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PPh_3-catalyzed intramolecular cyclization of hydroxypropargylamides: Synthesis of structurally diverse morpholinone derivatives

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The metal-free synthesis of substituted morpholinones through a sequential intramolecular post-Ugi cyclization strategy is described. In the subsequent step, Ugi adducts hydroxy propargylamides derivatives undergo chemo- and regioselective 6-*exo-dig* catalytic cyclization to afford *O*-cyclized products in the presence of triphenylphosphine. This sequence offers an engrossing functionalized morpholinone scaffold involving moderate reaction conditions with broad substrate scope and moderate to good yields.

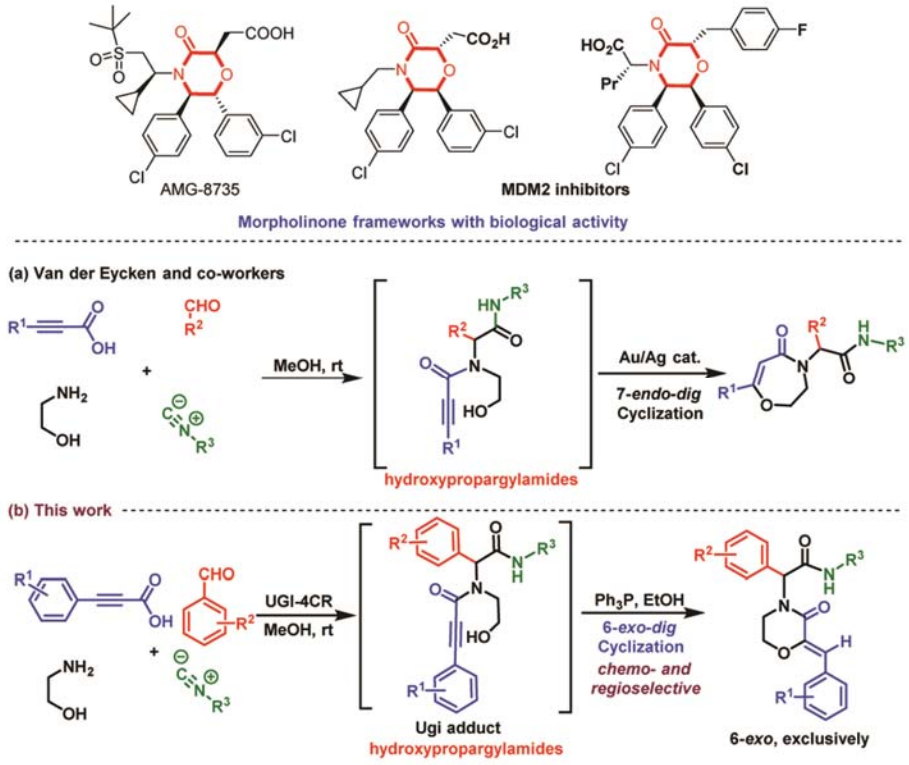
Keywords: Ugi four-component reaction (U-4CR), post-Ugi transformations, 6-*exo-dig* cyclization, morpholinone, hydroxypropargylamide

The synthesis of complex biologically active molecules with diverse role from simple commercially convenient starting materials is an attention seeking approach in modern synthetic glycochemistry and drug discovery. In this context, linking the isocyanide-based multicomponent reactions (IMCRs) with post-transformation has been widely applied in the construction of complex heterocyclic scaffolds[1-6] due to their unique advantages in medicinal chemistry. Among these, sequential Ugi four-component reaction (U-4CR) and post-transformation have a long history in organic chemistry and is the most powerful approach for the synthesis of polyfunctional compounds[7,8]. It permits a rapid instalment of precondition functional groups in the resulting Ugi adducts, while simultaneously served as a powerful tool for constructing innumerable heterocycles in an efficient and atom-economic manner.

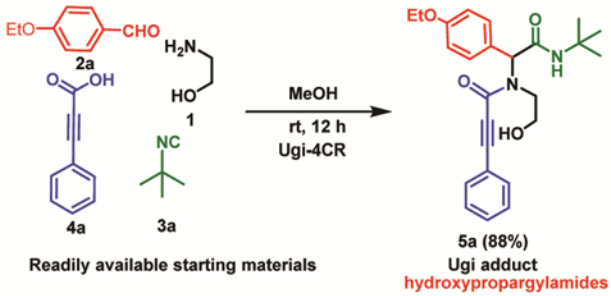
For example, using alkynoic acids, the alkyne moiety could be introduced in Ugi precursors, given the polyfunctionalized scaffolds from the similar starting materials by solely involving distinct metal catalysed post- Ugi hetero-[9-12] and carbo-cyclizations[13,14]. This method provides not only an efficacious entry to several common heterocycles but also develop the wide and structurally multifaceted heterocyclic scaffolds. In this regard, pioneering work was carried out by Van der Eycken and Balalaie group to access functionalized heterocyclic backbones such as oxindoles, pyrrolones, oxazepine, and benzazepines using a propiolic acid moiety as starting material in the Ugi-4CR[15-18]. In addition, Eycken group successfully established gold- and silver-catalyzed 7-*endo-dig* cyclizations for the synthesis of oxazepines from hydroxypropargylamides (Scheme Ia) [19].

In all the previous record, such cyclizations were performed in the presence of metal catalysts. In contrast, reaction pathways that can be changed by tuning the catalysts thus giving rise to completely different types of products from the same reactants still remain interesting challenge in organic synthesis. However, development of metal-free strategies are gaining importance because of increasing demand for the development of environmentally friendly methodologies and also will be of interest to the chemists. Albeit, the chemo-selective formation of Ugi product *via* intramolecular cyclization without using metal catalysts involving several nucleophilic/ electrophilic sites is still a challenging work.

Here, we attempted to develop intramolecular 6-*exo-dig* post-Ugi cyclization of hydroxypro-pargylamides Ugi adducts using triphenylphosphine for the synthesis of functionalized morpholinone derivatives (Scheme Ib). Morpholinone derivatives are ubiquitous heterocycles found in many biologically important molecules[20-24]. Compounds belonging to this structural class have been testified to evaluate their distinct biological roles, including MDM2 inhibitor[25,26] and menin-MLL1 inhibitor[27] (Scheme I).



Scheme I — Post-Ugi cyclization pathways of hydroxypropargylamide Ugi adducts



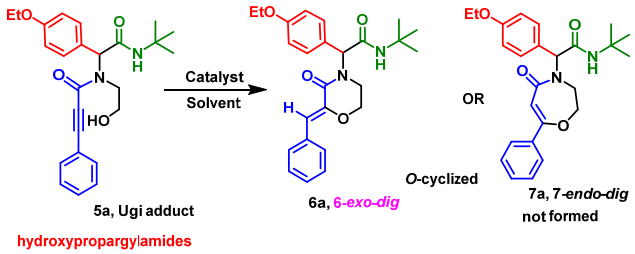
Scheme II — Synthesis of hydroxypropargylamides **5a** Ugi adducts through Ugi-4CR

Results and Discussion

To test the feasibility of our hypothesis, the acyclic substituted hydroxypropargylamides precursors **5a** was chosen as the model substrate and synthesized *via* Ugi-4CR reaction using 1,2-amino alcohol (**1**, 1.0 equiv), benzaldehyde (**2a**, 1.0 equiv) in the presence of *tert*-butyl isocyanide (**3a**, 1.0 equiv) and phenylpropiolic acid (**4a**, 1.0 equiv) in methanol at ambient temperature (Scheme II).

