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Cu(I)-Catalyzed Synthesis of Dihydropyrimidin-4-ones toward the Preparation of β- and β^3-Amino Acid Analogues

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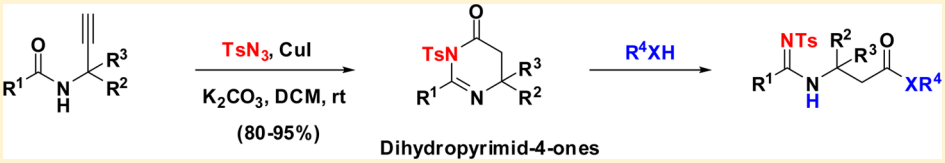
Supporting Information



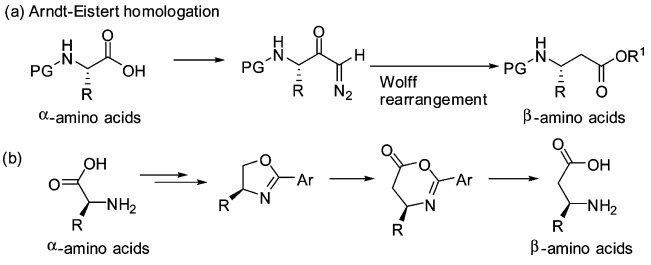
ABSTRACT: A copper(I)-catalyzed synthesis of substituted dihydropyrimidin-4-ones from propargyl amides via the formation of ketenimine intermediate has been successfully developed; the synthesis afforded good isolated yields (80−95%). The mild reaction conditions at room temperature allow the reaction to proceed to completion in a few hours without altering the stereochemistry. Further, by involving a variety of reactive nucleophiles, the obtained substituted dihydropyrimidin-4-ones were elegantly transformed into the corresponding β- and β^3-amino acid analogues.

INTRODUCTION

β-Amino acids are one-carbon homologues of α-amino acids. They can be incorporated into β-peptide chains to afford new secondary and tertiary structures and thus obtain new biological activity.[1] β-Amino acids are also vital components of important pharmaceuticals, such as emeriamine,[2] cispentacin, and taxol.[3] Hence, there has been an increasing demand for the development of new synthetic strategies for β-amino acids and their derivatives in the past decades.[4a,b] A majority of the methods employ asymmetry synthesis using non-β-amino acid substrates and chiral catalysts.[5] Moreover, several enantioselective synthetic routes to β-amino acids have been successfully developed in the past decade; these include Kowalski ester homologation, the transformation of chiral oxazolines, enantioselective radical reactions, the Mannich reaction, and asymmetric alkylation/hydroxylation of 1,3-oxazinan-6-ones.[6]

Because of the ready availability, low cost, and natural optical purity of α-amino acids, the direct transformation of α-amino acids to β-amino acids is of high interest. The classical Arndt-Eistert reaction and its modified procedures were effective for the one-carbon conversion of α-amino acids, as shown in Scheme 1a.[7a−e] In that strategy the α-amino acids are converted into the corresponding diazo keteone reactive intermediate by activating the acid group. Then subsequent Wolff rearrangement of the diazo ketone provides the corresponding β-amino acid. However, the difficulty in handling the hazardous reagent diazomethane (CH_2N_2) and the high cost of the silver catalyst needed in the Wolff rearrangement step makes it unsuitable for large-scale synthesis. Longobardo and co-workers have proposed a method for the synthesis of β-amino acids by the reduction of N-protected α-amino acids to the corresponding β-amino alcohol. Followed by an efficient iodide-formation step, the desired β-amino acids can be obtained without racemization.[8] Recently, Coates et al. reported a catalytic

Scheme 1. Reported Preparation Methods of β-Amino Acids from α-Amino Acids[7,9]



synthesis of β^3-amino acid derivatives from α-amino acids. The strategy involved the preparation of 2-oxazolines intermediates in a two-step process from α-amino acids. Then a novel catalytic carbonylation of these 2-oxazolines by using a silylcobalt precatalyst produced the important 2-oxazin-6-one intermediates. These oxazinone intermediates are subsequently hydrolyzed to the corresponding β^3-amino acids of interest, as shown in Scheme 1b.[9] The biorenewable, stereochemically rich resource of the starting α-amino acids successfully yielded enantiomerically pure β-amino acids. Therefore, the development of new synthetic methods via the formation of heterocyclic intermediates could provide a practical route to diverse β-amino acids.

In this study, we propose a scheme for Cu(I)-catalyzed formation of dihydropyrimidin-4-one (DHPM) (such as compound **6** in Scheme 2) intermediates, followed by hydrolysis or nucleophilic substitution reactions, to yield the desired β-amino acids and their important analogues. The concept is based on the utilization of labile sulfonyl triazole to

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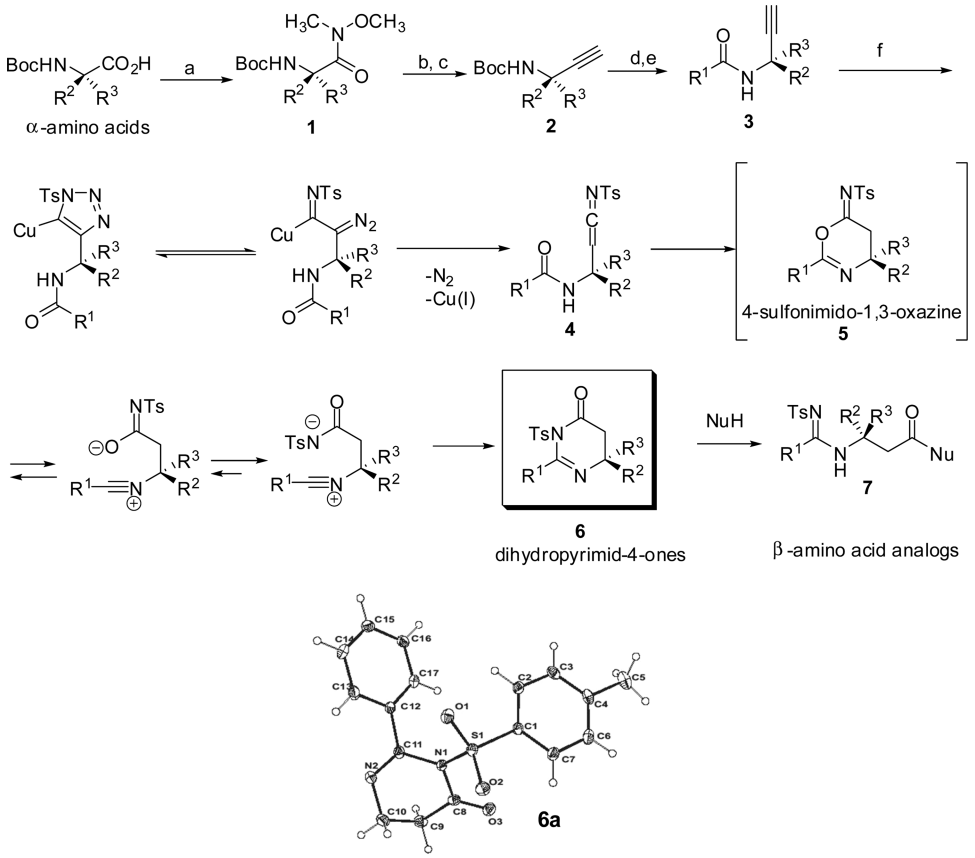
Scheme 2. Synthetic Pathway of β-Amino Acid Analogues from α-Amino Acids[a]



[a]Reaction conditions: (a) MeO(Me)NH.HCl (1.5 equiv), EDC·HCl (1.5 equiv), HOBt (1.5 equiv), DIEA (2.0 equiv), DCM, rt, 14 h; (b) $LiAlH_4$ (1.1 equiv), 0 °C, 20 min; (c) Dimethyl-2-oxopropylphosponate (2.0 equiv), TsN_3 (2.0 equiv), K_2CO_3 (2.0 equiv), CH_3CN, MeOH, rt, 14 h; (d) TFA and DCM (1:1), rt, 30 min; (e) R^1COCl (1.1 equiv), TEA (1.5 equiv), DCM, rt, 2 h; (f) CuI (0.1 equiv), TsN_3 (1.1 equiv), K_2CO_3 (1.5 equiv), DCM, rt, 12 h.

form a ketenimine intermediate via Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC).[10] The highly electrophilic ketenimine intermediates are obtained, and these immediately react with the nucleophiles present in the reaction medium. Different groups have applied this useful concept to develop a number of methodologies for the preparation of a variety of molecules,[11] such as amides,[12] imidates,[13] azetidinimines,[14] cumarines,[15] and quinolines.[16] Inspired by this promising chemistry, the cyclization of propargyl amides to form the oxazole or oxazinone hetercycles was believed to potentially conduct the formation of corresponding β-amino acids. To the preparation of the oxazole and oxazinone, a number of transition-metal-catalyzed cyclization reactions from propargyl amides have been successfully developed, in which gold was reported as an efficient catalyst.[17,18] Cook et al. reported a method for the preparation of oxazole-substituted steroids using copper-catalyzed cyclization of steroidal acylaminoacetylenes.[19] However, the use of the copper catalysts in such cyclic transformations is still rare. Thus, the reactive intermediate, sulfonyl ketenimine, obtained from the propargyl amides in the presence of the Cu(I) catalyst may facilitate the cyclization and allow further functionalization of the resultant cyclic products. However, during the synthetic course of this strategy, the expected oxazinone product was not isolated; DHPM analogues were obtained, which were identified by X-ray structural analysis. Nevertheless, the obtained DHPM could still be converted to the β-amino acid analogues of interest.

