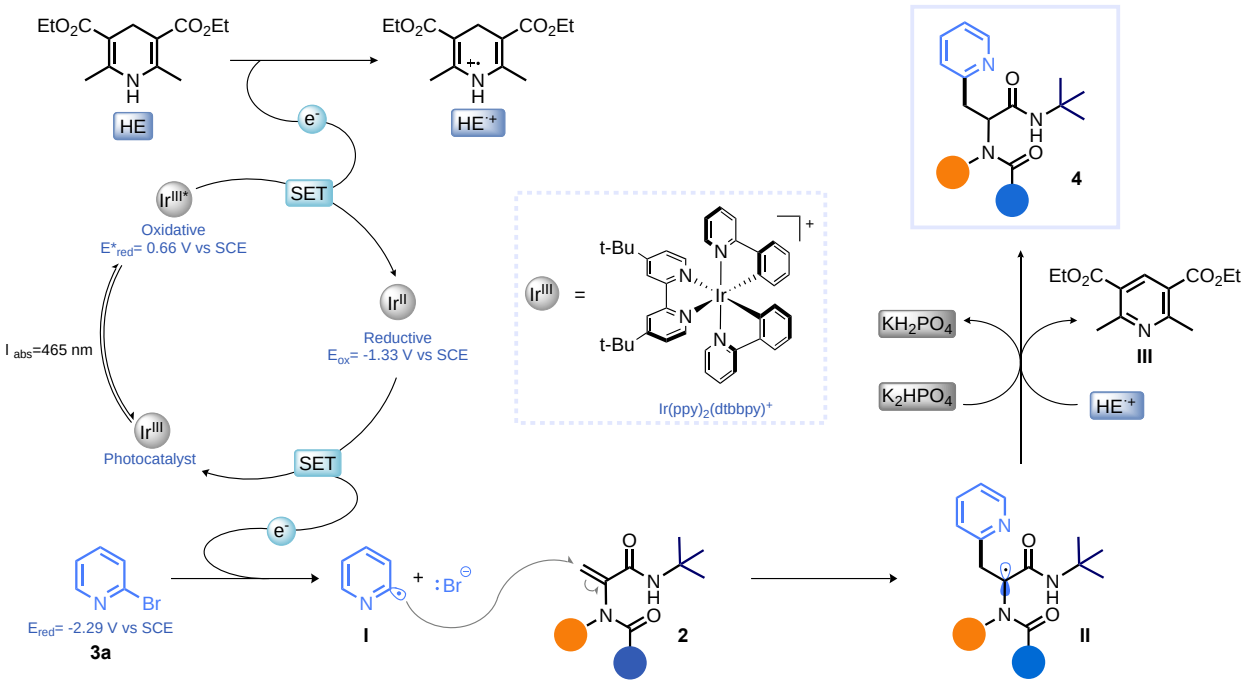

4n, (76%)


4o, (98%)


4p, (91%)

[a]Conditions: **2a-g** (0.11 mmol, 2.0 equiv), **3a-c** (0.22 mmol, 1.0 equiv), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol %), K_2HPO_4 (1.0 equiv) and Hantzsch ester (1.5 equiv) in DMSO:H_2O (5:1, 0.2 M), rt, 24 h. [b]Isolated yield after column chromatography.

Taking the reaction of 2-bromopyridine (**3a**) as an example, the reaction starts with the photoexcitation of the Ir catalyst by visible light irradiation. Subsequently, a SET process from a Hantzsch ester to a photoexcited Ir(III)* takes place to generate Ir(II) and a radical cation $\mathbf{HE}^{\bullet+}$. The strongly reducing Ir(II) can favorably undergo SET with **3a** to produce a 2-pyridyl radical **I** while the ground-state Ir(III) is regenerated. Radical conjugate addition of **I** onto dehydroalanine **2** gives rise to the intermediate radical **II**. The abstraction of hydrogen at the 4-position of $\mathbf{HE}^{\bullet+}$ by **II** leads to the hydroarylated product **4** and pyridine **III**. The use of K_2HPO_4 facilitates deprotonation of $\mathbf{HE}^{\bullet+}$ to give **III**.



Scheme 2. A proposed mechanism for the generation of heteroaryl radical and addition on dehydroalanine **2**.