Primarily, the process is followed by using catalyst triphenylphosphine as a nucleophile. Because, the uniqueness of adding nucleophiles to α-position of an alkyne moiety using triphenylphosphine was previously reported by Trost (1997) [28]. The beginning

Table I — Optimization of reaction conditions [a]



Entry	Catalyst (mol%)	Solvent	Yield of **6a** (%) [b]
1	PPh_3 (10)	Toluene	28
2	PPh_3 (10)	MeOHEtOH	48
3	PPh_3 (10)	CH_3CN	59
4	PPh_3 (10)		42
5	PPh_3 (10)	DMF	ND [c]
6	PPh_3 (20)	EtOH	70
7	PPh_3 (30)	EtOH	83
8	PPh_3 (40)	EtOH	83

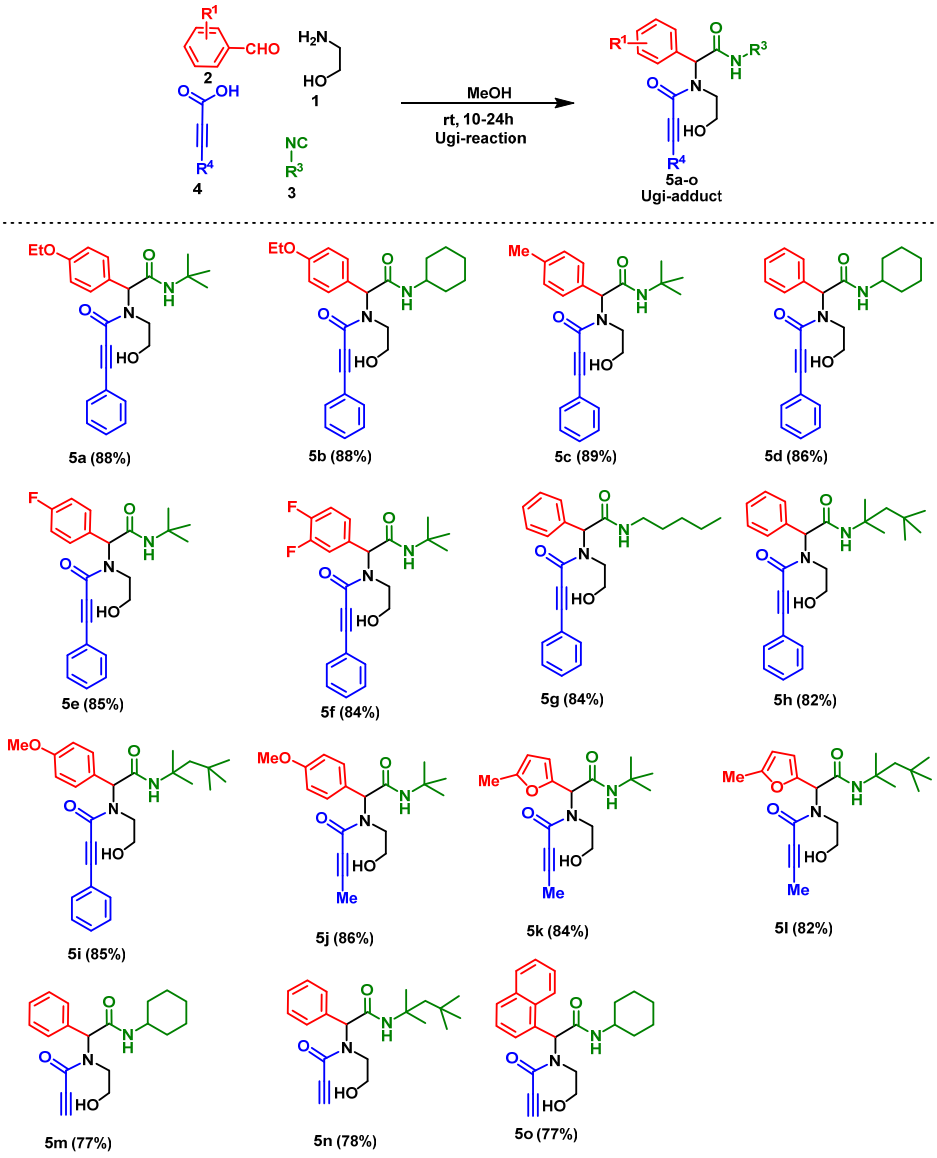
[a] Unless otherwise stated, all the reactions were run with **5a** (1.0 mmol), PPh_3 (x mol %), and solvent (5.0 mL) at 80°C for 10 h. [b] Isolated yield after silica gel chromatography. [c] Not detected (N.D.)

investigation was carried out using toluene as a solvent with 10 mol% of triphenylphosphine at 80°C showing a slight conversion (Table I, entry 1). Then, we planned to activate the hydroxypropargylamides (**5a**) using protic solvents such as alcohol for the cyclization

process (entry 2-3). Surprisingly, triphenylphosphine explored not only as an effective generation of **6a** but also provide control on the chemo- and regioselective 6-*exo-dig* oxocyclization to furnish the morpholinone **6a** exclusively. Howbeit, we have not obtained even a trace quantity of the corresponding 7-*endo-dig* **7a** product. The ethanol was the best reaction solvent in comparison with other solvents (entry 3). Thereafter, we investigated the effect of the amount[29-31] of catalyst on the obtained products yield by using 20, 30, and 40 mol % of triphenylphosphine (entry 6-8) and as a result, the best product yield obtained in case of 30 mol % of triphenylphosphine in ethanol (Table I, entry 7). Consequently we anticipated that lower yield was obtained in case of lower concentration due to the unfinished starting material remains in the reaction mixture as well as needed a longer time.