DHPMs are well-known for their biological activities and are present in many natural products. Despite the fact that the DHPM synthesis was reported in 1893 as the Biginelli multicomponent reaction,[20] the importance of the analogue's biological activity has only been realized in the 1980s.[21] In recent years, extensive studies have been reported on the pharmacological properties involving DHPM core.[22] For example, one of the DHPM analogue has been identified as a potential new anticancer lead that is involved in blocking mitosis by the inhibition of a kinesin motor protein.[23] In addition, a number of drugs containing the DHPM core are reported.[24,25] Hence, the development of methods for the preparation of DHPM analogues remains attractive, despite the presence of existing methods.[26] During the course of completion of this research, we found that Wang et al. reported a similar methodology for the production of DHPMs using propargylamides efficiently. In their study, they had converted the propargylamides into the corresponding DHPMs by converting the alkyne group into a reactive ketenimine intermediate followed by an intramolecular nucleophilic addition. After, the amide oxygen's attack on the ketenimine intermediate subsequent ring-opening and ring closure process afforded the desired DHPM. The reaction conditions are involved with the use of molecular sieves under argon atmosphere in 70 °C. The yields were reported moderate to excellent.[27] In this article we have demonstrated the preparation of those DHPM analogues using a relatively

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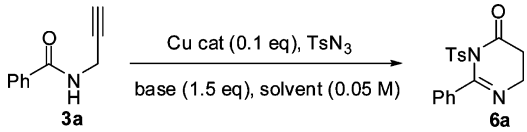
different reaction conditions involving ambient temperature, different base, nonusage of molecular sieves as a dehydrating agent and a purification method that avoids the column chromatography. Further, we have provided a synthetic pathway to prepare the chiral DHPMs, and consequently by using these DHPM analogues we have demonstrated the preparation of β/β^3-amino acids and their analogues. On the basis of a comparative analysis of the two methodologies, we believe that the relatively mild reaction conditions, better yields, and the production of a series of novel ring-opening products by one-pot method make our study important; it will be an add-on to the recently reported methodology by Wang et al.[27] Herein, we report the preparation of substituted DHPMs using the CuAAC and their subsequent transformation to the β/β^3-amino acids and their analogues.

RESULTS AND DISCUSSION

In order to achieve the transformation of the α-amino acids to the β-amino acids, a synthetic strategy was proposed in Scheme 2. First, Boc-protected α-amino acids were converted to the corresponding Weinreb amides **1** and subsequently reduced to aldehydes. Then the aldehydes were subjected to a homologation using Bestmann−Ohira reagent to produce Boc-protected amino alkynes **2**. Deprotection of the Boc group afforded the substituted propargyl amines, which were then allowed to couple with benzoylchloride to give the corresponding propargyl amides **3**. When the obtained propargyl amides were treated with tosyl azide in the presence of catalytic amount of copper iodide (CuI) and potassium carbonate (K_2CO_3), the starting materials were consumed to form new products in a few hours. Isolation and characterization of the major spot by column chromatography indicated a probable six-membered cyclized product. We assumed that the highly electrophilic carbon center in ketenimine intermediate **4** could be favorably attacked in an intramolecular fashion by the pendant amide oxygen through a six-membered transition state; subsequent proton transfer occurs to form 4-sulfanimido-1,3-oxazines analogues (compound **5**, Scheme 2). Characterization of the isolated product using NMR seems to support the initially predicted structure of 6-sulfonamido-1,3-oxazine. The product of the reaction can be rationalized by a mechanistic pathway in which the initially formed sulfonyl triazole (which is in equilibrium with the diazoimine) goes through the copper(I)-catalyzed azide−alkyne cycloaddition (CuAAC) pathway, the Dimroth rearrangement leads to the formation of diazoimino copper intermediate, and it is subsequently transformed to the reactive ketenimine intermediate via the Wolff rearrangement. Then, the adjacent oxygen atom of the amide attacks the electrophilic carbon of the ketenimine, and a subsequent proton transfer takes place with the aid of the base to form the predicted reaction product 4-sulonamido-1,3-oxazine. However, the X-ray studies of the compound **6a** indicated that the NTs group is adjacent to the phenyl group, suggesting a possible rearrangement process during the course of the reaction. Hence, the initially formed 1,3-oxazine intermediate probably goes through a ring-opening process to form an unstable nitrilium intermediate with the equilibrium between the imidate and the amidate intermediates in which the amidate was stabilized by an electron-withdrawing Ts group. Subsequently, an intramolecular reaction was triggered to close the ring and furnish the DHPMs (**6**). The stability of the proposed nitrilium intermediate could be affected by the electronic nature of the R^1 groups. The electron-withdrawing R^1 groups destabilize the already unstable nitrilium intermediate.

Table 1 summarizes the attempts in the optimization of suitable reaction conditions to produce DHPMs. For instance,

Table 1. Optimization of Reaction Conditions for the Preparation of 2-Phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one via Cu(I)-Catalyzed Reaction



3a 6a

entry	catalyst	base	solvent	temp (°C)	time (h)	yield (%)
1	CuI	TEA	DCM	rt	3	17
2	CuI	pyridine	DCM	rt	4	22
3	CuI	2,6-luditine	DCM	rt	4	19
4	CuI	K_2CO_3	DCM	rt	12	87
5[a]	CuI	K_2CO_3	DCM	rt	12	85
6[b]	CuI	K_2CO_3	DCM	rt	12	86
7	CuI	K_2CO_3	DCM	40	12	80
8	CuI	K_2CO_3	DMF	rt	1	–
9	CuI	K_2CO_3	THF	rt	12	–
10	CuBr	K_2CO_3	DCM	rt	12	40
11	CuBr/DMS	K_2CO_3	DCM	rt	12	42
12	CuI	Cs_2CO_3	DCM	rt	1	–
13	CuI	Na_2CO_3	DCM	rt	12	68
14	CuI	$NaHCO_3$	DCM	rt	24	55
15	CuI	–	DCM	rt	1	–

[a]CuI (0.15 equiv). [b]CuI (0.2 equiv).

the use of triethylamine as a base for the reaction (entry 1) and other organic bases such as pyridine and 2,6-luditine (entries 2 and 3) showed less yields. However, to our surprise, the use of the inorganic base potassium carbonate (K_2CO_3) was found to assist the clean transformation of the starting materials into the product in 12 h despite its poor solubility in the reaction medium. However, the reaction time could not be reduced by increasing the amount of CuI (entries 5 and 6) and elevating the temperature (entry 7). We assume that the longer reaction hours are probably due to the poor solubility of K_2CO_3 in DCM. Comparison of few different brands of K_2CO_3 with different particle size does not show considerable difference in the reaction optimization. Further, the better results of using K_2CO_3 as a base in the reaction may be attributed to the fact that it can also act as a dehydrating agent, which would prevent the formed DHPM from being hydrolyzed. Polar solvents such as DMF and THF resulted in the formation of the complex mixtures (entries 8 and 9). Screening of the copper catalysts such as CuBr and CuBr-dimethylsulfide complex afforded low yields (entries 10 and 11). Further, keeping DCM as the solvent, different inorganic bases were screened. Cesium carbonate (Cs_2CO_3) resulted in the formation of a mixture of products within 30 min (entry 12). The bases sodium carbonate (Na_2CO_3) and sodium bicarbonate ($NaHCO_3$) were also found to yield moderate results with the drawbacks of relatively long reaction times and lower yields compared to the use of K_2CO_3 (entries 13 and 14). In a control reaction, no new product was obtained in the absence of the base (entry 15). The yields of the isolated products were greatly influenced by the workup procedure. Our initial attempts, which employed

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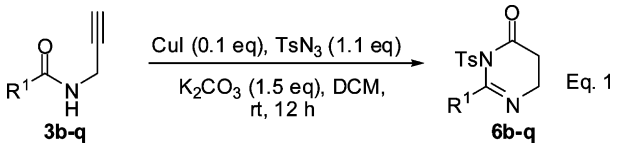
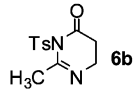
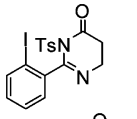
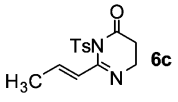
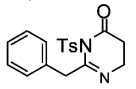
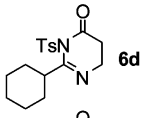
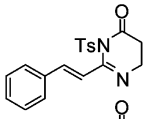
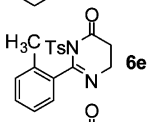
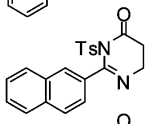
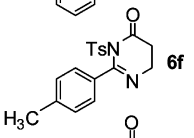
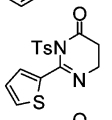
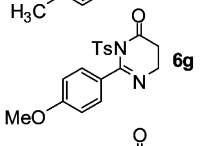
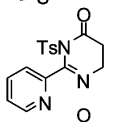
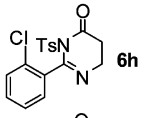
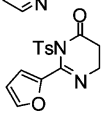
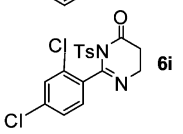
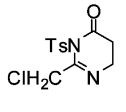
Table 2. Screening of Different R^1-Substituted Propargyl Amide Groups[a]



entry	R^1	product	yield (%)	entry	R^1	product	yield (%)
1	CH_3	 **6b**	85	9	C_6H_4I	 **6j**	81
2	C_3H_5	 **6c**	94	10	C_7H_7	 **6k**	88
3	C_6H_{11}	 **6d**	82	11	C_8H_7	 **6l**	90
4	C_7H_7	 **6e**	91	12	$C_{10}H_7$	 **6m**	88
5	C_7H_7	 **6f**	95	13	C_4H_3S	 **6n**	38
6	C_7H_7O	 **6g**	95	14	C_5H_4N	 **6o**	NR
7	C_6H_4Cl	 **6h**	90	15	C_4H_3O	 **6p**	NR
8	$C_6H_3Cl_2$	 **6i**	82	16	$ClCH_2$	 **6q**	NR

[a]NR = No reaction; starting materials intact.

the aqueous workup to remove K_2CO_3 and subsequent silica gel column chromatography, resulted in low reaction yields (40−50%) despite the clean conversion of the starting materials to the products, as observed on the TLC. The low isolated yields might be attributed to the reason that the product is unstable under the aqueous workup condition and in the slightly acidic medium in the silica gel chromatography; this can decompose the product by ring-opening process. Even the purification attempts using neutral alumina did not improve the yield. Eventually, the aqueous workup and the column chromatography were not used; instead, the reaction mixture was treated with Cuprisorb resin (for the removal of the copper ions) and then filtered through a Celite pad to give the crude compound and followed by a washing step using the ethyl acetate/hexane solvent system to afford the products in high yields.