Conclusions

In summary, the two-step synthetic strategy proposed in this work gives access to a series of highly functionalized non-natural β-heteroaryl α-amino acid derivatives through a free radical reductive conjugated addition and an Ir-based photocatalytic system. As the key point, peptoid-type dehydroalanines were prepared by a Ugi 4-CR/elimination reaction sequence. The importance of combining a multicomponent reaction with a homolytic addition is demonstrated, resulting in the construction of molecular complexity in just a few steps.

Experimental Section

General. The ^{1}H and ^{13}C NMR spectra were recorded on JEOL Eclipse 300 MHz, Bruker AV 400 MHz, and Bruker AVANCE III HD 500 and 700 MHz spectrometers. Chemical shifts are reported in parts per million (ppm) relative to residual proton signal of $CHCl_3$ (δ7.26) for ^{1}H NMR, and $CDCl_3$ (δ77.0) for ^{13}C NMR. The multiplicity of signals is described as follows: singlet (s), doublet (d), triplet (t), quartet (q), broad singlet (bs) or multiplet (m). NMR coupling constants are expressed in Hertz (Hz). High-resolution DART+ mass spectra were obtained on a JEOL JMS-T100LC spectrometer. Infrared spectra (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. The solvents used were purchased from Tecsiquim and Merck. All reagents used were purchased from Merck and used without further purification. Melting points were determined using a Fisher-Johns apparatus and were not corrected. Flash column chromatography was carried out using silica gel (Merck 230–400 mesh). The progress of reactions was monitored by thin-layer chromatography using silica gel 60 F254 plates purchased from Merck. UV lamp at 254 nm, vanillin and ninhydrin were used for visualizing thin-layer

chromatography. Photocatalysis reactions were carried out in a homemade photoreactor[27] equipped with 24 W blue LED lights and a fan to maintain a temperature of 25-30 °C.

General procedure for the preparation of UGI 4-CR adducts 1a-g. In a round-bottom flask, aldehyde (1 equiv.) and the corresponding amine (1 equiv.) were dissolved in methanol (0.6 M). The mixture was stirred for 15 min at room temperature. Then, the corresponding carboxylic acid (1 equiv.) and isocyanide (1 equiv.) were added, and the reaction was stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography.

Ugi 4-CR adducts **1a**–**e** were synthesized according to the previously reported procedure[24] and the NMR spectra corresponded to those reported.

3-(*tert*-Butylamino)-2-(*N*-butylfuran-2-carboxamido)-3-oxopropyl benzoate (1f). From the general procedure, the crude reaction mixture was purified by flash column chromatography (Hex:EtOAc 8:2), affording the product **1f** (201 mg, 0.48 mmol, 53% yield). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* 7.7 Hz, 2H), 7.54 (t, *J* 7.4, 1H), 7.51 – 7.42 (m, 1H), 7.40 (t, *J* 7.8 Hz, 2H), 7.05 (bs, 1H), 6.49 (dd, *J* 3.6, 1.8 Hz, 1H), 5.16 (dd, *J* 9.2, 5.6 Hz, 1H), 4.88 (dd, *J* 11.9, 5.5 Hz, 1H), 4.77 – 4.65 (m, 1H), 3.72 (bs, 1H), 3.52 (bs, 1H), 1.75 – 1.54 (m, 2H), 1.36 (s, 9H), 1.34 – 1.21 (m, 2H), 0.88 (t, *J* 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.93, 166.17, 161.87, 147.85, 144.32, 133.27, 130.24, 129.78, 128.51, 117.65, 111.82, 61.60, 59.18, 51.62, 46.56, 31.81, 28.76, 20.37, 13.78. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{23}H_{31}N_2O_5$, 415.2233 found 415.2224. IR (ATR): 3314, 3065, 2961, 2873, 1721, 1679, 1611, 1538, 1415, 1365, 1356, 1269 cm^{-1}.