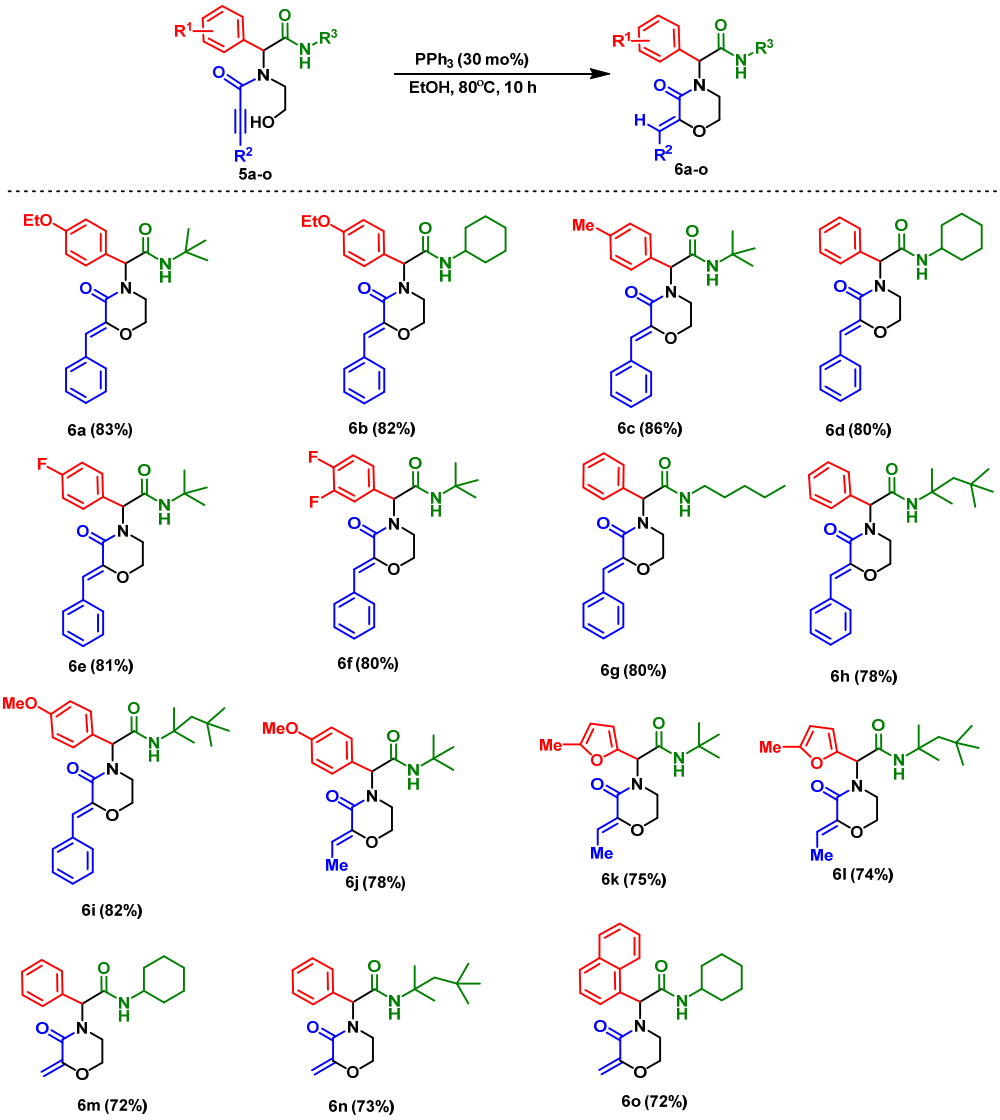
In order to explore the generality of this reaction, a library of Ugi adducts hydroxypropargylamides are obtained from using distinct Ugi precursors like glycosyl amino alcohol, aldehydes, isocyanides, as well as phenyl propiolic acid derivatives. In all cases, the Ugi-adduct (**5a–5o**) were produced as a mixture of rotamers with good to high yields (Table II).

Table II — Synthesis of hydroxypropargylamide Ugi adducts [a,b]



[a] Reaction conditions: 2-aminoethanol **1** (1 mmol), aldehyde **2** (1 mmol), isocyanide **3** (1 mmol), and acid **4** (1 mmol) in 5 mL of methanol was stirred at RT for 10-24 h. The precipitate was filtered. [b] Isolated yield.

Table III — One-pot Ugi-cyclization for the synthesis of morpholoninone [a,b]

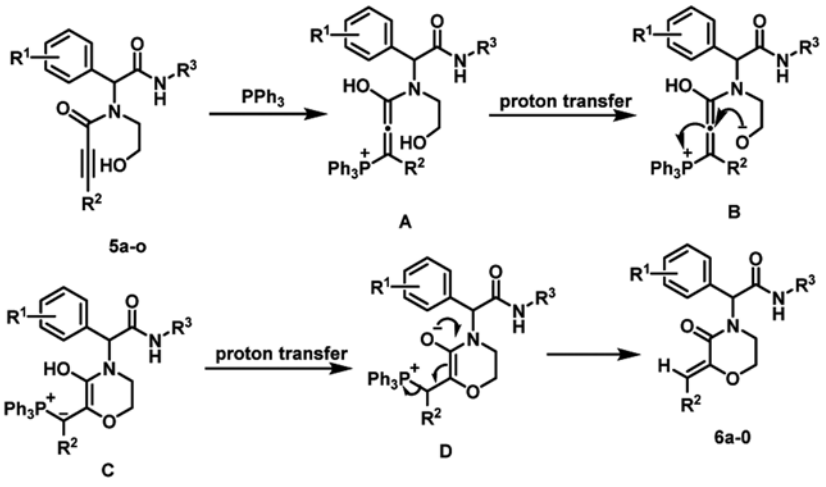


[a] General conditions: PPh_3 (30 mol%), EtOH (5 mL); [b] Isolated yield.

To further simplify the process, the synthesized Ugi products directly undergo intramolecular cyclization without any purification catalysed by triphenylphosphine under optimized reaction conditions (Table I, entry 7).Various substituents on the alkynes, isonitriles and aldehydes were well tolerated in this process. Even, several aldehyde derivatives containing electron-donating or halogen substituents have successfully followed this pathway to provide the desired products in moderate to good yields. Further different derivatives of desired product were obtained by varying isocyanides moiety, although, there is no any specific electronic effect on the product yield was noticed when *tert*-butyl isocyanide (**6a, 6c, 6e−6f**), and cyclohexyl isocyanide (**6b, 6d**), 1-pentyl isocyanide (**6g**) and 1,1,3, 3-tetramethylbutyl isocyanide (**6h-i**) were subjected to reaction, provided the desired products in good yields (Table III).

Whereas on switching to simple propiolic acid, the reaction furnished the corresponding **6m-o** in lower yields of 72−73%. However, the nucleophilic addition of ethanol to terminal alkyne substrate leads to the generation of unwanted side product *i.e.* ethyl ether or may cause self-oligomerization[32] also.

Plausible mechanism pathways for this process are provided in Scheme III. The first triphenylphosphine activates the alkyne π-bond of Ugi adduct **5** through



Scheme III — Plausible mechanism for morpholinone **6a-o** formation

nucleophilic addition to form intermediate **A.** Then proton transfer from the OH group of the sugar forming intermediate **B** undergoes umpolung Michael addition at the α position resulting in **C**[33]. After the elimination of triphenylphosphine, the desired morpholinone **6a-o** were generated (Scheme III).

Experimental Section

General Experimental Information

Unless otherwise specified, all reactions were carried out under air atmosphere in oven-dried round-bottom flasks and the heating reactions were performed in oil bath. All commercially available reagents were purchased from commercial sources and were used without further purification. All reactions were monitored by thin layer chromatography over silica gel-coated TLC plates. Thin-layer chromatography (TLC) was performed on 60 F254 silica gel, pre-coated on aluminum plates, and revealed with either a UV lamp (λ_{max} = 254 nm) with a specific color reagent (iodine vapors) was used. Silica gel 230-400 mesh was used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV 400 MHz spectrometer. Chemical shifts δ are given in ppm relative to the residual signals of tetramethylsilane in $CDCl_3$ for ^{1}H and ^{13}C NMR. Coupling constants are given in hertz. The HRMS spectra were recorded as ESI-HRMS on Q-TOF mass spectrometer. Commercially available grades of organic solvents of adequate purity are used in all reactions.

General procedure for the synthesis of compounds 6a-o

To the stirred solution of Ugi-hydroxypropargylamides adduct **5a-o** (1 mmol) in 5 mL of EtOH was added triphenylphosphine (30%) at RT. The reaction mixture was stirred at 80 °C for 10 h until the reaction reached completion as evidenced by TLC. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: hexane/ EtOAc) to afforded morpholinone products (**6a-o**).

General procedure for one-pot synthesis of morpholinone 6a-o

A solution of aromatic aldehyde (**2**, 1.0 mmol), 1,2-amino alcohol (**1**, 1.0 mmol), acid (**4**, 1.0 mmol), isocyanide (**3**, 1.0 mmol) in MeOH (5 mL) was stirred at rt for 10-24 hrs. Solvents were removed under vacuum. This crude Ugi-hydroxypropargylamides adduct **5** was treated with added triphenylphosphine (30%) in EtOH (5 mL) at 80 ºC and was allowed to stir at same temperature for 10 hrs until the reaction reached completion as evidenced by TLC. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: hexane/ EtOAc) to afforded morpholinone products (**6a-o)**.

