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A rapid entry to amino acids derived diverse 3,4-dihydropyrazines and dihydro[1,2,3]triazolo[1,5-a]pyrazines through 1,3-dipolar cycloaddition

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An efficient, general and practical synthesis of diverse 3,4-dihydropyrazines, 6,7-dihydro-[1,2,3]triazolopyrazines and 7,8-dihydro[1,2,3]triazolodiazepines through intramolecular 1,3-dipolar cycloaddition from amino acids derived common intermediate with high yields is described. Moreover, one-pot access to optically active 3-aryl substituted 6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazines under palladium–copper co-catalytic system has also been achieved in this work. The easy substrate availability and operational simplicity make the process suitable for further exploration.

Introduction:

Click chemistry is a modular synthetic approach towards the assembly of new molecular entities by efficiently and reliably joining small units together. By applying this concept, it is now possible to produce manmade compounds of enormous diversity than what is currently known or available. The traditional cycloaddition between azides and acetylenes studied by Huisgen1a–c during the 1960’s led to the development of a straightforward synthesis of 1,4- and 1,5-substituted 1,2,3-triazoles as regioisomeric mixtures. This classical reaction gained enormous importance after its discovery.1d The regio-selective synthesis of 1,4-substituted 1,2,3-triazoles through the use of a copper catalyst was established independently by Sharpless2a and Meldal2b which ensured dramatic acceleration of the reaction rate and lowering of the reaction temperature. The structural and electronic properties of 1,2,3-triazoles are applicable in peptidomimetic chemistry for introducing global and local conformational restrictions.3 1,2,3-Triazoles have been used as replacements of backbone peptide bonds4 or to stabilize turn5,6 or helical7 architectures by cyclization between side chain or backbone modified amino acid residues.8 Several compounds of the 1,2,3-triazole class possess a broad spectrum of biological importance including anti-HIV,9a anti-allergic,9b anti-bacterial,9c and fungicidal activity.9d On the other hand, piperazine fused triazole compounds are found in a number of biologically active natural products, synthetic agents, and drugs.

Besides, 1,2,3-triazolo[1,5-a]quinoxaline 1 (Figure 1) has also been shown good affinity toward benzodiazepine and adenosine receptors.10a,b In view of the frequent occurrence of 1,2,3-triazoles and piperazines in various biologically active compounds, we envisioned that 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-a]pyrazines 2 and/or their fused analogues could be novel pharmacophores or important building blocks. Only a few methods are available in the literature for the synthesis of compounds of type 211 and of its 6-keto derivatives.12 Most of the syntheses used the conventional intramolecular cycloaddition between azide and terminal alkyne, limiting the diversity of substitutions at C-3 and C-4 of the product. Despite the significant interest of these heterocyclic systems in medicinal chemistry,13 arising from its close structural similarity with benzodiazepine drugs such as Estazolam 3 and Alprazolam 4, synthetic methods for their
preparation are limited,14,15 and all chiral approaches to these compounds are based on the construction of the molecules on carbohydrate motifs.16

Our work centered on chemical synthesis and properties of S-amino acids-derived chiral heterocycles and natural product-like molecules.17 Recently, we have published a series of amino acids derived benzoazepines as antitumor agents in breast cancer17b and a novel methodology for the synthesis of trans-2,5-disubstituted morpholines, piperazines and thiomorpholines through a straight forward and modular pathway involving iodine mediated 6-exo-trig cyclization.17a In conjunction with our continued interest, we hereby report an extremely simple and mild method for the diversity oriented synthesis of amino acids derived substituted dihydro[1,2,3]triazolo [1,5-a]pyrazines and their ring fused analogues (Scheme 1).

![Scheme 1: Synthesis of amino acids derived substituted 5-methyl-3,4-dihydropyrazine and dihydro[1,2,3]triazolo[1,5-a]pyrazines](image)

**Results and discussion:**

The synthesis of the required substrates for 1,3-dipolar cycloaddition reaction began with S-amino acids 1a-f which was converted to their methyl esters 2a-f followed by boc protection of primary amine to give 3a-f (Scheme 2). Ester reduction to 4a-f proceeded smoothly, followed by tosyl protection of primary alcohol affording 5a-f. Amino acid-derived azido substrates 6a-f for intramolecular click reaction was synthesized by an S$_\text{N}_2$ displacement of the corresponding tosylates with NaN$_3$. All of these steps were accomplished in excellent yields and are amenable to easy scale-up. In this letter, we reveal an effective integration of click chemistry onto amino acid substrates in order to synthesize 1,2,3-triazole-fused bicyclic compounds in high yields.