After identifying the optimal reaction condition for the preparation of compound **6**, we screened various R^1 groups of the propargyl amides for the cyclization (Table 2). The starting materials, i.e., different substituted propargyl amides, were prepared by the acylation of propargyl amine using the conventional acid−propargylamine or acyl chloride−propargylamine coupling reactions. When the R^1 position was substituted by aliphatic groups including methyl, *trans*-propene, and cyclohexyl residues (**6b−d**), the propargyl amides showed smooth conversion to the corresponding DHPMs. In case of substitution with residues containing different aromatic groups, the results indicated that the electronic effects of the benzene ring did not affect the yield of the reaction severely. Electron-donating substituents such as the methyl group (**6e** and **6f**) and 4-methoxy groups (**6g**) on the benzene ring afforded good yields (higher than 90%). When phenyl rings with electron-withdrawing residues such as chloro, dichloro, and iodo (**6h−j**) were used, the transformations were slightly affected, but reasonable yields were obtained (81−90%). Benzyl, *trans*-2-phenyl, and naphthalene residues also gave good results (88−90%, **6k−m**). Furthermore, aromatic groups containing heteroatoms in the ring were found unsuitable for this type of cyclization. For example, the substrates with the R^1 groups containing a heteroatom did not show any progress of the reaction (**6o** and **6p**). Use of additional copper catalyst and a prolonged reaction period accompanied with heating did not

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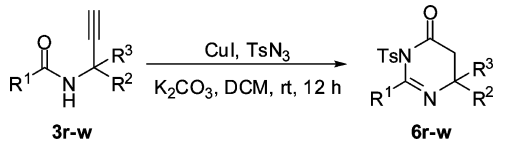
improve the result. The results can be rationalized by assuming that the copper catalyst might be chelated to the heteroatoms in the R^1 substituents, and thereby the formation of sulfonyl triazoles is arrested. Apparently, a combination of the chelating effect of the heteroatoms in the R^1 ring and its electron-withdrawing nature, which inhibits the attack of the amide oxygen on the ketenimine intermediate, could rationalize these unexpected results. However, when excess CuI catalyst (0.5 equiv) and an extended reaction period (48 h) were used, the thiophene analogue (**6n**) afforded 38% product along with some other nonisolable byproducts. Surprisingly, unlike the methyl group (**6b**) the chloromethyl substituent (**6q**) was found inert under the reaction conditions. The loading of excess CuI catalyst (0.4 equiv) and the extension of the reaction period (48 h) did not improve the result either. Probably, the electron-withdrawing chloro substituent inhibits the neighboring carbonyl oxygen atom from attacking the ketenimine intermediate, thereby preventing the subsequent cyclization. The complete screening suggests that the substrates containing electron-donating alkyl, alkene, and aromatic R^1 groups can be elegantly transformed into the corresponding DHPMs (**6**). On the contrary, the alkyl groups containing the electron-withdrawing groups and the aromatic residues with heteroatoms are found to be unsuitable for this type of conversion.

The developed method was further evaluated using substituted propargyl amides (Table 3). We anticipated that the presence of R^2 and R^3 alkyl groups adjacent to the alkyne group may affect the reaction because of the steric effect. However, the substituted propargyl amide substrates had shown efficient conversion to furnish the products in good yields (83−91%) under the optimized conditions. The achiral dimethyl propargyl amide **3r** and the achiral cyclohexyl propargyl amide **3s** were obtained from the available substituted propargyl amine precursors; however, for the others, three L-α-amino acids, alanine, valine, and leucine, were successfully converted to the chirally substituted propargyl amides using the synthetic pathway depicted in Scheme 2.[28] The obtained chiral propargyl amides were then transformed to the desired chiral DHPMs (**6t**, **6u**, and **6v**) with good yields (83−88%). Furthermore, to examine the stereochemistry, a racemic mixture of D/L-leucine was used in the preparation of the racemic isobutyl-substituted DHPM (**6w**) and used as the racemic standard for chiral HPLC analysis. The HPLC chromatogram clearly indicated that the chiral integrity in the compound **6v** derived from L-leucine is reasonably maintained (enantiomeric excess = 92%) despite the use of a number of bases in several synthesis steps.[28]

The structural features of the synthesized DHPMs (**6**) are favorable for the nucleophilic attack with the ring-opening process to produce the substituted β-amino acid analogues. This may be a potential extension to the proposed methodology; the addition of a fourth component, such as amine or alcohol in the reaction mixture would directly provide the corresponding amide or ester in a one-pot process (Table 4). We added the fourth reactant after the formation of DHPMs (**6**) in order to avoid the possible attack on the reactive ketenimine by the added nucleophiles. To our delight, β-amino acid analogues were formed when amines were added as the fourth component after the formation of DHPMs (**6**) in the reaction mixture (**7a** (82%) and **7b** (75%)). Similarly, the in situ addition of alcohols provided the corresponding esters (**7c**−**e**, 80−83%) in 3 h at the ambient temperature. The developed four-component synthetic strategy could be used to produce β-amino acid analogues with good yields under mild conditions.

Table 3. Scope of Substituted Propargyl Amides



3r-w 6r-w

entry	R^1	R^2 & R^3	product		yield (%)
1	Ph	CH_3 & CH_3		**6r**	89
2	Ph	-$(CH_2)_5$-		**6s**	91
3	Ph	CH_3 & H		**6t**	83
4	Ph	C_3H_7 & H		**6u**	88
5 [a]	Ph	C_4H_9 & H		**6v**	84
6	Ph	C_4H_9 & H		**6w**	83

[a]Enantiomeric excess (ee) = 92.6%

Moreover, we also observed that these ring-opening reactions work well in a step-by-step manner. When the isolated DHPMs were treated with alcohols or amines in the absence of a base, the expected ring-opening products were obtained in high conversion efficiency.

The DHPMs (**6**) have similar structural features to that of the 1,3-oxazines; therefore, we anticipated that the hydrolysis of the isolated DHPMs (**6**) would provide the corresponding β- and β^3-amino acids. As predicted, β-alanine (**7f**) was obtained in good yield by hydrolyzing the compound **6a** using 6 N HCl at the reflux temperature for 3 h. Similarly, the hydrolysis of the dimethyl substituted DHPM (**6r**) afforded the corresponding β^3-methyl amino acid analogue (**7g**) in 62% yield (Scheme 3).

CONCLUSION

In summary, we have developed a method for the preparation of β-amino acid analogues via substituted DHPM intermediates. The core structure of DHPMs (**6**) is present in many medicinally important compounds; therefore, the developed methodology allows us to rapidly and efficiently expand the structural complexity of the substituted DHPMs. Further, we demonstrated that the isolated products could be conveniently transformed into the β- and β^3-amino acid analogues on hydrolysis or via various nucleophilic reactions by a novel four-

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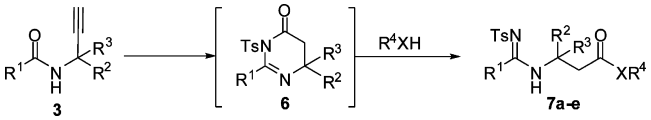
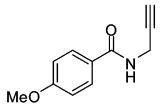
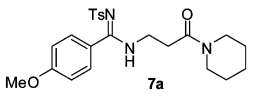
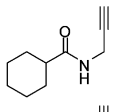
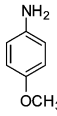
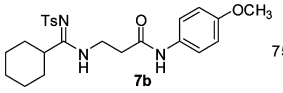
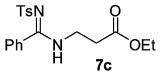
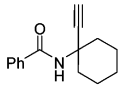
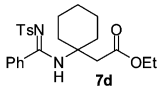
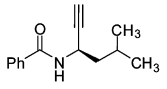
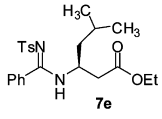
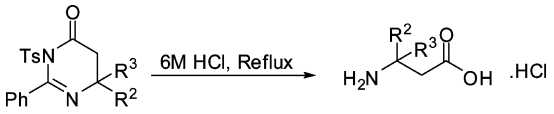
Table 4. Nucleophilic Attack on Dihydropyrimid-4-ones by Amines and Alcohols



entry	substrate	R^4XH	product	yield (%)
1			 7a	82
2			 7b	75
3		EtOH	 7c	80
4		EtOH	 7d	78
5		EtOH	 7e	82

Scheme 3. Hydrolysis of the Dihydropyrimid-4-ones



7f: Where R^2 & R^3 = H (3h; 88%)
7g: Where R^2 & R^3 = Me (12 h; 62%)

component reaction. The mild reaction condition and the good product yields make the current strategy useful for the construction of various DHPMs and *β*-amino acid molecular libraries.

EXPERIMENTAL SECTION

General Considerations. All reactions were performed under an atmosphere of nitrogen, and the workups were carried out in air. All the solvents used for the condition optimization were dried using reported procedures. Unless noted, all materials were purchased from commercial suppliers and used as received. Cuprisorb resin was dried in a high vacuum before use. ^{1}H and ^{13}C NMR spectra were recorded on 300 and 75 MHz spectrometer respectively. NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constants (Hz). Solvent residual peaks references for ^{1}H NMR: $CDCl_3$, 7.2600 ppm; MeOD, 3.3100 ppm. For ^{13}C NMR: $CDCl_3$, 77.2300 ppm; MeOD, 49.1500 ppm. Melting points of the products were calculated in open capillary tubes. High resolution mass spectra (HRMS) were performed on electron ionization time-of-flight (EI-TOF) and fast atom bombardment (FAB) mass spectrometers. Flash column chromatography was performed using silica gel (43−60 mm).