6a: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6a** (350 mg, yield 83%); eluent, hexane-EtOAc (4:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.8 Hz, 2 H, ArH), 7.34-7.21 (m, 5 H, ArH), 6.89 (d, *J* = 8.8 Hz, 2 H, ArH), 6.84 (s,1 H, H_C), 6.24 (s, 1 H, H_D), 5.69 (s, 1 H, N*H*), 4.30-4.25 (m, 1 H, H_B), 4.10-4.06 (m, 1 H, H_B), 4.03 (dd, *J* = 6.9 Hz, 2 H, -O$CH_2$$CH_3$), 3.82-3.77 (m, 1 H, H_A), 3.19-3.13 (m, 1 H, H_A), 1.42 (t, *J* = 7.2 Hz, 3 H, -OCH_2CH_3), 1.37 (s, 9 H, C(CH_3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6 (C=O), 160.6 (C=O), 159.2,

144.5, 134.5, 130.6, 129.9, 128.3, 127.6, 126.2, 114.9, 113.3 (C_C), 64.6 (C_B), 63.6 (-O*C*H_2CH$_3$), 59.8 (C_D), 51.9 (*C*(CH$_3$)), 43.1 (C_A), 28.7 (C(*C*H$_3$)), 14.8 (-OCH$_2$*C*H$_3$); HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{25}H_{31}N_2O_4$: 423.2278. Found: 423.2279.

6b: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6b** (367 mg, yield 82%); eluent, hexane-EtOAc (4:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.8 Hz, 2 H), 7.33-7.27 (m, 4 H), 7.24-7.21 (m, 1 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 6.82 (s,1 H), 6.33 (s, 1 H), 5.90 (d, *J* = 7.4 Hz, 1 H), 4.29-4.24 (m, 1 H), 4.12-4.06 (m, 1 H), 4.02 (dd, *J* = 6.9 Hz, 2 H), 3.86-3.79 (m, 1 H), 3.22-3.16 (m, 1 H), 1.95-1.92 (m, 2 H), 1.71-1.66 (m, 2 H), 1.61-1.51 (m,1 H), 1.41 (t, *J* = 7.2 Hz, 3 H), 1.38-1.30 (m, 2 H), 1.20-1.07 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 160.6, 159.2, 144.5, 134.4, 130.6, 129.9, 128.3, 127.6, 126.0, 114.9, 113.4, 64.6, 63.6, 59.9, 48.7, 43.1, 32.9, 32.8, 25.5, 24.8, 24.7, 14.8; HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{27}H_{33}N_2O_4$: 449.2435. Found: 449.2436.

6c: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6c** (337 mg, yield 86%); eluent, hexane-EtOAc (4:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.8 Hz, 2 H), 7.34-7.28 (m, 3 H), 7.25-7.19 (m, 4 H), 6.85 (s, 1 H), 6.25 (s, 1 H), 5.61 (s, 1 H), 4.31-4.25 (m, 1 H), 4.10-4.06 (m, 1 H), 4.12-4.06 (m, 1 H), 3.83-3.77 (m, 1 H), 3.19-3.13 (m, 1 H), 2.36 (s, 3 H), 1.36 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 160.7, 144.5, 138.7, 134.5, 131.4, 129.9, 129.8, 129.2, 128.3, 127.6, 113.3, 64.6, 60.1, 51.9, 43.2, 28.7, 21.2; HRMS (ESI): *m/z* [M + H]$^+$Calcd for $C_{24}H_{29}N_2O_3$: 393.2173. Found: 393.2172.

6d: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6d** (323 mg, yield 80%); eluent, hexane-EtOAc (4:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.8 Hz, 2 H), 7.41-7.35 (m, 5 H), 7.34-7.30 (m, 2 H), 7.25-7.21 (m, 1 H), 6.84 (s, 1 H), 6.39 (s, 1 H), 5.94 (d, *J* = 7.8 Hz, 1 H), 4.29-4.24 (m, 1 H), 4.12-4.07 (m, 1 H), 3.88-3.80 (m, 1 H), 3.25-3.17 (m, 1 H), 1.96-1.94 (m, 2 H), 1.73-1.67 (m, 2 H), 1.62-1.57 (m, 1 H), 1.41-1.29 (m, 3 H), 1.18-1.12 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 160.7, 144.4, 134.4, 134.3, 129.9, 129.2, 129.0, 128.7, 128.3, 127.7, 113.3, 64.6, 59.9, 48.8, 43.3, 32.9, 32.8, 25.5, 24.8, 24.7; HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{25}H_{29}N_2O_3$: 405.2173. Found: 405.2171.

6e: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6e** (320 mg, yield 81%); eluent, hexane-EtOAc (4:1); brown semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.8 Hz, 2 H), 7.39-7.36 (m, 2 H), 7.34-7.30 (m, 2 H), 7.25-7.22 (m, 1 H), 7.11-7.06 (m, 2 H), 6.84 (s, 1 H), 6.30 (s, 1 H), 5.84 (s, 1 H), 4.29-4.24 (m, 1 H), 4.12-4.07 (m, 1 H), 3.86-3.80 (m, 1 H), 3.20-3.14 (m, 1 H), 1.38 (s, 9 H);^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 163.7 (C-F, $^1J_{C\text{-}F}$ =249.0 Hz), 161.8 (C-F, $^1J_{C\text{-}F}$ =249.0 Hz), 160.7, 144.3, 134.3, 131.0 (C-F, $^3J_{C\text{-}F}$ = 8.7 Hz), 130.9 (C-F, $^3J_{C\text{-}F}$ = 8.7 Hz), 130.4, 130.3, 129.9, 128.3, 127.8, 116.1(C-F, $^2J_{C\text{-}F}$ = 21.8 Hz), 115.9 (C-F, $^2J_{C\text{-}F}$ = 21.8 Hz), 113.7, 64.6, 59.4, 51.9, 42.2, 28.7; HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{23}H_{26}FN_2O_3$: 397.1922. Found: 397.1922.

6f: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6f** (331 mg, yield 80%); eluent, hexane-EtOAc (4:1); brown semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.8 Hz, 2 H), 7.35-7.30 (m, 2 H), 7.28-7.22 (m, 2 H), 7.20-7.13 (m, 2 H), 6.83 (s, 1 H), 6.28 (s, 1 H), 5.96 (s, 1 H), 4.29-4.24 (m, 1 H), 4.15-4.09 (m, 1 H), 3.88-3.83 (m, 1 H), 3.25-3.19 (m, 1 H), 1.38 (s, 9 H);^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 160.8, 151.7 (dd, *J* = 12.2, 1.4 Hz), 149.2 (dd, *J* = 12.2, 1.4 Hz), 144.1, 134.1, 131.5 (dd, *J* = 4.8, 4.4 Hz), 129.9, 128.3, 127.9, 125.4 (dd, *J* = 2.8, 3.8 Hz), 118.1 (dd, *J* = 18.2, 16.7 Hz), 114.0, 64.5, 58.9, 52.1, 43.2, 28.6; HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{23}H_{25}F_2N_2O_3$: 415.1828. Found: 415.1828.