The derived azido compound 6a-e reacted smoothly with allylbromide and NaN$_3$ in presence of dry DMF at 0 °C to give 7a-e (Scheme 3). The peak at $\nu_{\max}$ 2108 cm$^{-1}$ in the IR spectra of the products clearly indicated the presence of azide functionality. Finally, 1,3-dipolar cycloaddition reaction was carried out under reagent-free conditions by heating a toluene solution of azidoalkene 7a-e at 100 °C for 2 h to provide 5-methyl-3,4-dihydropyrazine in good yield. In the $^{13}$C NMR spectrum of 8a-e, the presence of carbon signals at $\delta$ 162.8, 151.1, 155.2 and 20.7 suggested the presence of amide carbonyl, olefinic quaternary as well as methine carbons. Additionally, the methyl proton signal at $\delta$ 2.14 (d, $J = 1.8$ Hz, allylic coupling) testified the location of a vinylic methyl group. In addition, the Boc protection of 8 can be removed using TFA in dry DCM to afford 9 which provides additional opportunity for diversity oriented synthesis through derivatization of the resulting secondary amine.

![Scheme 3: Synthesis of 5-methyl-3,4-dihydropyrazine](image)

With intermediate azido compound 6a-f in hand, synthesis of dihydro [1,2,3]triazolo [1,5-a]pyrazines was attempted. Compounds 6a-f was treated with propargyl bromide and NaN$_3$ in presence of dry DMF at 0 °C to furnish azidoalkynes 10a-f. As above, reagent-free conditions by heating a toluene solution of the azidoalkene at 100 °C gave triazolo [1,5-a]pyrazines 11a-f in good yield (Scheme 4). With these optimized conditions, the scope of the reaction with terminal alkynes was investigated. The copper catalyzed 1,3-dipolar cycloaddition reaction proceeds well in both aqueous and organic solvents under very simple experimental conditions. In this case, the starting materials were fully consumed within 30 min as monitored by TLC even at rt. This mild condition instead of unnecessary requirement of high temperatures radically improves the utility of this reaction. In order to increase the structural diversity, functionality at C-3 position of compound 11 was investigated. Thus, employment of Pd(OAc)$_2$/PPh$_3$ as catalyst and Cul as cocatalyst along with K$_2$CO$_3$ as base allowed the reaction to proceed to completion within 1 hr, affording exclusively the desired product 12a,e with good yield (81%).
Another pathway was adopted for the synthesis of chiral triazolo-[1,5-a][1,4]diazocine from the common carbinol precursor (Scheme 5). Compound 4b was oxidized to aldehyde 5 which was subjected to HWE olefination in dry DCM (ratio of E:Z = 95:5) without any further purification furnishing 14b. Double bond and ester group was reduced simultaneously using LAH (3 equiv.) to produce 15b. Tosylation of the primary alcohol 15b in the presence of p-toluenesulphonyl chloride and triethylamine followed by nucleophilic substitution with sodium azide affords 17b. The azido compound was treated with propargylbromide and NaH in presence of dry DMF at 0 °C to give 18b. Under similar 1,3-dipolar cycloaddition reaction condition, 18b provided triazolo-[1,5-a][1,4]diazocine 19b with excellent yield.

A plausible reaction mechanism for the formation of 5-methyl-3,4-dihydropyrazine

A plausible reaction mechanism for the formation of compound 12 could be explained by applying features of palladium chemistry. The oxidative addition of aryl iodide 25 to Pd(0), formed in situ through the interaction of palladium acetate and triphenyl phosphine affords arylpalladium(II) complex 26 which undergoes transmetalation with copper-acetylide 27 to generate arylalkynylpalladium complex 28 (Scheme 7). This on reductive elimination of palladium (0) affords the arylated internal alkyne 29. Palladium (0) then activate the triple bond through a complex 30, in which palladium is stabilised by the nitrogen in proximity. Insertion of palladium into the triple bond possibly leads to the vinylidene like transition state 31. The increase of electron density in the dipolarophile due to the palladium insertion accelerates the cycloaddition through a HOMO-LUMO interaction leading to the formation of the desired cycloadduct 12 with regeneration of palladium (0).

Conclusion:

In summary, we have described a simple and powerful synthetic route that provides access to chirally pure diverse 5-methyl-3,4-dihydropyrazine, triazolo[1,5-a]pyrazines and triazolo[1,5-a][1,4]diazocine starting from commercially available S-amino acids derived synthetic intermediates. The key step involves 1,3-
dipolar cycloaddition under reagent free condition, giving heterocycles that can be further elaborated in several ways, such as by nucleophilic substitution on the rings as well as incorporation of substituent at 6-position from amino acids constituents.

EXPERIMENTAL SECTION

General
IR spectra were recorded on a Perkin-Elmer FT-IR RXI spectrometer. ¹H NMR and ¹³C NMR spectra were recorded on Brucker DPX-200 (operating at 200 MHz for ¹H and 50 MHz for ¹³C) or DPX-300 (operating at 300 MHz for ¹H and 75 MHz for ¹³C) spectrometer using CDCl₃ as solvent. Tetramethyldisilane (0.00 ppm) served as an internal standard in ¹H NMR and CDCl₃ (77.0 ppm) in ¹³C NMR. All spectra were recorded at 25 °C. Coupling constants (J values) are given in Hz (MHz). Chemical shifts are expressed in parts per million (ppm). Mass spectra were recorded using electron spray ionization (ESMS). Glycerol or m-nitro benzylic alcohol was used as matrix. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel). Detecting agents used (for TLC) were iodine vapors and/or spraying with an aqueous solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over silica gel (100-200 mesh) procured from Qualigens (India) using freshly distilled solvents.