2-(2-Bromo-*N*-butylbenzamido)-3-(*tert*-butylamino)-3-oxopropyl benzoate (1g). From the general procedure, the crude reaction mixture was purified by flash column chromatography (Hex:EtOAc 8:2), affording the product **1g** (133 mg, 0.26 mmol, 29% yield) as a mixture of rotamers in 1:1 ratio, as shown in NMR spectra. Yellow solid, mp: 113-115 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* 7.7 Hz, 2H), 7.59 – 7.46 (m, 2H), 7.46-7.34 (m, 2H), 7.34 – 7.24 (m, 1H), 7.24 – 7.16 (m, 1H), 7.09 – 7.00 (m, 1H), 5.41 (dd, *J* 9.4, 5.6 Hz, 0.5H-*rotamer A*), 5.05 (dd, *J* 9.1, 5.6 Hz, 0.5H-*rotamer B*), 4.95 – 4.79 (m, 1H), 4.78 – 4.69 (m, 1H), 3.38 – 3.04 (m, 2H), 1.65 – 1.39 (m, 2H), 1.33 (s, 9H), 1.07 – 0.95 (m, 2H), 0.62 (t, *J* 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.92, 167.60, 165.89, 137.52, 133.23, 132.70, 130.60, 129.71, 128.66, 128.47, 128.34, 127.60, 119.31, 61.24, 56.59, 51.54, 46.93, 31.39, 28.63, 19.93, 13.13. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{25}H_{32}BrN_2O_4$, 503.15454 found 503.15305. IR (ATR): 3264, 3062, 2959, 2873, 1721, 1671, 1618, 1551, 1427, 1327, 1272, 1252 cm^{-1}.

General procedure for the preparation of dehydroalanines 2a-g. To a solution of the corresponding Ugi 4-CR adduct (1 equiv.) in dichloroethane (0.6 M) were added DBU (6 equiv.) and TEA (3 equiv.). The mixture was stirred at room temperature for 24 h. Then, the crude reaction mixture was concentrated to dryness under reduced pressure, and the residue was purified by column chromatography.

Dehydroalanines **2a**–**e** were synthesized according to the previously reported procedure[24] and the NMR spectra corresponded to those reported.

***N*-Butyl-*N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)furan-2-carboxamide (2f).** From the general procedure, the crude reaction mixture was purified by flash column chromatography (Hex:EtOAc 7:3), affording the product **2f** (102 mg, 0.34 mmol, 82% yield). Pale yellow solid, mp: 82-85 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.40 (m, 1H), 6.98 – 6.95 (m, 1H), 6.41 – 6.38 (m, 1H), 6.21 (bs, 1H), 5.90 (bs, 1H), 5.33 – 5.29 (m, 1H), 3.59 (t, *J* 7.8 Hz,

2H), 1.62 (p, *J* 7.6 Hz, 2H), 1.39 – 1.31 (m, 2H), 1.27 (s, 9H), 0.92 (tdd, *J* 7.4, 2.9, 1.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.82, 159.68, 147.10, 144.72, 143.49, 120.24, 117.45, 111.62, 51.57, 49.40, 29.67, 28.58, 20.26, 13.87. HRMS (DART+) (*m/z*) [M+H]+ calc. for: $C_{16}H_{25}N_2O_3$, 293.18652 found 293.18713. IR (ATR): 3333, 3116, 2960, 2872, 1615, 1523, 1477, 1393, 1362, 1267, 1225, 753 cm^{-1}.

2-Bromo-*N*-butyl-*N*-(3-(*tert*-butylamino)-3-oxoprop-1-en-2-yl)benzamide (2g). From the general procedure, the crude reaction mixture was purified by flash column chromatography (Hex:EtOAc 8:2), affording the product **2g** (88 mg, 0.23 mmol, 95% yield) as a mixture of rotamers in 7:3 ratio, as shown in NMR spectra. Colorless oil. *Major rotamer:* ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* 8.1 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.25 – 7.18 (m, 2H), 5.85 (s, 1H), 5.75 (bs, 1H), 5.49 (s, 1H), 3.66 (bs, 2H), 1.67 (p, *J* 7.8 Hz, 2H), 1.44 – 1.36 (m, 2H), 1.31 (s, 9H), 0.95 (t, *J* 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.63, 162.58, 142.63, 138.10, 132.95, 130.47, 128.28, 126.95, 120.89, 118.47, 51.80, 47.95, 29.66, 28.79, 20.23, 13.93. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{18}H_{26}BrN_2O_2$, 381.11777 found 381.11622. IR (ATR): 3343, 3057, 2960, 2872, 1623, 1520, 1392, 1363, 1257, 1226, 742 cm^{-1}.