6g: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6g** (314 mg, yield 80%); eluent, hexane-EtOAc (4:1); semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.8 Hz, 2 H), 7.39-7.36 (m, 5 H), 7.34-7.30 (m, 2 H), 7.25-7.23 (m, 1 H), 6.84 (s, 1 H), 6.40 (s, 1 H), 6.12 (s, 1 H), 4.29-4.24 (m, 1 H), 4.13-4.07 (m, 1 H), 3.88-3.82 (m, 1 H), 3.39-3.19 (m, 3 H), 1.56-1.48 (m, 2 H), 1.33-1.26 (m, 4 H), 0.87 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 160.8, 144.3, 134.4, 134.3, 129.9, 129.2, 129.0, 128.7, 128.2, 127.7, 113.6, 64.6, 60.1, 43.3, 39.7, 29.1, 29.0, 22.3, 13.9; HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{24}H_{29}N_2O_3$: 393.2173. Found: 392.2176.

6h: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6h** (438 mg, yield 78%); eluent, hexane-EtOAc (4:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.8 Hz, 2

H), 7.41-7.30 (m, 7 H), 7.25-7.21 (m, 1 H), 6.85 (s, 1 H), 6.28 (s, 1 H), 5.73 (s, 1 H), 4.30-4.25 (m, 1 H), 4.13-4.08 (m, 1 H), 3.86-3.81 (m, 1 H), 3.24-3.18 (m, 1 H), 1.87 (d, *J* = 14.8 Hz, 1 H), 1.58 (d, *J* = 14.8 Hz, 1 H), 1.47 (s, 3 H), 1.43 (s, 3 H), 0.96 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 160.7, 144.4, 134.4, 129.9, 129.3, 129.0, 128.7, 128.3, 127.7, 113.5, 64.6, 60.5, 55.5, 52.4, 43.3, 31.6, 31.5, 29.1, 28.6; HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{27}H_{35}N_2O_3$: 435.2642. Found: 435.2644.

6i: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6i** (380 mg, yield 82%); eluent, hexane-EtOAc (4:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.8 Hz, 2 H), 7.34-7.31 (m, 3 H), 7.24-7.21 (m, 1 H), 6.90 (d, *J* = 7.8 Hz, 2 H), 6.85 (s, 1 H), 6.22 (s, 1 H), 5.67 (s, 1 H), 4.30-4.25 (m, 1 H), 4.12-4.07 (m, 1 H), 3.80 (s, 3 H), 3.83-3.78 (m, 1 H), 3.23-3.17 (m, 1 H), 1.86 (d, *J* = 14.8 Hz, 1 H), 1.57 (d, *J* = 14.8 Hz, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 0.96 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 159.8, 144.5, 134.5, 130.7, 129.9, 128.3, 127.6, 126.2, 114.4, 113.3, 64.6, 60.0, 55.9, 55.3, 52.4, 43.1, 31.6, 31.5, 29.0, 28.6; HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{28}H_{37}N_2O_4$: 465.2748. Found: 465.2749.

6j: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6j** (270 mg, yield 78%); eluent, hexane-EtOAc (5:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.8 Hz, 2 H), 6.90 (d, *J* = 8.8 Hz, 2 H), 6.18 (s, 1 H), 6.05 (dd, *J* = 7.6 Hz, 1 H), 5.61 (s, 1 H), 4.12-4.07 (m, 1 H), 3.94-3.81 (m, 1 H), 3.81 (s, 3 H), 3.72-3.67 (m, 1 H), 3.08-3.02 (m, 1 H), 1.68 (d, *J* = 7.8 Hz, 3 H), 1.36 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 160.3, 159.7, 145.0, 130.6, 126.5, 114.3, 111.9, 64.3, 59.4, 55.3, 51.8, 43.4, 28.7, 10.3; HRMS (ESI): *m/z* [M + H]$^+$Calcd for $C_{19}H_{27}N_2O_4$: 347.1965. Found: 347.1967.

6k: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6k** (240 mg, yield 75%); eluent, hexane-EtOAc (5:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40 (d, *J* = 3.8 Hz, 2 H), 6.16 (s, 1 H), 6.06 (dd, *J* = 7.6 Hz, 1 H), 5.95-5.94 (m, 1 H), 5.74 (s, 1 H), 4.13-4.08 (m, 1 H), 4.05-4.00 (m, 1 H), 3.72-3.66 (m, 1 H), 3.28-3.22 (m, 1 H), 2.27 (s, 3 H), 1.69 (d, *J* = 7.8 Hz, 3 H), 1.34 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 160.2, 153.4, 145.9, 144.9, 112.5, 112.2, 106.5, 64.2, 54.9, 51.8, 43.6, 28.6, 13.6, 10.3; HRMS (ESI): *m/z* [M + H]$^+$Calcd for $C_{17}H_{25}N_2O_4$: 321.1801. Found: 321.1807.

6l: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6l** (278 mg, yield 74%); eluent, hexane-EtOAc (5:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.43 (d, *J* = 3.8 Hz, 2 H), 6.18 (s, 1 H), 6.06 (dd, *J* = 7.5 Hz, 1 H), 5.95-5.94 (m, 1 H), 5.74 (s, 1 H), 4.14-4.08 (m, 1 H), 4.06-4.01 (m, 1 H), 3.73-3.67 (m, 1 H), 3.34-3.28 (m, 1 H), 2.26 (s, 3 H), 1.75-1.62 (m, 5 H), 1.39 (s, 6 H), 0.95 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 160.1, 153.3, 145.9, 144.9, 112.7, 112.2, 106.5, 64.2, 55.7, 54.9, 52.1, 43.7, 31.6, 31.4, 29.1, 28.7, 13.6, 10.3; HRMS (ESI): *m/z* [M + H]$^+$Calcd for $C_{21}H_{33}N_2O_4$: 377.2435. Found: 377.2436.

6m: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6m** (236 mg, yield 72%); eluent, hexane-EtOAc (5:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.33 (m, 5 H), 6.33 (s, 1 H, H_D), 5.91 (brs, 1 H, N*H*), 5.47 (s, 1 H, H_C), 4.81 (s, 1 H, H_C), 4.12-4.07 (m, 1 H, H_B), 3.93-3.88 (m, 1 H, H_B), 3.86-3.74 (m, 2 H, H_E,H_A), 3.14-3.08 (m, 1 H, H_A), 1.93-1.92 (m, 2 H, -CH_2-), 1.73-1.67 (m, 2 H, -CH_2-), 1.63-1.58 (m, 1 H, -CH_2-), 1.40-1.31 (m, 2 H, -CH_2-), 1.18-1.09 (m, 3 H, -CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 159.9, 150.9, 134.3, 129.2, 129.0, 128.7, 99.4 (C_C), 64.3 (C_B), 59.7 (C_D), 48.8 (C_E), 43.6 (C_A), 32.9 (-*C*H_2-), 32.8 (-*C*H_2-), 25.4 (-*C*H_2-), 24.8 (-*C*H_2-), 24.7 (-*C*H_2-); HRMS (ESI): *m/z* [M + H]$^+$Calcd for $C_{19}H_{25}N_2O_3$: 329.1860. Found: 329.1862.

6n: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6n** (261 mg, yield 73%); eluent, hexane-EtOAc (5:1); semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.35 (m, 5 H), 6.20 (s, 1 H), 5.61 (s, 1 H), 5.51 (s, 1 H), 4.82 (s, 1 H), 4.13-4.08 (m, 1 H), 3.94-3.89 (m, 1 H), 3.78-3.72 (m, 1 H), 3.15-3.09 (m, 1 H), 1.85 (d, *J* = 14.8 Hz, 1 H), 1.56 (d, *J* = 14.8 Hz, 1 H), 1.46 (s, 3 H), 1.42 (s, 3 H), 0.95 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 159.8, 150.9, 134.2, 129.3, 129.0, 128.7, 99.3, 64.3, 60.2, 55.9, 52.4, 43.3, 32.6, 31.5, 29.0, 28.5; HRMS (ESI): *m/z* [M + H]$^+$ Calcd for $C_{21}H_{31}N_2O_3$: 359.2329. Found: 359.2329.