Experimental Procedures and Characterization Data

General experimental procedure for the synthesis of 5a-e: The compound 4a-e (1 eqiv) was dissolved in 20 mL dry DCM and then it was cooled at 0 °C, followed by addition of Et₃N (2 equiv) and p-toluene sulfonyl chloride (1.2 equiv). Then it was stirred for 3 h at RT and diluted with 30 mL water. The aqueous layer was extracted with DCM (2 X 50 mL) and dried over anhydrous sodium sulphate. The solvent was removed under vacuum and the crude product was then chromatographed over silica gel with eluent AcOEt-Hexane (1:9) to afford the title compound 5a-e.

(S)-2-(tert-butoxy carbamylamino)-3-phenylpropyl-4-methylbenzenesulfonate 5a: Colourless oil; yield, 86%; Rₛ 0.52 (8/2, hexane/ethyl acetate); [α]D²⁰ = -7.46 (c 0.26, CHCl₃); IR (neat, cm⁻¹): 3508, 2959, 1716, 1360, 1177, 771; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 2H, J = 8.0 Hz), 7.21 (d, 2H, J = 7.9 Hz), 7.10-6.96 (m, 5H), 4.75 (s, 1H), 4.03-3.80 (m, 3H), 2.73-2.66 (m, 2H), 2.32 (s, 3H), 1.26 (s, 9H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 154.9, 144.9, 136.7, 132.5, 129.9, 129.1, 128.5, 127.9, 126.6, 79.7, 69.9, 50.7, 37.1, 28.2, 21.5 ppm; MS (ESI): m/z 406 [M+H⁺]; Anal. Calcd for C₂₃H₂₇NO₅S: C, 62.20; H, 6.71; N, 3.45; O, 19.73; S, 7.91. Found: C, 62.26; H, 6.74; N, 3.49.

(S)-2-(tert-butoxy carbamylamino)propyl-4-methylbenzenesulfonate 5c: Colourless oil; yield, 85%; Rₛ 0.51 (8/2, hexane/ethyl acetate); [α]D²⁰ = -15.8 (c 0.25, CHCl₃); IR (neat, cm⁻¹): 3393, 2367, 1692, 1355, 1177, 932; ¹H NMR (300 MHz, CDCl₃) δ 7.64 (d, 2H, J = 8.1 Hz), 7.21 (d, 2H, J = 7.9 Hz), 4.98 (s, 1H), 3.84-3.71 (m, 3H), 2.28 (s, 3H), 1.26 (s, 9H), 0.99 (d, 3H, J = 6.5 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 154.6, 144.6, 139.3, 129.4, 128.4, 125.5, 78.8, 47.8, 27.7, 23.4, 16.4 ppm; MS (ESI): m/z 330 [M+H⁺]; Anal. Calcd for C₁₃H₁₅NO₃S: C, 54.69; H, 7.04; N, 4.25; O, 24.28; S, 9.73. Found: C, 54.66; H, 7.14; N, 4.29.

(S)-2-(tert-butoxy carbamylamino)-4-methylpenty1-4- methylbenzenesulfonate 5d: Colourless oil; yield, 87%; Rₛ 0.50 (8/2, hexane/ethyl acetate); [α]D²⁰ = -11.34 (c 0.22, CHCl₃); IR (neat, cm⁻¹): 3500, 2962, 1737, 1364, 1178, 771; ¹H NMR (300 MHz, CDCl₃) δ 7.68 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 7.7 Hz), 4.62 (s, 1H), 3.94-3.73 (m, 3H), 2.33 (s, 3H), 1.46 (d, 1H, J = 5.6 Hz), 1.30 (s, 9H), 1.17 (s, 2H), 0.77 (t, 6H, J = 5.4 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 154.9, 144.6, 132.4, 129.6, 127.6, 79.1, 71.7, 47.4, 39.7, 28.0, 24.2, 22.5, 21.3 ppm; MS (ESI): m/z 372 [M+H⁺]; Anal. Calcd for C₁₃H₁₇NO₅S: C, 58.20; H, 7.87; N, 3.77; O, 21.53; S, 8.63. Found: C, 58.26; H, 7.84; N, 3.70.

(2S,3R)-2-(tert-butoxy carbamylamino)-3-methylpentyl 4- methylbenzenesulfonate 5e: Colourless oil; yield, 86%; Rₛ 0.52 (8/2, hexane/ethyl acetate); [α]D²⁰ = -21.13 (c 0.25, CHCl₃); IR (neat, cm⁻¹): 3512, 2956, 1721, 1343, 1177, 769; ¹H NMR (300 MHz, CDCl₃) δ 7.71 (d, 2H, J = 8.1 Hz), 7.27 (d, 2H, J = 7.9 Hz), 4.56 (d, 1H, J = 8.4 Hz), 3.98 (s, 2H), 3.49 (bs, 1H), 2.37 (s, 3H), 1.47 (s, 2H), 1.33 (s, 9H), 1.06-0.97 (m, 1H), 0.80-0.74 (m, 6H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 155.2, 144.7, 132.4, 129.7, 127.7, 79.1, 68.0, 56.8, 38.6, 28.0, 23.8, 21.5, 15.0, 10.7 ppm; MS (ESI): m/z 372 [M+H⁺]; Anal. Calcd for C₁₃H₁₆NO₅S: C, 58.20; H, 7.87; N, 3.77; O, 21.53; S, 8.63. Found: C, 58.26; H, 7.82; N, 3.71.