General procedure for the synthesis of hydroheteroarylated products 4a-p. In a microwave tube previously dried in an oven with a magnetic stirring bar were added DHA **2** (2 equiv.), heteroarene **3** (1 equiv.), Hantzsch ester (1.5 equiv.), $[Ir(dtbbpy)(ppy)_2]PF_6$ (1 mol%), and K_2HPO_4 (1 equiv.). Then, the tube was sealed and degassed using three freeze-pump-thaw cycles with liquid nitrogen. Next, 1.5 mL of a mixture of DMSO/H_2O (5:1), previously degassed, was added; and the reaction mixture was irradiated with blue LED light. After complete consumption of the starting materials (monitored by TLC, ca. 24 h), crude reaction mixture was extracted with EtOAc/H_2O. The organic phases were combined, dried over anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by flash column chromatography using the indicated solvent mixture to afford the title compound.

***N*-(1-(*tert*-Butylamino)-1-oxo-3-(pyridin-2-yl)propan-2-yl)-*N*-(4-methoxybenzyl)benzamide (4a).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4a** (34 mg, 0.07 mmol, 92% yield). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.56 (bs, 1H), 7.60 (bs, 1H), 7.41–7.27 (m, 3H), 7.25 – 7.09 (m, 4H), 7.06 –6.69 (m, 4H), 4.90 (bs, 1H), 4.53 (d, *J* 15.3 Hz, 1H), 4.26 (d, *J* 16.0 Hz, 1H), 3.76 (s, 3H), 3.50 (bs, 2H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.21, 169.32, 159.19, 158.70, 149.15, 136.83, 136.44, 129.86, 129.33, 129.06, 128.61, 126.85, 124.31, 121.89, 114.17, 61.32, 55.41, 52.94, 51.11, 37.56, 28.65. HRMS (DART+) (*m/z*) [M+H]+ calc. for: $C_{27}H_{32}N_3O_3$ 446.24437, found 446.24446. IR (ATR): 3278, 3072, 3969, 2953, 2834, 1671, 1610, 1556, 1508, 1390, 1362, 1288, 1243 cm^{-1}.

***N*-(1-(*tert*-Butylamino)-3-(3-hydroxy-6-methylpyridin-2-yl)-1-oxopropan-2-yl)-*N*-(4-methoxybenzyl)benzamide (4b).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4b** (30 mg, 0.06 mmol, 89% yield). Yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (bs, 2H), 7.46 – 7.40 (m, 3H), 7.14 (bs, 1H), 7.07 (d, *J* 7.9 Hz, 2H), 6.94 (d, *J* 8.2 Hz, 1H), 6.80 (d, *J* 8.3 Hz, 2H), 4.87 (bs, 1H), 4.70 (bs, 2H), 3.77 (s, 3H), 3.47 (bs, 1H), 3.01 (bs, 1H), 2.46 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.42, 170.55, 159.56, 149.14, 144.26, 144.24, 136.55, 135.53, 130.39, 129.68, 128.86, 128.60, 127.37, 123.48, 114.42, 60.55, 59.68, 55.44, 51.87, 28.62, 21.20, 14.34. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{28}H_{34}N_3O_4$ 476.25493, found 476.25289. IR (ATR): 3246, 3078, 2966, 1609, 1512, 1453, 1393, 1362, 1279, 1245 cm^{-1}.

***N*-(1-(*tert*-Butylamino)-3-(isoquinolin-1-yl)-1-oxopropan-2-yl)-*N*-(4-methoxybenzyl)benzamide (4c).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4c** (25 mg, 0.05 mmol, 69% yield). Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (bs, 1H), 8.09 (bs, 1H), 7.79 (bs, 1H), 7.73–7.44 (m, 3H), 7.40–7.14 (m, 6H), 6.99 (bs, 2H),

6.73 (dd, *J* 9.1, 2.5 Hz, 2H), 5.16 (dt, *J* 8.5, 4.2 Hz, 1H), 4.49 (bs, 1H), 4.26 (bs, 1H), 4.16–4.05 (m, 1H), 3.97 (bs, 1H), 3.73 (s, 3H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.74, 169.39, 158.39, 148.98, 140.83, 136.48, 136.17, 130.16, 130.07, 129.54, 129.18, 129.04, 128.41, 127.47, 127.28, 126.64, 125.08, 119.96, 114.05, 60.38, 55.23, 52.98, 51.0, 33.66, 28.56. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{31}H_{34}N_3O_3$ 496.26002, found 496.26043. IR (ATR): 3407, 3303, 3054, 2963, 2853, 1674, 1623, 1511, 1452, 1389, 1361, 1244 cm^{-1}.