6o: Synthesized according to one-pot procedure in 1 mmol scale, afforded **6o** (273 mg, yield 72%); eluent, hexane-EtOAc (5:1); colorless semi solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.89 (m, 3 H), 7.59-7.54 (m, 3 H), 7.48-7.45 (m, 1 H), 6.92 (s, 1 H),

5.71 (d, *J* = 7.8 Hz, 1 H), 5.55 (s, 1 H), 4.81 (s, 1 H), 4.09-4.03 (m, 1 H), 3.91-3.83 (m, 1 H), 3.78-3.71 (m, 2 H), 2.79-2.76 (m, 1 H), 1.98-1.95 (m, 2 H), 1.72-1.67 (m, 2 H), 1.63-1.59 (m, 1 H), 1.41-1.32 (m, 2 H), 1.16-1.05 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 159.6, 150.8, 133.9, 131.9, 130.0, 129.9, 128.9, 127.8, 127.7, 126.5, 125.1, 123.0, 99.3, 64.3, 57.1, 48.9, 43.3, 32.8, 25.4, 24.8, 24.7; HRMS (ESI): *m/z* $[M + 2H]^{2+}$Calcd for $C_{23}H_{28}N_2O_3$: 380.2049. Found: 380.2051.

General procedure for the synthesis of 5a-o

To solution of aromatic aldehyde **2** (1.0 mmol) in methanol (10 mL) was added with 1,2-amino alcohol (**1**, 1.0 mmol) and the the mixture was stirred at RT for 1 h. Then, acid **4** (1 mmol) was added, and stirring was continued, followed by addition of isocyanides **3** (1 mmol). The mixture was stirred for 10-24 hrs at RT. Reaction was monitored by TLC (*n*-hexane/EtOAc 2:1). After the completion of the reaction, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: hexane/ EtOAc) to afforded Ugi-hydroxypropargylamides adduct (**5a-o**).

5a: Synthesized according to general procedure in 1 mmol scale, afforded **5a** as a 1:4 mixture of rotamers (371 mg, yield 88%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.51 (m, 2 H), 7.46-7.34 (m, 3 H), 7.29-7.25 (m, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.36-6.31 (m, 0.2 H), 6.01 (s, 0.2 H), 5.67 (brs, 0.8 H), 5.63 (s, 0.8 H), 5.32-5.28 (m, 0.8 H), 4.14-3.98 (m, 2.4 H), 3.87-3.80 (m, 2 H), 3.76-3.68 (m, 1 H), 3.48 (brs, 0.2 H), 3.29-3.25 (m, 0.8 H), 2.98-2.92 (m, 0.2 H), 1.43 (t, *J* = 7.6 Hz, 3 H), 1.35 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.9, 159.4, 155.9, 132.6, 132.4, 131.2, 131.0, 130.4, 130.1, 128.6, 128.5, 125.5, 125.5, 120.4, 120.1, 115.1, 115.0, 92.2, 91.1, 81.8, 81.6, 66.7, 63.7, 63.6, 61.6, 60.9, 52.2, 52.1, 50.0, 46.3, 28.6, 28.5, 14.8; HRMS (ESI): *m/z* $[M + Na]^+$Calcd for $C_{25}H_{30}N_2NaO_4$: 445.2098. Found: 445.2099.

5b: Synthesized according to general procedure in 1 mmol scale, afforded **5b** as a 1:4 mixture of rotamers (394 mg, yield 88%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.51 (m, 2 H), 7.43-7.40 (m, 6 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 6.49-6.41 (m, 0.2 H), 6.12 (s, 0.2 H), 5.67-5.65 (m, 0.8 H), 5.64 (s, 0.8 H), 5.18-5.15 (m, 0.8 H), 4.08-4.02 (m, 2 H), 3.91-3.74 (m, 4 H), 3.54-3.47 (m, 0.2 H), 3.41-3.37 (m, 0.8 H), 2.98-2.92 (m, 0.2 H), 1.94- 1.91 (m, 2 H), 1.68-1.65 (m, 2 H), 1.61-1.57 (m, 1 H), 1.43 (t, *J* = 7.6 Hz, 3 H), 1.36-1.31 (m, 2 H), 1.17-1.09 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 159.5, 155.9, 132.6, 132.4, 131,2, 130.9, 130.2, 128.6, 128.5, 125.2, 120.4, 115.1, 115.0, 91.2, 81.7, 63.6, 61.6, 61.1, 50.4, 49.1, 32.6, 25.4, 24.7, 24.6, 14.8; HRMS (ESI): *m/z* $[M + Na]^+$Calcd for $C_{27}H_{32}N_2NaO_4$: 471.2254. Found: 471.2257.

5c: Synthesized according to general procedure in 1 mmol scale, afforded **5c** as a 1:4 mixture of rotamers (336 mg, yield 89%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.50 (m, 2 H), 7.44-7.39 (m, 1 H), 7.37-7.33 (m, 2 H), 7.27-7.23 (m, 4 H), 6.34 (m, 0.2 H), 6.03 (s, 0.2 H), 5.69 (m, 0.8 H), 5.66 (s, 0.8 H), 5.30-5.27 (m, 0.8 H), 4.15-4.11 (m, 0.2 H), 3.87-3.89 (m, 0.7 H), 3.76-3.65 (m, 1 H), 3.51-3.38 (0.3 H), 3.28-3.23 (m, 0.7 H), 2.97-2.91 (m, 0.2 H), 2.37 (s, 3 H), 1.35 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.7, 156.5, 155.9, 139.1, 132.6, 132.4, 130.9, 130.7, 130.4, 130.2, 129.9, 129.8, 129.6, 128.6, 128.5, 120.4, 120.1, 92.1, 91.2, 81.8, 81.6, 66.9, 63.9, 61.5, 60.9, 52.2, 52.1, 50.1, 46.4, 28.6, 28.5, 21.2; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{24}H_{29}N_2O_3$: 379.2173. Found: 379.2177.

5d: Synthesized according to general procedure in 1 mmol scale, afforded **5d** as a 1:4 mixture of rotamers (347 mg, yield 86%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.52 (m, 2 H), 7.41-7.35 (m, 8H), 6.67-6.65 (m, 0.2 H), 6.19 (s, 0.2 H), 5.73-5.71 (m, 1.4 H), 3.91-3.76 (m, 4 H), 3.54-3.50 (m, 0.3 H), 3.41-3.37 (m, 0.8 H), 2.96-2.92 (m, 0.2 H), 1.94-1.92 (m, 2 H), 1.68-1.57 (m, 3 H), 1.39-1.31 (m, 2 H), 1.17-1.10 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 168.9, 155.9, 133.9, 133.6, 132.6, 132.4, 130.5, 130.2, 129.8, 129.6, 123.3, 129.1, 128.6, 128.5, 120.3, 119.9, 91.4, 81.6, 67.0, 64.1, 61.5, 60.9, 50.7, 49.2, 48.9, 46.3, 32.7, 25.4, 24.8, 24.7, 24.6; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{25}H_{29}N_2O_3$: 405.2173. Found: 405.2174.