General experimental procedure for the synthesis of 6a-f: To a stirred solution of compound 5a-f (1 equiv.) in anhydrous DMF (10 mL) sodium azide (2 equiv.) was added. Reaction mixture was stirred for 2 h at 80 °C. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 X 50 mL) and the organic layer was dried.
over anhydrous Na₂SO₄. After concentration under vacuum, the crude product was chromatographed on silica gel with (eluent = hexane/ethyl acetate, 9.2/0.8) as eluent to furnish the compound 6a-f (78% yield) as a colourless oil.

(S)-tert-butyl 1-azido-3-methylbutan-2-ylicarbamate 6a:
Colourless oil; yield, 77%; Rₖ 0.60 (8/2, hexane/ethyl acetate); [α]₀D = -31.15 (c 0.17, CHCl₃); IR (neat, cm⁻¹): 3348, 2971, 2101, 1701, 1507, 1169, 760; ¹H NMR (300 MHz, CDCl₃): δ 4.51 (s, 1H), 3.44 (s, 1H), 3.34 (d, 2H, J = 3.8 Hz), 1.74-1.67 (m, 1H), 1.38 (s, 9H), 0.86 (t, 6H, J = 6.4 Hz) ppm; ¹³C NMR (50 MHz, CDCl₃): δ 154.5, 79.4, 55.5, 53.0, 29.7, 28.3, 19.4 ppm; MS (ESI): m/z 229 [M⁺]+; Anal. Calcd for C₆H₁₂N₂O₂C: 52.61; H: 8.83; N: 24.54; O: 14.02. Found: C: 52.64; H: 8.85; N: 24.50.

(S)-tert-butyl 1-azido-3-phenylpropan-2-ylicarbamate 6b:
This product was isolated as colourless oil; yield, 78%; Rₖ 0.61 (8/2, hexane/ethyl acetate); [α]₀D = -21.67 (c 0.18, CHCl₃); IR (neat, cm⁻¹): 3455, 2975, 2110, 1716, 1513, 763; ¹H NMR (300 MHz, CDCl₃): δ 7.25-7.10 (m, 5H), 4.63 (s, 1H), 3.88 (s, 1H), 3.37-3.15 (m, 2H), 2.77-2.66 (m, 2H), 1.34 (s, 9H) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 155.0, 137.0, 129.1, 128.5, 126.6, 79.6, 53.1, 51.3, 38.1, 28.2 ppm; MS (ESI): m/z 277 [M⁺]+; Anal. Calcd for C₁₀H₁₅N₂O₂: C: 60.85; H: 7.30; N: 20.28; O: 11.58. Found: C: 60.80; H: 7.36; N: 20.23.

(S)-tert-butyl 1-azido-3-phenylpropan-2-ylicarbamate 6c:
Colourless oil; yield, 78%; Rₖ 0.63 (8/2, hexane/ethyl acetate); [α]₀D = -24.34 (c 0.16, CHCl₃); IR (neat, cm⁻¹): 3352, 2965, 2107, 1689, 1512, 1160, 765; ¹H NMR (300 MHz, CDCl₃): δ 4.61 (s, 1H), 3.77 (s, 1H), 3.30-3.22 (m, 2H), 1.37 (s, 9H), 1.11 (d, 3H, J = 6.7 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 154.0, 79.4, 55.8, 46.1, 28.2, 18.0 ppm; MS (ESI): m/z 201 [M⁺]+; Anal. Calcd for C₁₀H₁₄N₂O₂: C: 64.50; H: 8.01; N: 27.98. Found: C: 48.04; H: 8.01; N: 27.91.

(S)-tert-butyl 1-azido-4-methylpentan-2-ylicarbamate 6d:
Colourless oil; yield, 78%; Rₖ 0.60 (8/2, hexane/ethyl acetate); [α]₀D = -22.19 (c 0.15, CHCl₃); IR (neat, cm⁻¹): 3359, 2977, 2112, 1700, 1523, 1162, 757; ¹H NMR (300 MHz, CDCl₃): δ 4.54 (s, 1H), 3.73 (s, 1H), 3.34-3.22 (m, 2H), 1.65-1.53 (m, 1H), 1.37 (s, 9H), 1.31-1.18 (m, 2H), 0.85 (d, 6H, J = 6.8 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 152.9, 79.4, 55.1, 48.5, 45.1, 28.3, 24.7, 22.9, 22.0 ppm; MS (ESI): m/z 243 [M⁺]+; Anal. Calcd for C₁₁H₁₇N₂O₂C: C: 54.52; H: 9.15; N: 23.12; O: 13.21. Found: C: 54.48; H: 9.19; N: 23.20.