Representative Procedure for the Preparation of Dihydropyrimid-4-ones (6a−6w): Preparation of 2-Phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6a). To a stirred solution of *N*-(prop-2-ynyl)benzamide (**3a**) (100 mg, 0.628 mmol) in dichloromethane (12.5 mL) were added copper iodide (11.9 mg, 0.062 mmol), potassium carbonate (130 mg, 0.942 mmol) and tosyl azide (136 mg, 0.691 mmol) under nitrogen atmosphere, and the resultant mixture was stirred at 25 °C for 12 h. After completion of the reaction monitored by TLC, the reaction mixture was diluted with dichloromethane (10 mL), stirred with cuprisorb resin (200 mg) for 20 min to remove the copper traces in the reaction mixture, and filtered through a pad of Celite. The Celite pad was washed with excess dichloromethane (10 mL), and the combined filtrate was concentrated under reduced pressure to afford the crude compound. The crude compound was stirred with 1:9 ethyl acetate in hexane (10 mL) for 30 min at 0 °C and the resultant solid was filtered, washed with hexane (5 mL) and dried over high vacuum to afford 2-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (**6a**) (179 mg; 87%) as a pale yellow powder.

2-Phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6a).[27] Pale yellow powder (179 mg, 0.546 mmol, 87%): mp 157−159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 7.4 Hz, 2H), 7.50−7.45 (m, 1H), 7.42−7.37 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 3.74 (t, J = 6.3 Hz, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 154.7, 145.9, 136.4, 136.2, 130.9, 129.6, 128.5, 127.6, 43.6, 34.2, 21.9; IR (KBr) v 3662, 3264, 3072, 2869, 2314, 1738, 1644, 1594, 1493, 1368, 1281, 1002, 882, 770, 669 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_2O_3S$ [M + H]$^+$, 329.0960, found 329.0959.

2-Methyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6b). Off white powder (233 mg, 0.876 mmol, 85%): mp 116−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.2 Hz, 2H), 3.53 (t, J = 6.3 Hz, 2H), 2.49 (s, 3H), 2.47−2.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 151.8, 145.8, 136.3, 129.8, 129.1, 42.5, 33.4, 24.3, 21.9; IR (KBr) v 3386, 3068, 2924, 2867, 1820, 1733, 1665, 1596, 1557, 1367, 1275, 1224, 816, 667 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{15}N_2O_3S$ [M + H]$^+$, 267.0803, found 267.0808.

(*E*)-2-(Prop-1-enyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6c). White powder (220 mg, 0.75 mmol, 94%): mp 90−95 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.07 Hz, 2H), 6.75−6.58 (m, 1H), 6.26 (d, J = 15.3 Hz, 1H), 3.57 (t, J = 6.3 Hz, 2H), 2.45 (s, 3H), 2.49−2.40 (m, 2H), 1.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 151.1, 145.7, 136.5, 136.2, 129.7, 129.0, 125.8, 42.7, 33.7, 21.8, 18.4; IR (KBr) v 1735, 1625, 1597, 1443, 1361 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{14}H_{17}N_2O_3S$ [M + H]$^+$, 293.0960, found 293.0954.

2-Cyclohexyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6d).[27] Off white powder (166 mg, 0.496 mmol, 82%): mp 115−117 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 3.54 (t, J = 6.3 Hz, 2H), 3.05−2.99 (m, 1H), 2.46 (s, 3H), 2.39 (t, J = 6.3 Hz, 2H), 1.85−1.66 (m, 5H), 1.52−1.22 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ170.9, 160.3, 145.6, 136.6, 129.8, 128.8, 44.2, 42.5, 34.2, 31.6, 29.7, 26.2, 26.1, 25.9, 21.9; IR (KBr) v 3295, 3061, 2856, 2667, 1913, 1735, 1654, 1596, 1084, 831, 667 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{23}N_2O_3S$ [M + H]$^+$, 335.1429, found 335.1423.

2-*o*-Tolyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6e). White powder (180 mg, 0.53 mmol, 91%): mp 95−100 °C; ^{1}H NMR (300 MHz, CD_3CN) δ 7.58 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 7.8 Hz, 3H), 7.25−7.11 (m, 3H), 3.74 (t, J = 6.4 Hz, 2H), 2.58 (t, J = 6.4 Hz, 2H), 2.42 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 153.5, 145.7, 136.7, 135.4, 135.0, 130.8, 129.8, 129.3, 128.9, 125.4, 43.6, 34.3, 21.9, 19.4; IR (KBr) v 3059, 1738, 1665, 1451, 1368 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O_3S$ (M + H)$^+$, 343.1116, found 343.1119.

2-*p*-Tolyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6f).[27] White powder (187 mg, 0.55 mmol, 95%): mp 170−175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 7.8 Hz, 2H), 3.71 (t, J = 6.3 Hz, 2H), 2.53 (t, J = 6.3 Hz, 2H), 2.46 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 154.6, 145.8, 141.2, 136.2, 133.6, 129.5, 129.1, 127.5, 43.4, 34.2, 21.8, 21.6; IR (KBr) v 3048, 1744, 1635, 1449, 1344 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O_3S$ (M + H)$^+$, 343.1116, found 343.1108.

2-(4-Methoxyphenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6g).[27] Pale yellow powder (180 mg, 0.501 mmol, 95%): mp 144−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.91 (d, J = 8.6 Hz,

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2H), 3.86 (s, 3H), 3.68 (t, J = 6.2 Hz, 2H), 2.52 (t, J = 6.2 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 161.9, 154.3, 145.8, 136.4, 129.6, 129.5, 129.3, 128.9, 113.9, 55.6, 43.4, 34.3, 21.9; IR (KBr) v 3374, 3058, 2965, 2934, 2840, 1738, 1636, 1607, 1512, 1366, 1254, 1148, 823, 685 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O_4S$ $[M + H]^+$, 359.1066, found 359.1073.

2-(2-Chlorophenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6h).[27] Off-white powder (163 mg, 0.45 mmol, 90%): mp 115.1−116.7 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (dd, J = 5.8, 3.5 Hz, 1H), 7.51 (d, J = 8.3 Hz, 2H), 7.38 (dd, J = 5.8, 3.5 Hz, 2H), 7.18 (d, J = 8.3 Hz, 3H), 3.86 (t, J = 6.3 Hz, 2H), 2.67 (t, J = 6.2 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 151.7, 145.7, 135.1, 134.4, 132.5, 132.0, 131.0, 129.3, 129.1, 127.0, 43.8, 34.1, 21.9; IR (KBr) ν 3058, 1743, 1652, 1596, 1494, 1378 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{16}N_2O_3S^{35}Cl$ $(M + H)^+$, 363.0570, found 363.0562.

2-(2,4-Dichlorophenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6i). Off white powder (142 mg, 0.359 mmol, 82%): mp 122−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.3 Hz, 1H), 7.36 (d, J = 9.4 Hz, 1H), 7.23−7.22 (m, 3H), 3.84 (t, J = 6.3 Hz, 2H), 2.65 (t, J = 6.3 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 150.8, 146.0, 136.5, 135.0, 133.3, 133.1, 132.7, 129.5, 129.1, 129.0, 127.4, 43.8, 33.98, 21.9; IR (KBr) v 3384, 3069, 2128, 1744, 1655, 1589, 1474, 1374, 1286, 1237, 1174, 1006, 885, 786, 666 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{15}N_2O_3S^{35}Cl_2$ $[M + H]^+$, 397.0180, found 397.0183.

2-(2-Iodophenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6j). Off white powder (129 mg, 0.284 mmol, 81%): mp 122−124 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, J = 7.7 Hz, 1H), 7.56−7.54 (m, 1H), 7.49−7.47 (m, 3H), 7.20−7.11 (m, 3H), 3.87 (t, J = 6.42 Hz, 2H), 2.75 (t, J = 6.4 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 154.1, 145.8, 139.6, 138.7, 132.3, 131.1, 129.4, 129.3, 128.1, 96.1, 43.8, 34.3, 21.9; IR (KBr) v 2922, 2127, 1742, 1652, 1596, 1494, 1371, 1174, 1005, 815, 665 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{17}H_{16}N_2O_3SI$ $[M + H]^+$, 454.9926, found 454.9922.

2-Benzyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6k). White powder (174 mg, 0.51 mmol, 88%): mp 118−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.1, 2H), 7.32−7.16 (m, 7H), 4.23 (s, 2H), 3.58 (t, J = 6.6, 2H), 2.43 (s, 3H), 2.40 (t, J = 6.6, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.38, 154.71, 145.62, 136.54, 135.88, 129.67, 129.40, 128.90, 128.84, 127.26, 42.90, 42.76, 33.56, 21.86 ppm; IR (KBr) ν 3056, 1723, 1650, 1592, 1560, 1365 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_3S$ $[M + H]^+$ 343.1116, found 343.1119.

(*E*)-2-Styryl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6l).[27] Pale yellow powder (178 mg, 0.50 mmol, 93%): mp 124−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 8.4 Hz, 2H), 7.56−7.32 (m, 8H), 6.88 (d, J = 15.6 Hz, 1H), 3.68 (t, J = 6.3, 2H), 2.51 (t, J = 6.3, 2H), 2.47 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.26, 151.50, 145.94, 137.33, 136.59, 135.59, 129.87, 129.64, 129.13, 129.04, 127.87, 122.19, 43.05, 33.87, 21.96 ppm; IR (KBr) ν 3059, 1738, 1644, 1607, 1577, 1363 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{19}N_2O_3S$ $[M + H]^+$ 355.1116, found 355.1111.

2-(Naphthalen-2-yl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6m). White powder (158 mg, 0.42 mmol, 88%): mp 134−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95−7.80 (m, 5H), 7.80−7.67 (m, 2H), 7.59−7.48 (m, 2H), 7.29 (d, J = 8.1 Hz, 2H), 3.82 (t, J = 6.3 Hz, 2H), 2.62 (t, J = 6.3, 2H), 2.47 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.88, 154.79, 145.87, 136.21, 134.61, 133.66, 132.50, 129.58, 128.85, 128.62, 128.07, 127.55, 126.82, 124.69, 43.81, 34.43, 21.93 ppm; IR (KBr) ν 3059, 1728, 1647, 1593, 1369 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{19}N_2O_3S$ $[M + H]^+$ 379.1116, found 379.1113.