5e: Synthesized according to general procedure in 1 mmol scale, afforded **5e** as a 3:7 mixture of rotamers (336 mg, yield 85%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58-7.52 (m, 2 H), 7.46-7.34 (m, 5 H), 7.14-7.09 (m, 2 H), 6.45 (brs, 0.15 H), 6.03 (s, 0.2 H), 5.62 (m, 1.4 H), 3.91-3.79 (m, 1.8 H), 3.75-3.70 (m, 0.9 H), 3.53-3.48 (0.2 H), 3.34-3.29 (m, 0.8 H), 2.96-2.90 (m, 0.2 H), 1.36 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 169.1, 164.2 (C-F, $^1J_{C\text{-}F}$ =249.0 Hz), 161.7 (C-F, $^1J_{C\text{-}F}$ =249.0 Hz), 156.6, 155.9, 132.6, 132.4, 131.8, 131.7 (C-F, $^3J_{C\text{-}F}$ = 8.7 Hz), 131.6 (C-F, $^3J_{C\text{-}F}$ = 8.7 Hz), 131.5, 130.6, 130.3, 129.7, 129.6, 128.7, 128.6, 120.2, 116.3 (C-F,

$^{2}J_{C\text{-}F}$ = 21.8 Hz), 116.2 (C-F, $^{2}J_{C\text{-}F}$ = 21.8 Hz), 91.5, 81.6, 66.5, 63.4, 61.6, 52.3, 50.3, 46.2, 28.5, 28.4; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{23}H_{26}FN_2O_3$: 397.1922. Found: 397.1925.

5f: Synthesized according to general procedure in 1 mmol scale, afforded **5f** as a 1:4 mixture of rotamers (347 mg, yield 84%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.51 (m, 2 H), 7.47-7.41 (m, 1 H), 7.39-7.35 (m, 2 H), 7.30-7.20 (m, 2 H), 7.18-7.14 (m, 1 H), 6.85 (brs, 0.2 H), 5.99 (s, 0.2 H), 5.84 (m, 0.8 H), 5.59 (m, 0.8 H), 5.08-5.05 (m, 0.8 H), 3.91-3.73 (m, 2.8 H), 3.69-3.67 (m, 0.2 H), 3.41-3.36 (m, 0.8 H), 3.01-2.95 (m, 0.2 H), 1.39 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 168.4, 156.6, 155.9, 151.9, 151.8 (dd, *J* = 12.2, 1.4 Hz), 149.4, 149.3 (dd, *J* = 12.2, 1.4 Hz), 132.7, 131.0, 130.9 (dd, *J* = 4.8, 4.4 Hz), 130.8, 130.7, 130.4, 128.7, 128.6, 126.2, 126.1 (dd, *J* = 2.8, 3.8 Hz), 120.1, 119.7, 118.9, 118.8, 118.1, 117.9, 91.7, 81.4, 81.2, 66.3, 63.4, 61.6, 60.6, 52.4, 52.3, 50.6, 46.4, 28.5, 28.4; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{23}H_{25}F_2N_2O_3$: 415.1828. Found: 415.1829.

5g: Synthesized according to general procedure in 1 mmol scale, afforded **5g** as a 1:4 mixture of rotamers (330 mg, yield 84%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.51 (m, 2 H), 7.45-7.34 (m, 8 H), 6.91 (brs, 0.2 H), 6.22 (s, 0.2 H), 5.93 (m, 0.8 H), 5.72 (m, 0.8 H), 5.15-5.12 (m, 0.8 H), 3.87-3.71 (m, 3 H), 3.54-3.39 (m, 0.2 H), 3.43-3.22 (m, 2.8 H), 3.03-2.97 (m, 0.2 H), 1.54-147 (m, 2 H), 1.33-1.24 (m, 4 H), 0.87 (t, *J* = 7.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 169.9, 156.7, 155.9, 134.0, 133.6, 132.7, 132.4, 130.5, 130.2, 129.8, 129.6, 129.2, 129.1, 128.6, 128.5, 120.3, 119.9, 92.6, 91.4, 81.6, 81.3, 67.1, 64.1, 61.5, 60.8, 50.6, 46.5, 40.2, 40.0, 29.0, 28.9, 28.8, 22.2, 13.9, 13.8; HRMS (ESI): *m/z* $[M + Na]^+$ Calcd for $C_{24}H_{28}N_2NaO_3$: 415.1992. Found: 415.1995.

5h: Synthesized according to general procedure in 1 mmol scale, afforded **5h** as a 1:5 mixture of rotamers (335 mg, yield 82%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.52 (m, 2 H), 7.44-7.33 (m, 8 H), 6.09 (brs, 0.18 H), 6.06 (s, 0.16 H), 5.64 (m, 0.8 H), 5.54 (m, 0.9 H), 5.25 (brs, 0.6 H), 3.91-3.85 (m, 1 H), 3.83-3.75 (m, 1.4 H), 3.72-3.69 (m, 0.7 H), 3.66-3.63 (m, 0.13 H), 3.53-3.47 (m, 1 H), 3.17-3.11 (m, 0.2 H), 1.75 (d, *J* = 14.8 Hz, 1 H), 1.47 (d, *J* = 14.8 Hz, 1 H), 1.46 (s, 3 H), 1.41 (s, 3 H), 0.87 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 169.4, 155.8, 133.9, 132.5, 132.4, 130.5, 130.2, 129.9, 129.7, 129.3, 129.2, 129.1, 129.0, 128.6, 120.4, 91.2, 81.7, 65.3, 61.6, 56.3, 56.2, 52.9, 50.9, 31.5, 31.4, 28.8, 28.6, 28.3, 27.9; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{27}H_{35}N_2O_3$: 435.2642. Found: 435.2648.

5i: Synthesized according to general procedure in 1 mmol scale, afforded **5i** as a 1:4 mixture of rotamers (394 mg, yield 85%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.51 (m, 2 H), 7.44-7.31 (m, 5 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 6.04 (brs, 0.2 H), 6.06 (s, 0.2 H), 5.65 (m, 0.8 H), 5.50 (m, 0.8 H), 5.32 (brs, 0.7 H), 3.91-3.88 (m, 0.8 H), 3.85-3.83 (m, 3.3 H), 3.79-3.74 (m, 1.9 H), 3.67-3.65 (m, 0.15 H), 3.45-3.42 (m, 0.8 H), 3.15-3.09 (m, 0.2 H), 1.77 (d, *J* = 14.8 Hz, 1 H), 1.49 (d, *J* = 14.8 Hz, 1 H), 1.45 (s, 3 H), 1.39 (s, 3 H), 0.91 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 160.1, 156.4, 155.7, 132.5, 132.4, 131.3, 131.0, 130.4, 130.1, 128.6, 128.5, 125.9, 125.7, 120.4, 120.1, 114.6, 114.5, 91.1, 81.8, 81.6, 66.8, 64.5, 61.7, 61.1, 56.4, 56.2, 55.4, 52.8, 52.3, 50.6, 46.8, 31.5, 31.4, 28.8, 28.6, 28.3, 28.1; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{28}H_{37}N_2O_4$: 465.2748. Found: 465.2749.

5j: Synthesized according to general procedure in 1 mmol scale, afforded **5j** as a 1:4 mixture of rotamers (298 mg, yield 86%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.45 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.23 (brs, 0.2 H), 5.93 (s, 0.2 H), 5.66 (m, 0.8 H), 5.57 (m, 0.8 H), 3.82 (s, 3 H), 3.80-3.72 (m, 1.7 H), 3.67-3.58 (m, 1 H), 3.46-3.41 (m, 0.2 H), 3.17-3.12 (m, 0.7 H), 2.91-2.86 (m, 0.2 H), 2.00 (s, 3 H), 1.33 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 169.9, 159.9, 156.6, 156.0, 131.2, 131.0, 125.9, 125.5, 114.6, 114.5, 91.4, 90.3, 73.5, 66.4, 63.4, 61.2, 60.9, 55.3, 52.1, 49.7, 46.1, 28.6, 28.4, 4.2, 4.1; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{19}H_{27}N_2O_4$: 347.1965. Found: 347.1968.