***N*-Benzyl-*N*-(1-(*tert*-butylamino)-1-oxo-3-(pyridin-2-yl)propan-2-yl)benzamide (4d).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4d** (32 mg, 0.07 mmol, 87% yield). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (bs, 1H), 7.53 (bs, 1H), 7.45 – 7.01 (m, 12H), 6.95 (bs, 1H), 4.93 (bs, 1H), 4.59 (bs, 1H), 4.39 (bs, 1H), 3.49 (bs, 2H), 1.21 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.37, 169.21, 158.60, 149.16, 137.21, 136.78, 136.39, 129.85, 128.76, 128.58, 127.88, 127.65, 126.80, 124.28, 121.89, 61.35, 53.37, 51.16, 37.74, 28.63. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{26}H_{30}N_3O_2$ 416.23380, found 416.23417. IR (ATR): 3277, 3069, 2985, 2955, 2923, 1670, 1614, 1554, 1441, 1410, 1356, 1340, 1265, 1225 cm^{-1}.

***N*-Benzyl-*N*-(1-(*tert*-butylamino)-3-(3-hydroxy-6-methylpyridin-2-yl)-1-oxopropan-2-yl)benzamide (4e).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4e** (30 mg, 0.06 mmol, 85% yield). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (bs, 2H), 7.45–7.36 (m, 3H), 7.29–7.23 (m, 3H), 7.16 (bs, 3H), 6.94 (dd, *J* 8.1, 4.7 Hz, 2H), 4.92 (bs, 1H), 4.84–4.64 (m, 2H), 3.57–3.43 (m, 1H), 3.08 (d, *J* 13.5 Hz, 1H), 2.46 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.41, 170.52, 144.00, 136.79, 135.47, 130.34, 129.12, 129.03, 128.82, 128.53, 128.20, 127.88, 127.24, 126.92, 123.58, 59.82, 52.14, 51.85, 28.54, 27.65, 21.18. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{27}H_{32}N_3O_3$ 446.24437, found 446.24308. IR (ATR): 3401, 3259, 3061, 3030, 2966, 2926, 1642, 1619, 1576, 1493, 13952, 1363, 1279, 1258 cm^{-1}.

***N*-Benzyl-*N*-(1-(*tert*-butylamino)-3-(isoquinolin-1-yl)-1-oxopropan-2-yl)benzamide (4f).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4f** (22 mg, 0.04 mmol, 67% yield). Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (bs, 1H), 8.08 (bs, 1H), 7.81 (bs, 1H), 7.71 – 7.61 (m, 1H), 7.59 – 7.49 (m, 2H), 7.38 – 7.17 (m, 8H), 7.11 (bs, 1H), 7.00 (bs, 1H), 5.24 (bs, 1H), 4.62 (d, *J* 17.0 Hz, 1H), 4.37 (d, *J* 14.8 Hz, 1H), 4.17 – 3.84 (m, 2H), 1.25 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.28, 169.49, 152.63, 143.06, 141.21, 136.55, 136.30, 130.53, 130.29, 129.72, 128.82, 128.55, 127.91, 127.80, 127.65, 127.47, 126.78, 125.25, 120.11, 60.46, 53.64, 51.18, 33.90, 28.71. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{30}H_{32}N_3O_2$ 466.24945, found 466.24751. IR (ATR): 3311, 3058, 2970, 2927, 2853, 1669, 1620, 1549, 1450, 1389, 1361, 1269, 1250 cm^{-1}.

***N*-Benzyl-*N*-(1-(*tert*-butylamino)-1-oxo-3-(pyridin-2-yl)propan-2-yl)-2-iodobenzamide (4g).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4g** (28 mg, 0.05 mmol, 83% yield) as a mixture of rotamers in 1:1 ratio, as shown in NMR spectra. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, *J* 14.1 Hz, 1H), 7.90 – 7.73 (m, 1H), 7.65 – 7.45 (m, 1H), 7.38–7.06 (m, 9H), 6.91–6.59 (m, 2H), 5.26–5.10 (m, 0.5H-*rotamer A*), 4.96–4.76 (m, 0.5H-*rotamer B*), 4.66–4.21 (m, 2H), 3.82–3.44 (m, 2H), 1.25 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, *the signals described are attributable to a single rotamer*) δ 171.78, 168.62, 158.56, 149.18, 141.77, 139.61, 136.69, 130.49, 128.77, 128.58, 128.50, 128.17, 127.87, 126.80, 124.23, 121.87, 93.29, 59.33, 52.40, 51.29, 37.68, 28.77. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{26}H_{29}IN_3O_2$ 542.13044, found 542.13207. IR (ATR): 3411, 3279, 3061, 2956, 2927, 1674, 1638, 1452, 1433, 1391, 1361, 1299, 1224 cm^{-1}.