tert-butyl (2S,3R)-1-azido-3-methylpentan-2-ylicarbamate 6e:
Colourless oil; yield, 78%; Rₖ 0.61 (8/2, hexane/ethyl acetate); [α]₀D = -24.6 (c 0.16, CHCl₃); IR (neat, cm⁻¹): 3378, 2963, 2114, 1709, 1521, 1162, 769; ¹H NMR (300 MHz, CDCl₃): δ 4.58 (d, 1H, J = 8.0 Hz), 3.51 (s, 1H), 3.35 (s, 2H), 1.48-1.44 (m, 2H), 1.38 (s, 9H), 1.17-0.98 (m, 1H), 0.83 (t, 6H, J = 6.7 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 155.4, 79.3, 54.3, 52.7, 36.2, 28.2, 25.0, 15.3, 11.1 ppm; MS (ESI): m/z 243 [M⁺]+; Anal. Calcd for C₁₁H₁₇N₂O₂C: C: 54.52; H: 9.15; N: 23.12; O: 13.21. Found: C: 54.57; H: 9.20; N: 23.08.

(S)-tert-butyl 1-azido-4-(methylthio)butan-2-ylicarbamate 6f:
This product was isolated as colourless oil; yield, 76%; Rₖ 0.62 (8/2, hexane/ethyl acetate); [α]₀D = -39.72 (c 0.15, CHCl₃); IR (neat, cm⁻¹): 3486, 2112, 1689, 1410, 1167, 765, 700; ¹H NMR (300 MHz, CDCl₃): δ 4.58 (d, 1H, J = 8.0 Hz), 3.51 (s, 1H), 3.35 (s, 2H), 1.48-1.44 (m, 2H), 1.38 (s, 9H), 0.83 (t, 6H, J = 6.7 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃): δ 155.4, 79.3, 54.3, 52.7, 36.2, 28.2, 25.0, 15.3, 11.1 ppm; MS (ESI): m/z 243 [M⁺]+; Anal. Calcd for C₁₁H₁₇N₂O₂S: C: 54.52; H: 9.15; N: 23.12; O: 13.21. Found: C: 54.57; H: 9.20; N: 23.08.

General experimental procedure for the synthesis of 7a-e:
To a stirred solution of compound 6a-e (1 equiv.) in anhydrous DMF (10 mL) NaN₃ (19 mg, 60% suspension in mineral oil) was added at 0 °C. Then required amount of allylbromide (1 equiv.) was added at 0 °C. Reaction mixture was stirred for 1 h at RT. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (2 × 50 mL) and the organic layer was dried over anhydrous Na₂SO₄. After concentration under vacuum, the crude product was chromatographed on silica gel with (eluent = hexane/ethyl acetate, 9.4/0.6) as eluent to furnish the disubstituted morpholine 7a-e (80% yield).
6.9 Hz) ppm; MS (ESI): \textit{m/z} 241 [M+H]+; Anal. Caled for C₁₁H₂₀N₄O₂: C, 54.98; H, 8.39; N, 23.32; O, 13.32. Found: C, 54.93; H, 8.43; N, 23.38.

(S)-tert-butyl allyl(1-azido-4-methylpentan-2-yl)carbamate 7d: Colourless oil; yield, 81%; \( R = 0.60 \) (8.5/1.5, hexane/ethyl acetate); [\( \alpha \)] \( \text{D} \) \( = -97.2 \) (c 0.15, CHCl₃); IR (neat, cm\(^{-1}\)): 3488, 2962, 2110, 1683, 1413, 1168, 762; \( ^{1}H \) NMR (300 MHz, CDCl₃): \( \delta \) 5.78 (s, 1H), 5.10-5.01 (m, 2H), 4.04-3.97 (m, 1H), 3.66 (d, 2H, \( J = 13.6 \) Hz), 3.49-3.26 (m, 1H), 3.13-3.07 (m, 2H), 1.48 (d, 6H, \( J = 9.9 \) Hz), 1.39 (s, 10H), 0.89 (t, 6H, \( J = 6.9 \) Hz) ppm; \( ^{13}C \) NMR (75 MHz, CDCl₃): \( \delta \) 155.2, 135.5, 115.9, 80.0, 53.5, 53.2, 50.3, 39.0, 28.2, 24.7, 24.4, 22.0 ppm; MS (ESI): \textit{m/z} 283 [M+H]+; Anal. Caled for C₂₀H₂₅N₅O₂: C, 59.55; H, 9.28; N, 19.84; O, 11.33. Found: C, 59.50; H, 9.22; N, 19.79.