2-(Thiophen-2-yl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6n). White powder (63 mg, 0.19 mmol, 38%): mp 165.6−167.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.50−7.43 (m, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.10−7.03 (m, 1H), 3.65 (t, J = 6.2 Hz, 2H), 2.50 (t, J = 6.4 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 149.3, 146.0, 139.0, 136.3, 130.2, 129.7, 129.5, 127.4, 43.4, 34.4, 22.0; IR (KBr) ν 3051, 1735, 1622, 1593, 1492, 1362 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{15}N_2O_3S_2$ $(M + H)^+$, 335.0524, found 335.0532.

6,6-Dimethyl-2-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6r). Off white powder (169 mg, 0.475 mmol, 89%): mp 133−137 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H), 7.51−7.43 (m, 3H), 7.44−7.29 (m, 4H), 2.49 (s, 2H), 2.45 (s, 3H), 1.35 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 150.8, 145.9, 137.1, 135.8, 130.4, 130.0, 129.4, 128.4, 127.5, 54.3, 45.6, 27.5, 21.9; IR (KBr) v; HRMS (FAB) calcd for $C_{19}H_{21}N_2O_3S$ $[M + H]^+$, 357.1273, found 357.1275.

2-Phenyl-3-tosyl-1,3-diazaspiro[5.5]undec-1-en-4-one (6s). Off white powder (155 mg, 0.377 mmol, 91%): mp 126−128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 7.1 Hz, 2H), 7.45−7.29 (m, 5H), 2.46 (s, 2H), 2.45 (s, 3H), 1.85−1.76 (m, 4H), 1.63−1.60 (m, 1H), 1.54−1.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 150.0, 135.8, 130.4, 130.0, 129.3, 128.4, 127.6, 56.5, 44.7, 36.4, 25.7, 22.1, 21.9; IR (KBr) v 3448, 3261, 3060, 2931, 1738, 1644, 1582, 1030, 1030, 928, 882; HRMS (ESI-TOF) calcd for $C_{22}H_{25}N_2O_3S$ $[M + H]^+$, 397.1586, found 397.1590.

(*R*)-6-Methyl-2-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6t). White powder (98 mg, 0.290 mmol, 83%): mp 153−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 7.5 Hz, 2H), 7.51−7.27 (m, 5H), 3.89−3.72 (m, 1H), 2.57 (dd, J = 17.0, 3.6 Hz, 1H), 2.45 (s, 3H), 2.31 (dd, J = 11.7, 17.1 Hz, 1H′), 1.40 (d, J = 6.9, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.63, 152.92, 145.85, 136.50, 136.18, 130.81, 129.64, 129.52, 128.50, 127.71, 50.12, 40.93, 21.92, 20.83 ppm; $[\alpha]^{28}_D$ = +61.35 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3062, 1736, 1686, 1608, 1583, 1371 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{18}H_{18}N_2O_3SNa$ $[M + Na]^+$ 365.0936, found 365.0928.

(*S*)-6-Isopropyl-2-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6u). White powder (162 mg, 0.437 mmol, 88%): mp 111−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 7.2 Hz, 2H), 7.49−7.30 (m, 5H), 3.30−3.25 (m, 1H), 2.60−2.54 (dd, J = 2.8, 2.8 Hz, 1H), 2.46 (s, 3H), 2.3−2.2 (m, 1H), 1.90−1.88 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 145.8, 136.5, 136.2, 130.8, 129.6, 129.5, 128.4, 127.8, 60.1, 37.2, 32.2, 21.9, 19.1 ppm; $[\alpha]^{27}_D$ = +122.58 (c, 0.5, CH_2Cl_2) IR (KBr) ν 3451, 3060, 2962, 2874, 1735, 1638, 1596, 1367, 1173, 962, 769, 676 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{20}H_{23}N_2O_3S$ $[M + H]^+$ 371.1429, found 371.1420.

(*R*)-6-Isobutyl-2-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6v). Off white powder (150 mg, 0.390 mmol, 84%): mp 112−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.45−7.29 (m, 5H), 3.8−3.6 (m, 1H), 2.59−2.52 (dd, J = 3.6, 3.6 Hz, 1H), 2.45 (s, 3H), 2.30−2.20 (m, 1H), 1.97−1.90 (m, 1H), 1.70−1.68 (m, 1H), 1.32−1.28 (m, 1H), 0.97−0.93 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 152.8, 145.9, 136.5, 136.1, 130.8, 129.7, 129.5, 128.5, 127.7, 52.5, 43.8, 39.8, 24.9, 23.1, 22.4, 21.9 ppm; $[\alpha]^{28}_D$ = +28.86 (c, 0.5, CH_2Cl_2) IR (KBr) ν 3061, 2126, 1732, 1635, 1371, 1371, 868, 800 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{25}N_2O_3S$ $[M + H]^+$ 385.1586, found 385.1592.

6-Isobutyl-2-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (6w). Off white powder (148 mg, 0.385 mmol, 83%): mp 112−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 7.2 Hz, 2H), 7.45−7.29 (m, 5H), 3.8−3.6 (m, 1H), 2.59−2.52 (dd, J = 3.6, 3.6 Hz, 1H), 2.45 (s, 3H), 2.30−2.20 (m, 1H), 1.97−1.90 (m, 1H), 1.70−1.68 (m, 1H), 1.32−1.28 ((m, 1H), 0.97−0.93 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 152.7, 145.8, 136.4, 136.9, 130.7, 129.5, 129.4, 128.4, 127.6, 52.4, 43.6, 39.6, 24.8, 23.0, 22.2, 21.8 ppm; IR (KBr) ν 3061, 2126, 1732, 1635, 1371, 1371, 868, 800 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{21}H_{25}N_2O_3S$ $[M + H]^+$ 385.1586, found 385.1580.

Representative Procedure for the Preparation of β- and β^3-Amino Acid Analogues (7a−7e): Preparation of Ethyl 3-(*N*′-tosylbenzimidamido)propanoate (7c). To a stirred solution of *N*-(prop-2-ynyl)benzamide (**3a**) (100 mg, 0.628 mmol) in dichloromethane (12.5 mL) were added copper iodide (11.9 mg, 0.062 mmol), potassium carbonate (130 mg, 0.942 mmol) and tosyl azide (136 mg, 0.691 mmol) under nitrogen atmosphere, and the resultant mixture was stirred at rt for 12 h. After the complete formation of the required intermediate 2-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (**6a**) was confirmed by TLC, the fourth component ethanol (0.044 mL,

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1.2 equiv) was added to the reaction mixture and further stirred for another 3 h. The reaction mixture was diluted with dichloromethane (10 mL), stirred with cuprisorb resin (200 mg) for 20 min to remove the copper traces, and filtered through a pad of Celite. The Celite pad was washed with excess dichloromethane (10 mL), and the combined filtrate was concentrated under reduced pressure, and the resultant residue was purified using silica gel column chromatography using 20−30% ethyl acetate in hexane as an eluent to afford ethyl 3-(*N*′-tosylbenzimidamido)propanoate (**7c**) as a colorless liquid (188 mg, 80%).

(*Z*)-4-Methoxy-*N*-(3-oxo-3-(piperidin-1-yl)propyl)-*N*′-tosylbenzimidamide (7a). Yellow solid (193 mg, 0.440 mmol, 82%): mp 105−108 °C; ^{1}H NMR (300 MHz, MeOD) δ 7.55 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 3.61 (t, J = 7.2 Hz, 2H), 3.51 (t, J = 5.1 Hz, 2H), 3.39 (t, J = 5.1 Hz, 2H), 2.69 (t, J = 7.2 Hz, 2H), 2.38 (s,3H), 1.69−1.60 (m, 2H), 1.57−1.46 (m, 4H); ^{13}C NMR (75 MHz, MeOD) δ 171.2, 168.0, 163.4, 143.7, 142.6, 131.2, 130.3, 127.6, 127.5, 114.5, 56.1, 48.1, 44.1, 40.0, 32.9, 27.7, 26.8, 25.5, 21.5; IR (KBr) ν 3287, 2936, 2857, 1736, 1686, 1608, 1584 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{28}N_3O_4S$ (M − H)$^-$, 442.1801, found 442.1807.

(*Z*)-*N*-(4-Methoxyphenyl)-3-(*N*′-tosylcyclohexanecarboximidamido)propanamide (7b). White solid (208 mg, 0.450 mmol, 75%): mp 88−93 °C; ^{1}H NMR (300 MHz, MeOD) δ 7.76 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.84 (d, J = 9.0 Hz, 2H), 3.76 (s, 3H), 3.64 (t, J = 7.0 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), 2.17 (t, J = 11.4 Hz, 1H), 1.85−1.71 (m, 4H), 1.51−1.31 (m, 2H), 1.30−1.15 (m, 4H); ^{13}C NMR (75 MHz, MeOD) δ 179.8, 165.2, 159.1, 144.2, 142.2, 132.1, 130.6, 127.3, 125.0, 115.0, 56.0, 46.6, 38.7, 36.0, 30.8, 27.0, 26.9, 21.6; IR (KBr) ν 3302, 2930, 2855, 1735, 1644, 1540, 1511 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{24}H_{31}N_3O_4SNa$ (M + Na)$^+$, 480.1933, found 480.1927.

Ethyl 3-(*N*′-tosylbenzimidamido)propanoate (7c). Colorless liquid (188 mg, 0.50 mmol, 80%): ^{1}H NMR (300 MHz, MeOD) δ 7.52−7.41 (m, 3H), 7.38−7.26 (m, 4H), 7.20 (d, J = 8.0 Hz, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.66 (t, J = 6.7 Hz, 2H), 2.66 (t, J = 6.6 Hz, 2H), 2.38 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, MeOD)IR δ 173.2, 168.4, 143.8, 142.2, 135.4, 131.7, 130.3, 129.2, 129.1, 127.6, 62.0, 39.3, 33.9, 21.5, 14.7; IR (KBr) ν 3306, 3064, 2928, 1731, 1586, 1542, 1494, 1445, 1376, 720, 691 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{19}H_{22}N_2O_4SNa$ (M + Na)$^+$, 397.1198, found 397.1194.