***N*-Benzyl-*N*-(1-(*tert*-butylamino)-3-(3-hydroxy-6-methylpyridin-2-yl)-1-oxopropan-2-yl)-2-iodobenzamide (4h).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4h** (21 mg, 0.04 mmol, 82% yield) as

a mixture of rotamers, as shown in NMR spectra. Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (bs, 2H), 7.44 – 7.40 (m, 3H), 7.30 – 7.26 (m, 3H), 7.17 (bs, 3H), 6.93 (bs, 1H), 4.94 (bs, 1H), 4.76 (bs, 2H), 3.48 (bs, 1H), 3.01 (bs, 1H), 2.46 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.60, 171.88, 150.01, 149.09, 144.41, 139.61, 135.58, 130.83, 130.27, 128.97, 128.90, 128.76, 128.05, 127.20, 123.21, 93.47, 59.57, 51.76, 33.66, 32.87, 28.53, 23.83. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{27}H_{31}IN_3O_3$ 572.14101, found 572.13996. IR (ATR): 3246, 3078, 2966, 2929, 1609, 1573, 1512, 1453, 1393, 1362, 1279, 1245 cm^{-1}.

***N*-Benzyl-*N*-(1-(*tert*-butylamino)-3-(isoquinolin-1-yl)-1-oxopropan-2-yl)-2-iodobenzamide (4i).**From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4i** (17 mg, 0.03 mmol, 61% yield) as a mixture of rotamers, as shown in NMR spectra. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (bs, 1H), 7.83 – 7.70 (m, 3H), 7.61 (m, 2H), 7.45 – 7.11 (m, 8H), 7.03 (bs, 1H), 6.83 (bs, 1H), 5.53 (bs, 1H), 5.18 – 4.89 (m, 1H), 4.87 – 4.69 (m, 1H), 4.45 (bs, 1H), 4.25 (bs, 1H), 1.24 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.61, 168.87, 151.91, 142.00, 141.82, 139.45, 136.67, 135.96, 130.55, 130.42, 128.93, 128.68, 128.48, 128.35, 128.15, 127.71, 127.46, 126.80, 124.68, 120.52, 93.11, 61.95, 54.90, 51.34, 33.17, 28.79. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{30}H_{31}IN_3O_2$ 592.14609, found 592.14341. IR (ATR): 3410, 3305, 3054, 2964, 2925, 1972, 1673, 1624, 1584, 1562, 1515, 1389, 1361, 1266, 1224 cm^{-1}.

***N*-(1-(*Tert*-butylamino)-1-oxo-3-(pyridin-2-yl)propan-2-yl)-*N*-(4-methoxyphenethyl)benzamide (4j).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4j** (30 mg, 0.06 mmol, 93% yield). Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (bs, 1H), 7.62 (t, *J* 7.8 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.35 (t, *J* 7.4 Hz, 2H), 7.27 (bs, 1H), 7.16 (dd, *J* 7.5, 4.9 Hz, 1H), 7.13 – 7.06 (m, 3H), 6.70 (bs, 3H), 5.28 (bs, 1H), 3.73 (s, 3H), 3.60 – 3.39 (m, 2H), 3.34 (bs, 1H), 2.75 (bs, 1H), 2.45 (bs, 1H), 2.07 (bs, 1H), 1.37 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.63, 170.15, 158.36, 158.09, 149.32, 136.80, 136.39, 130.13, 129.87, 129.72, 128.63, 126.59, 124.13, 121.93, 114.03, 59.89, 55.37, 51.31, 50.40, 36.84, 35.12, 28.80. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{28}H_{34}N_3O_3$ 460.26002, found 460.25821. IR (ATR): 3298, 3060, 2964, 2835, 1677, 1620, 1537, 1511, 1452, 1392, 1363, 1247, 1262 cm^{-1}.