13-tet-butylallyl(2S,3R)-1-azido-3-methylpentan-2-ylcarbamate 7e: Colourless oil; yield, 80%; \( R = 0.62 \) (8.5/1.5, hexane/ethyl acetate); [\( \alpha \)] \( \text{D} \) \( = -7.6 \) (c 0.15, CHCl₃); IR (neat, cm\(^{-1}\)): 3388, 2117, 1680, 1423, 1208, 762, 677; \( ^{1}H \) NMR (300 MHz, CDCl₃): \( \delta \) 5.83-5.81 (m, 1H), 5.09-5.02 (m, 2H), 3.73 (bs, 1H), 3.65-3.48 (m, 3H), 3.36 (s, 1H), 1.39 (s, 9H), 1.07-0.94 (m, 3H), 0.83-0.78 (m, 6H) ppm; \( ^{13}C \) NMR (75 MHz, CDCl₃): \( \delta \) 154.8, 135.5, 116.0, 80.1, 67.6, 57.5, 56.5, 38.1, 38.5, 28.3, 24.5, 15.9, 11.6 ppm; MS (ESI): \textit{m/z} 283 [M+H]+; Anal. Caled for C₂₀H₂₅N₅O₂: C, 59.55; H, 9.28; N, 19.84; O, 11.33. Found: C, 59.60; H, 9.23; N, 19.80.

General experimental procedure for the synthesis of 8a-e: The compound 7a-e (1equiv.) was dissolved in 20 mL dry toluene, and then it was heated up to 100 °C and stirred for 2 h. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the organic layer was dried over anhydrous Na₂SO₄. After concentration under vacuum, the crude product was chromatographed on silica gel with (eluent = hexane/ethyl acetate, 8/2) as eluent to furnish 8a-e (80%) yield as a colourless oil.

(S)-tert-butyl 2-isopropyl-5-methyl-3,4-dihydropyrazine-1(2H)-carboxylic acid 8a: Colourless oil; yield, 85%; \( R = 0.45 \) (7/3, hexane/ethyl acetate); [\( \alpha \)] \( \text{D} \) \( = +35.6 \) (c 0.18, CHCl₃); IR (neat, cm\(^{-1}\)): 3490, 1718, 1651, 1286, 1157, 768; \( ^{1}H \) NMR (300 MHz, CDCl₃): \( \delta \) 4.70 (s, 1H), 4.33-4.27 (m, 1H), 3.94-3.88 (m, 1H), 3.65-3.57 (m, 1H), 2.18 (d, 3H, \( J = 2.3 \) Hz), 1.48 (s, 10H), 1.41 (d, 1H, \( J = 5.3 \) Hz), 1.35-1.24 (m, 2H), 0.87-0.84 (m, 6H) ppm; \( ^{13}C \) NMR (75 MHz, CDCl₃): \( \delta \) 163.1, 155.3, 150.9, 83.6, 51.1, 49.7, 40.1, 27.6, 24.8, 23.0, 21.2, 20.6 ppm; MS (ESI): \textit{m/z} 255 [M+H]+; Anal. Caled for C₁₅H₂₀N₂O₂: C, 66.10; H, 10.30; N, 11.01; O, 12.58. Found: C, 66.16; H, 10.25; N, 11.07.

(S)-tert-butyl 2-sec-butyl-5-methyl-3,4-dihydropyrazine-1(2H)-carboxylic acid 8b: Colourless oil; yield, 85%; \( R = 0.44 \) (7/3, hexane/ethyl acetate); [\( \alpha \)] \( \text{D} \) \( = +34.7 \) (c 0.18, CHCl₃); IR (neat, cm\(^{-1}\)): 3471, 2356, 1703, 1370, 1155, 768, 672; \( ^{1}H \) NMR (300 MHz, CDCl₃): \( \delta \) 4.67 (s, 1H), 4.16-4.12 (m, 1H), 4.04-3.98 (m, 1H), 3.63-3.57 (m, 1H), 2.16 (s, 3H, \( J = 6.9 \) Hz), 1.62-1.53 (m, 1H), 1.48 (s, 9H), 1.39-1.27 (m, 2H), 1.14-1.02(m, 1H), 0.85-0.77 (m, 6H) ppm; \( ^{13}C \) NMR (75 MHz, CDCl₃): \( \delta \) 163.3, 155.8, 151.8, 83.8, 56.8, 48.6, 37.2, 27.9, 25.6, 20.8, 16.4, 11.6 ppm; MS (ESI): \textit{m/z} 255 [M+H]+; Anal. Caled for C₁₅H₂₀N₂O₂: C, 66.10; H, 10.30; N, 11.01; O, 12.58. Found: C, 66.17; H, 10.36; N, 11.06.

General experimental procedure or the synthesis of 9: To a stirred solution of compounds 8 (1 equiv.) in anhydrous DCM (10 mL) TFA (1 equiv.) was added at 0 °C. The resulting solution was then warmed to RT and it was stirred for 30 min. The aqueous layer was extracted with DCM (3 x 50 mL) and the organic layer was dried over anhydrous Na₂SO₄. After concentration under vacuum, the crude product was chromatographed on silica gel (eluent = hexane/ethyl acetate, 7.5/2.5) to furnish the compound 9.