5k: Synthesized according to general procedure in 1 mmol scale, afforded **5k** as a 1:4 mixture of rotamers (268 mg, yield 84%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (brs, 0.2 H), 6.39-6.38 (m, 0.8 H), 6.34-6.33 (m, 0.2 H), 5.99-5.88 (m, 1 H), 5.92 (s, 0.2 H), 5.85 (m, 0.8 H), 5.59 (m, 0.8 H), 4.89-4.86 (m, 0.8 H), 3.95-3.89 (m, 0.8 H), 3.82-3.73 (m, 0.6 H), 3.69-3.68 (m, 1.8 H), 3.58-3.56 (m, 0.2 H), 3.23-3.17 (m, 0.8 H), 3.01-2.95 (m, 0.2 H), 2.29 (s, 3 H), 2.01 (s, 3 H), 1.34 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 155.6, 153.5, 153.4, 145.6, 113.0, 112.8, 106.9, 106.8, 90.3, 73.3, 73.2,

61.6, 60.9, 57.8, 52.1, 52.0, 50.4, 46.7, 28.5, 28.4, 13.6, 4.1; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{17}H_{25}N_2O_4$: 321.1809. Found: 321.1811.

5l: Synthesized according to general procedure in 1 mmol scale, afforded **5l** as a 1:4 mixture of rotamers (308 mg, yield 82%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.41-6.40 (m, 0.8 H), 6.36-6.35 (m, 0.2 H), 6.11 (brs, 0.2 H), 5.98-5.97 (m, 1.2 H), 5.82 (s, 0.8 H), 5.55 (m, 0.8 H), 4.90-4.87 (m, 0.8 H), 3.88-3.82 (m, 0.9 H), 3.76-3.67 (m, 2.3 H), 3.61-3.54 (m, 0.2 H), 3.37-3.33 (m, 0.8 H), 3.17-3.12 (m, 0.2 H), 2.28 (s, 3 H), 2.00 (s, 3 H), 1.84 (d, *J* = 14.8 Hz, 0.2 H), 1.72 (d, *J* = 14.8 Hz, 0.8 H), 1.65 (d, *J* = 14.8 Hz, 0.2 H), 1.56 (d, *J* = 14.8 Hz, 0.8 H), 1.41 (s, 3 H), 1.39 (s, 3 H), 0.94 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 155.5, 153.3, 145.6, 113.1, 112.9, 107.0, 106.8, 90.3, 73.3, 61.6, 61.0, 60.8, 58.2, 56.1, 52.6, 51.9, 50.9, 47.1, 31.5, 28.9, 28.5, 28.3, 13.5, 4.2; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{21}H_{33}N_2O_4$: 377.2435. Found: 377.2436.

5m: Synthesized according to general procedure in 1 mmol scale, afforded **5m** as a 1:5 mixture of rotamers (252 mg, yield 77%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.39 (m, 3 H), 7.35-7.30 (m, 2 H), 6.58 (brs, 0.16 H), 6.11 (m, 0.17 H), 5.79-5.77 (m, 0.8 H), 5.66 (s, 0.8 H), 5.55 (m, 0.8 H), 3.92-3.64 (m, 3.7 H), 3.49-3.47 (m, 0.2 H), 3.29-3.24 (m, 0.8 H), 3.23-3.18 (m, 0.7 H), 2.96-2.90 (m, 0.2 H), 1.96-1.90 (m, 2 H), 1.69-1.56 (m, 3 H), 1.39-1.26 (m, 2 H), 1.21-1.04 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 168.7, 155.3, 154.9, 133.8, 133.3, 129.8, 129.6, 129.3, 129.2, 80.9, 79.9, 75.8, 65.6, 63.8, 61.0, 60.6, 50.2, 49.2, 49.1, 46.6, 32.9, 32.7, 32.5, 25.4, 24.9, 24.7, 24.6; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{19}H_{25}N_2O_3$: 329.1860. Found: 329.1862.

5n: Synthesized according to general procedure in 1 mmol scale, afforded **5n** as a 1:5 mixture of rotamers (279 mg, yield 78%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.33 (m, 5 H), 6.03 (brs, 0.17 H), 6.00 (brs, 0.14 H), 5.66 (brs, 0.9 H), 5.49 (s, 0.9 H), 3.78-3.68 (m, 2.8 H), 3.63-3.58 (m, 0.2 H), 3.49-3.44 (m, 0.2 H), 3.39-3.33 (m, 0.8 H), 3.18 (s, 1 H), 3.11-3.04 (m, 0.2 H), 1.85 (d, *J* = 14.8 Hz, 0.17 H), 1.75 (d, *J* = 14.8 Hz, 0.8 H), 1.59 (d, *J* = 14.8 Hz, 0.2 H), 1.45 (d, *J* = 14.8 Hz, 0.8 H), 1.44 (s, 3 H), 1.38 (s, 3 H), 0.89 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 168.6, 155.0, 154.7, 133.5, 129.9, 129.7. 129.3, 129.2, 129.1, 80.7, 79.9, 75.9, 66.9, 64.9, 61.1, 60.7, 56.5, 52.8, 52.3, 50.5, 47.2, 31.5, 31.4, 28.9, 28.6, 28.4, 27.9; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{21}H_{31}N_2O_3$: 359.2329. Found: 359.2330.

5o: Synthesized according to general procedure in 1 mmol scale, afforded **5o** as a 1:5 mixture of rotamers (291 mg, yield 77%), colorless jelly. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.91 (m, 2 H), 7.67-7.66 (m, 1 H), 7.59-7.47 (m, 4 H), 6.76 (brs, 0.14 H), 6.69 (brs, 0.15 H), 6.52 (brs, 0.9 H), 5.81-5.79 (m, 0.9 H), 5.09-5.76 (m, 0.9 H), 4.01-3.85 (m, 2 H), 3.75-3.65 (m, 0.3 H), 3.61-3.54 (m, 0.9 H), 3.5103.46 (m, 0.9 H), 3.37 (brs, 0.17 H), 3.27-3.23 (m, 0.2 H), 3.18 (s. 0.8 H), 2.62-2.57 (m, 0.8 H), 2.54-2.44 (m, 0.2 H), 1.99-1.95 (m, 2 H), 1.72-1.57 (m, 3 H), 1.41-1.35 (m, 2 H), 1.16-1.07 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 168.9, 155.1, 133.8, 131.9, 130.3, 130.2, 129.3, 129.2, 128.6, 128.1, 127.8, 126.6, 126.5, 125.4, 125.3, 122.3, 122.2, 81.1, 80.2, 75.7, 63.9, 61.0, 60.6, 59.6, 49.4, 49.1, 45.6, 32.9, 32.6, 25.4, 24.8, 24.7; HRMS (ESI): *m/z* $[M + H]^+$ Calcd for $C_{23}H_{27}N_2O_3$: 379.2016. Found: 379.2018.

Conclusions

In conclusion, we have identified an environmentally benign method, in which Ugi adducts hydroxypropargylamides could easily undergo post intramolecular cyclization using triphenylphosphine catalyst to generate morpholinone. The primary features of this method involve the metal free conditions and chemo- and regioselective 6-*exo*-*dig* cyclization in one-pot. This robust and operationally simple two-step, air- and moisture-tolerant pathway leads to precise enlargement of scaffold divergence having complex molecules from simple starting materials.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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