***N*-(1-(tert-butylamino)-3-(3-hydroxy-6-methylpyridin-2-yl)-1-oxopropan-2-yl)-N-(4-methoxyphenethyl)benzamide (4k).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4k** (23 mg, 0.04 mmol, 90% yield). Pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.51 – 7.42 (m, 4H), 7.37 (d, *J* 7.4 Hz, 2H), 7.15 (d, *J* 8.3 Hz, 1H), 6.95 (d, *J* 8.3 Hz, 1H), 6.72 (s, 3H), 5.30 (bs, 1H), 3.83 (t, *J* 12.1 Hz, 1H), 3.73 (s, 3H), 3.66 – 3.56 (m, 1H), 3.51 – 3.40 (m, 1H), 2.98 (d, *J* 12.6 Hz, 1H), 2.90 – 2.82 (m, 1H), 2.58 – 2.50 (m, 1H), 2.47 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 173.80, 172.25, 158.51, 149.81, 143.95, 135.86, 130.20, 129.79, 129.61, 128.83, 126.69, 126.50, 123.36, 114.17, 58.62, 55.37, 51.92, 49.21, 35.41, 32.86, 28.60, 23.48. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{29}H_{36}N_3O_4$ 490.26522, found 490.26455. IR (ATR): 6258, 3219, 3062, 2963, 2925, 1612, 1576, 1511, 1453, 1362, 1321, 1280, 1246, 1109, 1033 cm^{-1}.

***N*-(1-(*tert*-butylamino)-1-oxo-3-(pyridin-2-yl)propan-2-yl)-4-methoxy-*N*-phenethylbenzamide (4l).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4l** (26 mg, 0.05 mmol, 95% yield). Pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.53 (bs, 1H), 7.60 (td, *J* 7.7, 1.8 Hz, 1H), 7.19 (bs, 4H), 7.17 – 7.13 (m, 2H), 7.07 (bs, 2H), 6.96 – 6.85 (m, 1H), 6.84 (d, *J* 8.7 Hz, 2H), 5.22 (bs, 1H), 3.82 (s, 3H), 3.50 (bs, 4H), 2.84 (bs, 1H), 2.53 (bs, 1H), 1.37 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 173.60, 170.23, 160.95, 158.07, 149.30, 138.51, 136.77, 128.87, 128.72, 128.62, 128.48, 126.56, 124.10, 121.88, 113.90, 60.19, 55.49, 51.32, 50.40, 36.92, 35.87, 28.80. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{28}H_{34}N_3O_3$ 460.26002, found 460.25894. IR (ATR): 3243, 3213, 3022, 2957, 2924, 1667, 1638, 1606, 1560, 1477, 1366, 1334, 1247, 1170, 1127 cm^{-1}.

***N*-Butyl-*N*-(1-(*tert*-butylamino)-1-oxo-3-(pyridin-2-yl)propan-2-yl)furan-2-carboxamide (4m).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4m** (19 mg, 0.05 mmol, 82% yield). Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (bs, 1H), 7.57 (td, *J* 7.7, 1.9 Hz, 1H), 7.45 (d, *J* 1.7 Hz, 1H), 7.19 (d, *J* 7.7 Hz, 1H), 7.11 (dd, *J* 7.6, 5.0 Hz, 1H), 6.91 (bs, 1H), 6.45 (dd, *J* 3.5, 1.7 Hz, 1H), 5.19 (bs, 1H), 3.61 (bs, 1H), 3.57 – 3.42 (m, 2H), 3.31 (bs, 1H), 1.62 – 1.52 (m, 1H), 1.40 – 1.37 (m, 1H), 1.31 (s, 9H), 1.30 – 1.23 (m, 2H), 0.86 (t, *J* 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.67, 161.58, 158.04, 149.09, 148.10, 143.98, 136.84, 124.09, 121.81, 116.73, 111.56, 60.83, 51.30, 46.83, 37.17, 32.10, 28.72, 20.34, 13.81. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{21}H_{30}N_3O_3$ 372.22872, found 372.22958. IR (ATR): 3417, 3315, 3065, 2961, 2931, 1679, 1614, 1537, 1477, 1392, 1364, 1261, 1225 cm^{-1}.