(S)-2-isopropyl-5-methyl-1,2,3,4-tetrahydropyrazine 9a: Colourless oil; yield, 74%; \( R = 0.41 \) (6/4, hexane/ethyl acetate); [\( \alpha \)] \( \text{D} \) \( = +23.12 \) (c 0.14, CHCl₃); IR (neat, cm\(^{-1}\)): 3721, 2352, 1659, 1237, 1011, 779, 674; \( ^{1}H \) NMR (300 MHz, CDCl₃): \( \delta \) 4.37 (s, 1H), 3.70-3.62 (m, 3H), 2.78 (bs, 1H), 2.11 (s, 1H), 1.79-1.72 (m, 1H), 0.93-0.89 (m, 5H) ppm; \( ^{13}C \) NMR (75 MHz, CDCl₃): \( \delta \) ...
(S)-2-isobutyl-1,2,3,4-tetrahydropyrazine 9d:
Colourless oil; yield, 73%; Rf 0.42 (6/4, hexane/ethyl acetate); 
\[\delta_{1}^{300} = +13.46 \text{ (c 0.15, CHCl)}; \text{IR (neat, cm}^{-1})\] 3709, 2351, 1670, 1222, 1031, 767; \[\delta_{1}^{1} \text{H NMR (300 MHz, CDCl)}; \delta = 4.58 \text{ (s, 1H), 3.36-3.48 (m, 2H), 2.76-2.65 (m, 1H), 2.13 (s, 3H), 1.69-1.61 (m, 3H), 1.30-1.20 (m, 2H), 0.88-0.85 (m, 6H) ppm}; \text{\^{13}C NMR (75 MHz, CDCl)}; \delta = 126.0, 108.0, 59.9, 49.8, 40.3, 25.0, 19.3, 15.5 ppm; MS (ESI): m/z = 155 [M+H]; Anal. Caled for C8H12N3: C, 70.04; H, 11.78; N, 18.16. Found: C, 70.04; H, 11.78; N, 18.12.

General experimental procedure or the synthesis of 10a-f: To a stirred solution of compound 6a-e (1 equiv.) in anhydrous DMF (10 mL), NaH (18 mg, 60% suspension in mineral oil) was added at 0°C. Then required amount of propargyl bromide (1 equiv.) was added at 0°C. Reaction mixture was stirred for 1 h at RT. The reaction mixture was diluted with water (30 mL). The aqueous layer was extracted with ethyl acetate (2 X 50 mL) and the organic layer was dried over anhydrous Na2SO4. After concentration under vacuum, the crude product was chromatographed on silica gel with (eluent = hexane/ethyl acetate, 9.6/0.4) as eluent to furnish 10a-f (78-81% yield).

(S)-tert-butyl 1-azido-3-methylbutan-2-yl(prop-2-ynyl)carbamate 10a:
Colourless oil; yield, 78%; Rf 0.85 (6/4, hexane/ethyl acetate); 
\[\delta_{1}^{300} = +19.6 \text{ (c 0.15, CHCl)}; \text{IR (neat, cm}^{-1})\] 3712, 2360, 1638, 1218, 1026, 771, 672; \[\delta_{1}^{1} \text{H NMR (300 MHz, CDCl)}; \delta = 4.57 \text{ (s, 1H), 3.79-3.69 (m, 1H), 3.38 (d, 2H, J = 5.3 Hz), 2.40 (bs, 1H), 2.14 (s, 3H), 1.49-1.36 (m, 3H), 1.18-1.07 (m, 1H), 0.88-0.84 (m, 6H) ppm}; \text{\^{13}C NMR (75 MHz, CDCl)}; \delta = 125.8, 108.0, 66.4, 48.6, 41.3, 24.8, 19.8, 12.0 ppm; MS (ESI): m/z = 155 [M+H]; Anal. Caled for C8H12N3O2: C, 59.98; H, 8.63; N, 19.98; O, 11.41. Found: C, 59.90; H, 8.67; N, 19.90.

(S)-tert-butyl 1-azido-4-(methylthio)butan-2-yl(prop-2-ynyl)carbamate 10d:
Colourless oil; yield, 81%; Rf 0.66 (8.5/1.5, hexane/ethyl acetate); 
\[\delta_{1}^{300} = +42.4 \text{ (c 0.14, CHCl)}; \text{IR (neat, cm}^{-1})\] 3431, 2132, 2104, 1441, 1161, 782, 704; \[\delta_{1}^{1} \text{H NMR (300 MHz, CDCl)}; \delta = 4.58 \text{ (d, 1H, J = 7.8 Hz), 3.72 (s, 1H), 3.33-3.32 (m, 2H), 1.58-1.56 (m, 1H), 1.42 (s, 2H), 1.37 (s, 9H), 1.29-1.19 (m, 2H), 0.85 (d, 6H, J = 6.5 Hz) ppm}; \text{\^{13}C NMR (75 MHz, CDCl)}; \delta = 153.9, 81.3, 78.1, 72.2, 53.3, 49.3, 38.7, 30.5, 28.2, 24.8, 24.5, 21.6 ppm; MS (ESI): m/z = 281 [M+H]; Anal. Caled for C8H16S2N3O2: C, 59.98; H, 8.63; N, 19.98; O, 11.41. Found: C, 59.92; H, 8.69; N, 19.92.