Ethyl 2-(1-(*N*′-tosylbenzimidamido)cyclohexyl)acetate (7d). Off white solid (151 mg, 0.351 mmol, 78%): mp 104−106 °C; ^{1}H NMR (300 MHz, MeOD) δ 7.46−7.44 (m, 3H), 7.33−7.30 (m, 4H), 7.21−7.19 (m, 2H), 4.10 (q, J = 7.1, 14.2 Hz, 2H), 2.96 (s, 2H), 2.35 (s, 3H), 2.34−2.33 (b, 1H), 1.50−1.29 (m, 10H), 1.17 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, MeOD) δ 172.3, 167.5, 143.6, 142.2, 136.1, 131.4, 130.2, 129.3, 128.9, 127.5, 61.5, 58.6, 35.6, 42.2, 26.6, 22.8, 21.5, 14.8 cm^{-1}; IR (KBr) ν 3420, 2930, 2857, 1727, 1584, 1530, 1281, 1146, 1087, 725. HRMS (ESI-TOF) calcd for $C_{24}H_{30}N_2O_4SNa$ (M + Na)$^+$, 465.1824, found 465.1817.

(*S*)-Ethyl 5-methyl-3-(*N*′-tosylbenzimidamido)hexanoate (7e). Colorless liquid (164 mg, 0.500 mmol, 82%): ^{1}H NMR (300 MHz, MeOD) δ 7.52−7.46 (m, 3H), 7.43−7.31 (m, 4H), 7.22−7.19 (m, 2H), 4.80−4.62 (b, 1H), 4.14 (q, J = 2.6, 7.0 Hz, 2H), 2.56−2.52 (m, 2H), 2.38 (s, 3H), 1.66−1.53 (m, 2H), 1.36−1.22 (m, 4H), 0.95−0.91 (m, 6H); ^{13}C NMR (75 MHz, MeOD) δ 172.7, 167.8, 143.6, 142.4, 135.6, 131.6, 130.1, 129.1, 129.0, 127.5, 61.9, 49.1, 44.3, 40.7, 26.3, 23.6, 22.4, 21.5, 14.7; $[\alpha]^{28}_D$ = −14.78 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3289, 3107, 2958, 2926, 2871, 1911, 1732, 1585, 1445, 1279, 1144, 1030, 728, 662 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{23}H_{31}N_2O_4S$ (M + H)$^+$, 431.2005, found 431.1997.

Representative Procedure for the Hydrolysis of the Dihydropyrimid-4-ones (7f and 7g): Hydrolysis of 2-Phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one to *β*-Alanine Hydrochloride (7f). 6 M HCl (5 mL) was added to 2-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (**6a**) and the resultant mixture was refluxed at 100 °C for 3 h. The reaction mixture was cooled and the diluted with H_2O (5 mL), stirred with ethyl acetate (2 × 10 mL). The organic layer was separated and discarded. The aqueous layer was collected and concentrated under reduced pressure to afford the desired *β*-alanine as an off white powder (34 mg, 88%).

3-Aminopropanoic Acid Hydrochloride (7f).[29] Off white solid (34 mg, 0.267 mmol, 88%): mp 205−208 °C; ^{1}H NMR (300 MHz, D_2O) δ 3.33 (t, J = 6.3 Hz, 2H), 2.86 (t, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, MeOD) δ 174.3, 36.6, 32.1; IR (KBr) ν 3626, 3418, 2011, 1723, 1622, 1409, 1219, 813 cm^{-1}; HRMS (EI) calcd for $C_3H_7NO_2$ (M + H)$^+$, 89.0477, found 89.0476.

3-Amino-3-methylbutanoic Acid Hydrochloride (7g). Off white solid (27 mg, 0.175 mmol, 62%): mp 231−233 °C; ^{1}H NMR (300 MHz, MeOD) δ 2.69 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (75 MHz, MeOD) δ 173.7, 53.4, 43.6, 26.1; IR (KBr) ν 3418, 2983, 2582, 2081, 1722, 1634, 1383, 1085 cm^{-1} ; HRMS (ESI-TOF) calcd for $C_5H_{11}NO_2Na$ (M + Na)$^+$, 140.0687, found 140.0683.

Representative Procedure for the Preparation of Chiral Propargyl Amides from *N*-Boc-*α*-Amino Acids: Preparation of (*R*)-*N*-(4-Methylpent-1-yn-3-yl)benzamide (3u) from *N*-Boc Valine. *Stage 1: Preparation of (R)-tert-Butyl 1-(methoxy(methyl)-amino)-3-methyl-1-oxobutan-2-ylcarbamate (**1u**).* To a stirred solution of *N*-Boc valine (2.0 g, 9.211 mmol) in dichloromethane (25 mL) were added EDC·HCl (2.64 g, 13.81 mmol) and HOBt (2.11 g, 13.81 mmol), and the mixture was stirred for 30 min. *N*,*O*-dimethylhydroxyamine·HCl (1.35 g, 13.81 mmol) was added to the reaction mixture followed by DIEA (3.2 mL, 18.42 mmol), and the mixture was stirred for 14 h at rt. The reaction mixture was diluted with H_2O (20 mL), extracted with dichloromethane (2 × 25 mL), washed again with 1 N HCl (10 mL), H_2O (10 mL), and brine solution (10 mL), dried over $MgSO_4$, filtered, and concentrated to afford the desired product as an off white powder (1.48 g, 80%).

Stage 2: Preparation of (R)-tert-Butyl 3-methyl-1-oxobutan-2-ylcarbamate. To a stirred solution of (*R*)-*tert*-butyl 1-(methoxy-(methyl)amino)-3-methyl-1-oxobutan-2-ylcarbamate (1.45 g, 7.213 mmol) in THF (20 mL) was added $LiAlH_4$ (301.7 mg, 7.935 mmol) portion wise at 0 °C and stirred for 20 min at 0 °C under nitrogen. The reaction mixture was carefully quenched with 2 N HCl by adjusting the pH ∼ 6−7. The reaction mixture was diluted with H_2O, extracted with ethyl acetate (2 × 10 mL), dried over with $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired aldehyde (860 mg, 59%) as an oil, which was taken to the taken next immediately.

*Stage 3: Preparation of (R)-tert-Butyl 4-methylpent-1-yn-3-ylcarbamate (**2u**).* To a stirred solution of dimethyl 2-oxopropylphosphonate (1.405 g, 8.457 mmol) in acetonitrile (20 mL) was added tosyl azide (1.667 g, 8.457 mmol) followed by potassium carbonate (1.167 g, 8.467 mmol) at 0 °C, and the resultant mixture was stirred at room temperature for 60 min under nitrogen. To this mixture was added a solution of aldehyde (850 mg, 4.228 mmol) in MeOH (10 mL) at 0 °C dropwise over a period of 10 min, and the mixture was stirred overnight. The reaction mixture was quenched with H_2O (10 mL) and concentrated under reduced pressure, and the resultant residue was diluted with ethyl acetate (30 mL), washed with H_2O (10 mL), dried over with $MgSO_4$, filtered, and concentrated to afford the crude. The crude was purified by silica gel column chromatography using 5−7% ethyl acetate in hexane as the solvent system to afford the desired alkyne as a pale yellow solid (347 mg, 42%).

Stage 4: Preparation of (R)-4-Methylpent-1-yn-3-amine. A mixture of trifluoroacetic acid and dichloromethane (1:1) (4 mL) was added to *N*-Boc alkyne (140 mg) and stirred for 30 min at rt. The reaction mixture was evaporated under pressure, and the resultant residue was diluted with 6 M NaOH (10 mL), extracted with dichloromethane (2 × 10 mL), dried over with $MgSO_4$, filtered, and taken to the next stage without evaporation (the yield of this step was considered as quantitative).

*Stage 5: Preparation of (R)-N-(4-Methylpent-1-yn-3-yl)-benzamide (**3u**).* To a stirred solution of propargylamine (69 mg, 0.709 mmol; considered as quant. yield in the previous stage) in dichloromethane (20 mL) was added triethylamine (0.1 mL, 1.06 mmol) followed by benzoyl chloride (0.091 mL, 0.779 mmol), and the resultant mixture was stirred at rt for 4 h under nitrogen atmosphere. The reaction mixture was diluted with dichloromethane (10 mL),

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washed with sat. $NaHCO_3$ solution (5 mL), H_2O (5 mL), dried over with $MgSO_4$, filtered, and concentrated under reduced pressure to afford the desired chiral propargyl amide as an off white powder (115 mg, 80%).

***N*-(Prop-2-ynyl)benzamide (3a).** Brown powder (208 mg, 1.306 mmol, 78%): mp 112−114 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79−7.54 (m, 2H), 7.54−7.41 (m, 3H), 6.29 (b, 1H), 4.26 (dd, J = 2.6, 5.1 Hz, 2H), 2.28 (t, J = 2.49, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 133.9, 131.9, 128.8, 127.2, 79.7, 72.0, 29.9 ppm; IR (KBr) ν 3292, 3059, 1961, 1998, 1812, 1651, 1603, 1651, 1603, 1492, 1051, 716 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_9NO$ $[M + Na]^+$ 182.0582, found 182.0584.

***N*-(Prop-2-ynyl)acetamide (3b).** Brown powder (120 mg, 1.235 mmol, 80%): mp 71−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (b, 1H), 4.04 (dd, J = 2.5, 5.3 Hz, 2H), 2.22 (s, 1H). 2.00 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 79.8, 71.4, 29.3, 23.0 ppm; IR (KBr) ν 3227, 3086, 2115, 1658, 1569, 1301, 1079, 718 cm^{-1}; HRMS (ESI-TOF) calcd for C_5H_7NONa $[M + Na]^+$ 120.0425, found 120.0420.