***N*-Butyl-*N*-(1-(*tert*-butylamino)-3-(3-hydroxy-6-methylpyridin-2-yl)-1-oxopropan-2-yl)furan-2-carboxamide (4n).** From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4n** (17 mg, 0.04 mmol, 76% yield). Pale yellow oil. ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.52 (dd, *J* 1.9, 0.9 Hz, 1H), 7.14 (d, *J* 8.3 Hz, 2H), 6.92 (d, *J* 8.3 Hz, 1H), 6.52 (dd, *J* 3.5, 1.8 Hz, 1H), 5.11 (d, *J* 11.1 Hz, 1H), 3.85 (bs, 1H), 3.78 (t, *J* 12.0 Hz, 1H), 3.56 (tt, *J* 10.9, 4.4 Hz, 1H), 2.88 (d, *J* 12.9 Hz, 1H), 2.43 (s, 3H), 1.75 – 1.64 (m, 1H), 1.57 (bs, 1H), 1.34 – 1.28 (m, 2H), 1.27 (s, 9H), 0.89 (t, *J* 7.4 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.14, 161.90, 149.76, 147.74, 144.49, 144.09, 126.59, 123.27, 117.80, 111.76, 59.92, 51.92, 46.34, 33.22, 32.50, 28.50, 23.36, 20.37, 13.77. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{22}H_{32}N_3O_4$ 402.23928, found 402.23726. **IR (ATR): 3265, 3221, 3140, 3077, 2960, 1650, 1606, 1578, 1485, 1363, 1297, 1280, 1223,1104 cm^{-1}.**

2-Bromo-*N*-butyl-*N*-(1-(*tert*-butylamino)-1-oxo-3-(pyridin-2-yl)propan-2-yl)benzamide (4o). From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4o** (34 mg, 0.07 mmol, 98% yield) as a mixture of rotamers in 1:1 ratio, as shown in NMR spectra. Pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (bs, 1H), 7.62 (td, *J* 7.7, 3.9 Hz, 1H), 7.57 – 7.47 (m, 1H), 7.31 – 7.25 (m, 2H), 7.23 – 7.18 (m, 1H), 7.17 – 7.12 (m, 1H), 6.92 – 6.85 (m, 1H), 5.52 (t, *J* 8.4 Hz, 0.5H-*rotamer A*), 5.06 (t, *J* 8.0 Hz, 0.5H-*rotamer B*), 3.68 – 3.47 (m, 2H), 3.34 – 3.30 (m, 1H), 3.15 – 3.09 (m, 1H), 1.55 – 1.45 (m, 2H), 1.39 – 1.33 (m, 9H), 1.07 – 0.94 (m, 2H), 0.70 – 0.62 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, *the signals described are attributable to a single rotamer*) δ 170.84, 169.65, 158.26, 149.39, 138.25, 136.66, 132.91, 130.44, 128.16, 127.55, 124.37, 121.83, 119.68, 57.90, 51.37, 47.41, 36.29, 31.40, 28.79, 20.19, 13.38. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{23}H_{31}BrN_3O_2$ 460.15996, found 460.16157. IR (ATR): 3406, 3323, 3058, 2960, 2872, 1678, 1622, 1536, 1475, 1432, 1391, 1363, 1259, 1225 cm^{-1}.

2-Bromo-*N*-butyl-*N*-(1-(*tert*-butylamino)-3-(3-hydroxy-6-methylpyridin-2-yl)-1-oxopropan-2-yl)benzamide (4p). From the general procedure, the crude reaction mixture was purified by flash column chromatography using Hex:EtOAc mixture (10:0 to 0:10 v/v) as eluent, affording the product **4p** (30 mg, 0.06 mmol, 91% yield) as a mixture of rotamers in, as shown in NMR spectra. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K) δ 7.61 – 7.45 (m, 1H), 7.45 – 7.09 (m, 4H), 6.93 (d, *J* 8.1 Hz, 1H), 5.46 (bs, 1H), 3.71 (t, *J* 12.2 Hz, 1H), 3.26 – 3.05 (m, 2H), 2.82 (d, *J* 12.2 Hz, 1H), 2.42 (s, 3H), 1.62 – 1.39 (m, 2H), 1.25 (s, 9H), 1.00 (p, *J* 7.2 Hz, 2H), 0.63 (t, *J* 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 223 K) δ 171.87, 170.92, 149.27, 143.52, 136.57, 133.14, 130.90, 128.65, 127.77, 127.63, 126.72, 123.50, 119.49, 57.00, 51.87, 46.43, 31.66, 31.28, 28.14, 23.47, 19.94, 13.39. HRMS (DART+) (*m/z*) $[M+H]^+$ calc. for: $C_{24}H_{33}BrN_3O_3$ 490.16198, found 490.16194. IR (ATR): 3268, 3069, 2960, 2929, 2873, 1648, 1618, 1454, 1423, 1363, 1300, 1280, 1257, 1105 cm^{-1}.

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Supplementary Material

^{1}H and ^{13}C NMR spectra of all products are available on the supplementary material file associated with this paper.

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