(*E*)-*N*-(Prop-2-ynyl)but-2-enamide (3c). White powder (210 mg, 1.70 mmol, 94%): mp 114−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96−6.79 (m, 1H), 5.79 (d, J = 15.5 Hz, 1H), 4.11 (dd, J = 5.1,2.4 Hz, 2H), 2.23 (t, J = 2.3 Hz, 1H), 1.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 140.6, 124.7, 79.9, 71.3, 29.1, 17.8; IR (KBr) v 3437, 3247, 2115, 1630 cm^{-1}; HRMS (ESI-TOF) calcd for $C_7H_{10}NO$ $[M + H]^+$, 124.0762, found 124.0761.

***N*-(Prop-2-ynyl)cyclohexanecarboxamide (3d).** Off white powder (230 mg, 1.391 mmol, 89%): mp 100−102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (b, 1H), 4.04 (dd, J = 2.6, 5.1 Hz, 2H), 2.22 (s, 1H), 2.13−2.04 (m, 1H), 1.88−1.78 (m, 4H), 1.68−1.33 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 79.9, 71.7, 45.4, 29.7, 29.3, 25.8 ppm; IR (KBr) ν 3445, 3302, 3054, 2931, 2855, 1638, 1534, 1450, 1392, 1265, 995, 739 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{15}NO$ $[M]^+$ 165.1154, found 165.1149.

2-Methyl-*N*-(prop-2-ynyl)benzamide (3e). White powder (360 mg, 2.08 mmol, 99%): mp 68−73 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.37−7.29 (m, 2H), 7.28−7.18 (m, 2H), 4.13 (d, J = 2.2 Hz, 2H), 2.61 (t, J = 2.3 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 172.8, 137.5, 137.1, 131.9, 131.2, 128.1, 126.9, 80.8, 72.2, 29.8, 19.7; IR (KBr) v 3282, 3265, 2117, 1628 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{12}NO$ $[M + H]^+$, 174.0919, found 174.0926.

4-Methyl-*N*-(prop-2-ynyl)benzamide (3f). White powder (370 mg, 2.14 mmol, 99%): mp 99−104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 7.9 Hz, 2H), 4.24 (dd, J = 5.1, 2.4 Hz, 2H), 2.39 (s, 3H), 2.27 (t, J = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 142.0, 130.9, 129.1, 127.3, 79.9, 71.3, 29.6, 21.4; IR (KBr) v 3287, 3305, 2120, 1640 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{12}NO$ $[M + H]^+$, 174.0919, found 174.0924.

4-Methoxy-*N*-(prop-2-ynyl)benzamide (3g). Off white powder (222 mg, 1.173 mmol, 83%): mp 120−122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.23 (b, 1H), 4.23 (dd, J = 2.6, 5.1 Hz, 2H), 3.84 (s, 3H), 2.26 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 162.6, 129.1, 126.3, 114.0, 79.9, 71.9, 55.6, 29.9 ppm; IR (KBr) ν 3263, 2963, 2838, 1641, 1611, 1545, 1249, 1029, 836, 677 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{11}H_{11}NO_2$ $[M]^+$ 189.0790, found 189.0790.

2-Chloro-*N*-(prop-2-ynyl)benzamide (3h). White powder (276 mg, 1.43 mmol, 71%): mp 78.1−79.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74−7.66 (m, 1H), 7.44−7.28 (m, 3H), 6.47 (b, 1H), 4.26 (dd, J = 5.2, 2.5 Hz, 2H), 2.28 (t, J = 2.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 134.4, 131.9, 131.0, 130.6, 130.5, 127.4, 79.2, 72.3, 30.0; IR (KBr) ν 3285, 3269, 3049, 2126, 1643, 1593 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{10}H_9NOCl$ $(M + H)^+$, 194.0373, found 194.0380.

2,4-Dichloro-*N*-(prop-2-ynyl)benzamide (3i). Off white powder (308 mg, 1.350 mmol, 62%): mp 98−99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.3 Hz, 1H), 7.44 (s, 1H), 7.33 (d, J = 9.6 Hz, 1H), 6.4 (b, 1H), 4.26 (dd, J = 2.5, 5.0 Hz, 2H), 2.29 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 137.2, 132.7, 131.8, 131.4, 130.2, 127.6, 79.0, 72.2, 29.9 ppm; IR (KBr) ν 3297, 3056, 2824, 1903, 1644, 1589, 1538, 1299, 864, 686 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_7NO^{35}Cl_2$ $[M + H]^+$ 227.9983, found 227.9977.

2-Iodo-*N*-(prop-2-ynyl)benzamide (3j). Off white powder (378 mg, 1.326 mmol, 73%): mp 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.9 Hz, 1H), 7.43−7.36 (m, 2H), 7.14−7.08 (m, 1H), 5.95 (b, 1H), 4.26 (dd, J = 2.5, 5.1 Hz, 2H), 2.29 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 141.4, 140.1, 131.5, 128.5, 128.3, 92.6, 79.1, 72.3 29.9 ppm; IR (KBr) ν 3290, 3050, 2912, 2839, 1961, 1658, 1651, 1537, 1063, 947, 637 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_8NOI$ $[M]^+$ 284.9651, found 284.9652.

2-Phenyl-*N*-(prop-2-ynyl)acetamide (3k). Pale yellow powder (473 mg, 2.73 mmol, 92%): mp 80−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.30 (m, 3H), 7.30−7.22 (m, 2H), 5.56 (b, 1H), 4.01 (dd, J = 2.4, 5.1 Hz, 2H), 3.60 (s, 2H), 2.18 (t, J = 2.4, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.77, 134.58, 129.67, 129.29, 127.71, 79.55, 71.76, 43.71, 29.53 ppm; IR (KBr) ν 3277, 3239, 3046, 2125, 1666, 1633, 1543 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}NO$ $[M + H]^+$ 174.0919, found 174.0917.

***N*-(Prop-2-ynyl)cinnamamide (3l).** White powder (496 mg, 2.68 mmol, 95%): mp 107−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (d, J = 15.6, 1H), 7.57−7.46 (m, 2H), 7.44−7.33 (m, 3H), 6.39 (d, J = 15.6, 1H), 5.78 (b, 1H), 4.20 (dd, J = 2.4, 5.1 Hz, 2H), 2.27 (t, J = 2.4, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.77, 142.12, 134.83, 130.09, 129.05, 128.07, 119.99, 79.67, 71.98, 29.66 ppm; IR (KBr) ν 3281, 3226, 3046, 2117, 1657, 1619, 1543 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{12}NO$ $[M + H]^+$ 186.0919, found 186.0915.

***N*-(Prop-2-ynyl)-2-naphthamide (3m).** White powder (503 mg, 2.40 mmol, 99%): mp 159−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.97−7.80 (m, 4H), 7.63−7.50 (m, 2H), 6.41 (b, 1H), 4.33 (dd, J = 2.4, 4.8 Hz, 2H), 2.32 (t, J = 2.4, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.41, 135.07, 132.78, 131.15, 129.16, 128.75, 128.01, 127.97, 127.87, 127.03, 123.70, 79.75, 72.15, 30.11 ppm; IR (KBr) ν 3284, 3324, 3050, 2127, 1644, 1626, 1600 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{12}NO$ $[M + H]^+$ 210.0919, found 210.0922.

***N*-(Prop-2-ynyl)thiophene-2-carboxamide (3n).** White powder (197 mg, 1.19 mmol, 79%): mp 117.3−118.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.46 (m, 2H), 7.15−7.04 (m, 1H), 6.17 (b, 1H), 4.24 (dd, J = 5, 2.2 Hz, 2H), 2.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 138.3, 130.6 128.8, 127.9, 79.5, 72.1, 29.8; IR (KBr) ν 3288, 3084, 2118, 1628, 1550 cm^{-1}; HRMS (FAB) calcd for C_8H_8NOS $(M + H)^+$, 166.0327, found 166.0330.

***N*-(Prop-2-ynyl)picolinamide (3o).** White powder (185 mg, 1.16 mmol, 58%): mp 77.4−78.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J = 4.5 Hz, 1H), 8.37−8.11 (m, 2H), 7.88−7.79 (m, 1H), 7.46−7.39 (m, 1H), 4.26 (dd, J = 5.6, 2.4 Hz, 2H), 2.26 (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 149.6, 148.4, 137.5, 126.6, 122.5, 79.6, 71.8, 29.3; IR (KBr) ν 3339, 3252, 3056, 2114, 1659, 1520 cm^{-1}; HRMS (ESI-TOF) calcd for $C_9H_8N_2ONa$ $(M + Na)^+$, 183.0534, found 183.0527.

***N*-(Prop-2-ynyl)furan-2-carboxamide (3p).** White powder (258 mg, 1.73 mmol, 86%): mp 88.5−89.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.14 (d, J = 3.4 Hz, 1H), 6.61−6.42 (m, 2H), 4.23 (dd, J = 5.3, 2.4 Hz, 2H), 2.27 (t, J = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 147.6, 144.4, 115.0, 112.4, 79.4, 72.0, 29.0; IR (KBr) ν 3289, 3270, 3050, 2108, 1640, 1528 cm^{-1}; HRMS (ESI-TOF) calcd for $C_8H_8NO_2$ $(M + H)^+$, 150.0555, found 150.0556.

2-Chloro-*N*-(prop-2-ynyl)acetamide (3q). Brown powder (200 mg, 1.52 mmol, 84%): mp 68−73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12 (t, J = 4.12 Hz, 2H), 4.08 (s, 2H), 2.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 78.8, 72.3, 42.5, 29.7; IR (KBr) v 3439, 3278, 2129, 1646 cm^{-1}; HRMS (ESI-TOF) calcd for $C_5H_6NO^{35}Cl$ $[M]^+$ 131.0138, found 133.0115.

***N*-(2-Methylbut-3-yn-2-yl)benzamide (3r).** Off white powder (400 mg, 1.987 mmol, 89%): mp 155−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 7.3 Hz, 2H), 7.49−7.42 (m, 3H), 6.18 (b, 1H), 2.39 (s, 1H), 1.77 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 134.9, 131.6, 128.6, 127.0, 87.3, 69.5, 48.2, 29.1 ppm; IR (KBr) ν 3243, 3062, 2931, 1640, 1580, 1542, 1361, 1076, 943, 693 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{13}NO$ $[M + H]^+$ 188.1075, found 188.1069.

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***N*-(1-Ethynylcyclohexyl)benzamide (3s).** Off white powder (139 mg, 0.575 mmol, 81%): mp 132−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 7.3 Hz, 2H), 7.50−7.41 (m, 3H), 6.08 (b, 1H), 2.45 (s, 1H), 2.25−1.99 (m, 2H), 1.96−1.92 (m, 2H), 1.76−1.53 (m, 5H), 1.35−1.32 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 135.2, 131.6, 128.7, 127.1, 85.6, 75.8, 71.7, 52.2, 37.1, 25.4, 22.7 ppm; IR (KBr) ν 3287, 2934, 2363, 1639, 1538, 1310, 1076, 714, 619 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{17}NONa$ [M + Na]$^+$ 250.1206, found 250.1206.

(*R*)-*tert*-Butyl 1-(methoxy(methyl)amino)-1-oxopropan-2-ylcarbamate (1t). White solid (2.18 g, 9.39 mmol, 89%): mp 144−147 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 4.57 (b, 1H), 3.81 (s, 3H), 3.20 (s, 3H), 1.44 (s, 9H), 1.25 (d, J = 6.9, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 175.69, 157.81, 80.59, 62.17, 32.73, 30.81, 28.86, 17.58 ppm; $[\alpha]^{28.0}_D$ = −3.32 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3296, 2975, 1704, 1660 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{21}N_2O_4$ [M + H]$^+$ 233.1501, found 233.1506.

(*R*)-*tert*-Butyl but-3-yn-2-ylcarbamate (2t). White powder (275 mg, 1.63 mmol, 41% (two steps)): mp 77−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (b, 1H), 4.48 (b, 1H), 2.25 (s, 1H), 1.45 (s, 9H), 1.40 (d, J = 6.9, 3H) ppm; ^{13}C NMR (75 MHz, CD_3OD) δ 154.84, 84.79, 80.19, 70.33, 38.59, 28.58, 22.79 ppm; $[\alpha]^{28.3}_D$ = −38.33 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3321, 3288, 1703 cm^{-1}; HRMS (ESI) calcd for $C_9H_{15}NO_2Na$ [M + Na]$^+$ 192.0995, found 192.0995.

(*R*)-*N*-(But-3-yn-2-yl)benzamide (3t). White powder (163.1 mg, 0.94 mmol, 58%): mp 78−81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 7.4 Hz, 2H), 7.55−7.41 (m, 3H), 6.27 (b, 1H), 5.12−4.94 (m, 1H), 2.31 (d, J = 1.9 Hz, 1H), 1.53 (d, J = 6.9 Hz,3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.53, 134.20, 131.95, 128.84, 127.20, 84.36, 70.93, 37.71, 22.60 ppm; $[\alpha]^{26.4}_D$ = −0.09 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3296, 3062, 2145, 1644, 1602, 1531 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}NO$ [M]$^+$ 173.0841, found 173.0844.

(*R*)-*tert*-Butyl 1-(methoxy(methyl)amino)-3-methyl-1-oxobutan-2-ylcarbamate (1u). Colorless oil (1910 mg, 7.3368 mmol, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14−5.11 (m, 1H), 4.56 (b, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 2.01−1.92 (m, 1H), 1.43 (s, 9H), 0.95 (d, J = 6.8 Hz; 3H), 0.90 (d, J = 6.8 Hz; 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 155.8, 79.3, 61.5, 54.9, 31.8, 31.3, 30.9, 28.3, 19.4, 18.9, 17.5 ppm; $[\alpha]^{28.6}_D$ = +9.4 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3325, 2968, 1714, 1660, 1506, 1173, 875 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{24}N_2O_4$ [M + H]$^+$ 261.1814, found 261.1808.

(*R*)-*tert*-Butyl 4-methylpent-1-yn-3-ylcarbamate (2u). Yellow oil (148 mg, 0.385 mmol, 25% (for 2 steps)) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.7 (b, 1H), 4.31 (b, 1H), 2.24 (s, 1H), 1.93−1.84 (m, 1H), 1.45 (s, 9H), 0.98 (d, J = 6.7 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 82.2, 79.8, 77.6, 77.2, 76.8, 71.8, 48.7, 33.1, 28.5, 18.8, 17.6 ppm; $[\alpha]^{28}_D$ = +28.3 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3313, 2967, 1694, 1515, 1339, 1172, 865 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{19}NO_2Na$ [M + Na]$^+$ 220.1313, found 220.1314.

(*R*)-*N*-(4-Methylpent-1-yn-3-yl)benzamide (3u). Off white powder (115 mg, 0.571 mmol, 80%): mp 82−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 6.8 Hz, 2H), 7.52−7.42 (m, 3H), 6.24 (b, 1H), 4.90−4.86 (m, 1H), 2.29 (d, J = 2.13 Hz, 2H), 2.11−2.04 (m, 1H), 1.06 (d, J = 6.8 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 134.4, 131.9, 128.8, 127.2, 81.8, 72.4, 47.8, 32.9, 19.0, 17.8 ppm; $[\alpha]^{27.0}_D$ = −36.7 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3300, 2964, 2114, 1959, 1638, 1528, 1490, 1308, 1148, 693 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{15}NO$ [M + H]$^+$ 202.1232, found 202.1229.

(*R*)-*tert*-Butyl 1-(methoxy(methyl)amino)-4-methyl-1-oxopentan-2-ylcarbamate (1v). Colorless oil (1100 mg, 4.009 mmol, 92.7%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (b, 1H), 4.72−4.69 (b, 1H), 3.78 (s, 3H), 3.19 (s, 3H), 1.74−1.67 (m, 1H), 1.55−1.40 (m, 11H), 0.97−0.92 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.13, 155.8, 79.6, 61.7, 49.1, 42.3, 32.3, 28.5, 24.9, 23.5, 21.7 ppm; $[\alpha]^{28.8}_D$ = −23.46 (c, 0.5, CH_2Cl_2) IR (KBr) ν 3333, 2959, 2871, 1713, 1660, 1170, 876 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{27}N_2O_4$ [M + H]$^+$ 275.1971, found 275.1977.

(*R*)-*tert*-Butyl 5-methylhex-1-yn-3-ylcarbamate (2v). Yellow oil (430 mg, 1.997 mmol, 51% (2 steps)) ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.61 (b, 1H), 4.4 (b, 1H), 2.24 (d, J = 1.8 Hz; 1H), 1.85−1.76 (m, 1H), 1.58−1.52 (m, 2H), 1.45 (s, 9H), 0.95−0.87 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 84.0, 79.9, 70.9, 45.3, 41.4, 28.5, 25.1, 22.8, 22.0 ppm; $[\alpha]^{28.7}_D$ = −40.22 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3314, 2959, 2872, 1699, 1515, 1367, 1249, 1171, 1015, 869, 648.7 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{22}NO_2$ [M + H]$^+$ 212.1651, found 212.1652.

(*R*)-*N*-(5-Methylhex-1-yn-3-yl)benzamide (3v). Off white powder (498 mg, 2.313 mmol, 78%): mp 72−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.08 Hz, 2H), 7.50−7.41 (m, 3H), 6.18 (b, 1H), 5.03- 4.99 (m, 1H), 2.30 (d, J = 2.2 Hz, 1H), 1.88−1.84 (m, 1H), 1.65−1.64 (m, 2H), 0.99 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 134.3, 131.9, 128.8, 127.2, 83.7, 71.4, 45.1, 40.5, 25.4, 22.9, 22.1 ppm; $[\alpha]^{27.4}_D$ = −25.6 (c, 0.5, CH_2Cl_2); IR (KBr) ν 3305, 3061, 2870, 1786, 1603, 1531, 1288, 1075, 801, 693 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{17}NO$ [M − H]$^+$ 214.1231, found 214.1232.

***tert*-Butyl 1-(methoxy(methyl)amino)-4-methyl-1-oxopentan-2-ylcarbamate (1w).** Colorless oil (1120 mg, 4.082 mmol, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.02 (b, 1H), 4.72−4.69 (b, 1H), 3.78 (s, 3H), 3.19 (s, 3H), 1.74−1.67 (m, 1H), 0.97−0.92 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 155.8, 79.5, 61.7, 49.1, 42.2, 32.3, 28.5, 24.9, 23.5, 21.7 ppm; IR (KBr) ν 3333, 2959, 2871, 1713, 1660, 1170, 876 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{27}N_2O_4$ [M + H]$^+$ 275.1971, found 275.1965.

***tert*-Butyl 5-methylhex-1-yn-3-ylcarbamate (2w).** Off white powder (270 mg, 1.007 mmol, 29% (2 steps)): mp 82−84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.60 (b, 1H), 4.42 (b, 1H), 2.24 (d, J = 1.8 Hz; 1H), 1.83−1.76 (m, 1H), 1.58−1.52 (m, 2H), 1.45 (s, 9H), 0.95−0.90 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 84.0, 79.9, 70.9, 45.3, 41.4, 28.5, 25.1, 22.8, 22.0 ppm; IR (KBr) ν 3314, 2959, 2872, 1699, 1515, 1367, 1249, 1171, 1015, 869, 648.7 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{22}NO_2$ [M + H]$^+$ 212.1651, found 212.1652.

(*R*)-*N*-(5-Methylhex-1-yn-3-yl)benzamide (3w). Off white powder (198 mg, 0.919 mmol, 79%): mp 72−74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.08 Hz, 2H), 7.50−7.41 (m, 3H), 6.42 (b, 1H), 5.05- 4.99 (m, 1H), 2.30 (d, J = 2.2 Hz, 1H), 1.88−1.84 (m, 1H), 1.65−1.64 (m, 2H), 0.99 (d, J = 6.5 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 134.3, 131.9, 128.8, 127.2, 83.7, 71.4, 45.1, 40.5, 25.4, 22.9, 22.1 ppm; IR (KBr) ν 3305, 3061, 2870, 1786, 1603, 1531, 1288, 1075, 801, 693 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{16}NO$ [M − H]$^+$ 214.1231, found 214.1232.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and crystallographic information (CIF file) for compound **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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