General experimental procedure or the synthesis of 11a-e: The procedure was followed as described for 8a-e.
(S)- tert-butyl 6-isopropyl-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate 11a: Colourless oil; yield, 80%; R<sub>y</sub> = 0.40 (7/3, hexane/ethyl acetate); δ<sub>α</sub><sup>13</sup>C = +11.12 (c 0.15, CHCl<sub>3</sub>); IR (neat, cm<sup>-1</sup>): 3312, 1712, 1211, 1067, 783, 656; δ<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46 (s, 1H), 5.06 (bs, 1H), 4.69 (d, 1H, J<sub>1</sub> = 12.8 Hz), 4.18-4.12 (m, 3H), 1.53-1.49 (m, 1H), 1.43 (s, 9H), 0.91 (d, 3H, <i>J</i> = 6.6 Hz), 0.85 (d, 3H, <i>J</i> = 6.6 Hz) ppm; δ<sup>1</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 154.8, 153.9, 128.8, 80.9, 63.9, 56.0, 46.5, 32.4, 27.9, 24.6, 15.6, 10.4 ppm; MS (ESI): m/z = 281 [M<sup>+</sup>]<sup>2</sup>; Anal. Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 59.98; H, 8.63; N, 19.98; O, 11.41. Found: C, 59.90; H, 8.67; N, 19.91.

(1S)- (2-methylthio)ethyl)-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate 11f: Colourless oil; yield, 83%; R<sub>y</sub> = 0.40 (7/3, hexane/ethyl acetate); δ<sub>α</sub><sup>13</sup>C = +16.21 (c 0.15, CHCl<sub>3</sub>); IR (neat, cm<sup>-1</sup>): 3411, 2918, 2362, 1779, 1431, 1253, 1213, 762; δ<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.26 (s, 1H), 2.44-2.42 (m, 5H), 2.11-2.10 (m, 5H), 2.07 (s, 3H), 1.38 (s, 9H) ppm; δ<sup>1</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 155.4, 147.9, 136.6, 79.7, 56.5, 55.1, 40.8, 33.8, 30.9, 28.7, 15.9 ppm; MS (ESI): m/z = 299 [M<sup>+</sup>]<sup>2</sup>; Anal. Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 52.32; H, 7.43; N, 18.78; O, 10.72; S, 10.75. Found: C, 52.30; H, 7.46; N, 18.77.

General experimental procedure or the synthesis of 12a,c: To a stirred solution of Pd(OAc)<sub>2</sub> (7 mol %) and PPh<sub>3</sub> (23 mol%) in dry DMF (2 mL) was stirred at room temperature for 20 min under argon atmosphere. Aryl iodide (0.9 mmol), K<sub>2</sub>CO<sub>3</sub> (1.8 mmol) and tetrabutylammonium bromide (7 mol%) were then added successively and the whole reaction mixture was allowed to stir at room temperature for another 15 min. A solution of azido-acytene 10a,c (1 equiv.) in dry DMF (3 mL) was added dropwise, followed by the addition of Cul (15 mol %). The resulting mixture was flushed with argon carefully and stirred for 45 min at room temperature. After disappearance of starting materials (monitored by TLC), the reaction mixture was allowed to heat at 90°C for 1 hr. The reaction mixture was diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After concentration under vacuum, the crude product was chromatographed on silica gel with (eluent = hexane/ethyl acetate, 9:1) as eluent to furnish 12c (81% yield).

(S)- tert-butyl 6-(4-methoxyphenyl)-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate 12a: Colourless oil; yield, 79%; R<sub>y</sub> = 0.50 (8/2, hexane/ethyl acetate); δ<sub>α</sub><sup>13</sup>C = +22.0 (c 0.15, CHCl<sub>3</sub>); IR (neat, cm<sup>-1</sup>): 3467, 1752, 1362, 1290, 1073, 771, 679; δ<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.17-7.14 (m, 3H), 7.05 (d, 1H, <i>J</i> = 5.5 Hz), 4.52-4.34 (m, 2H), 4.19-4.15 (m, 2H), 3.76 (s, 3H), 2.68-2.65 (m, 1H), 2.53-2.47 (m, 1H), 1.33 (s, 9H), 1.23 (s, 6H) ppm; δ<sup>1</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 163.4, 155.6, 146.9, 143.3, 128.3, 123.0, 114.0, 78.4, 66.6, 56.9, 55.4, 36.4, 28.1, 27.7, 20.6 ppm; MS (ESI): m/z = 373 [M<sup>+</sup>]<sup>2</sup>; Anal. Calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 64.39; H, 7.58; N, 15.04; O, 12.89. Found: C, 64.47; H, 7.61; N, 15.07.

(S)- tert-butyl 6-(3-methyl-phenyl)-6,7-dihydro-[1,2,3]triazolo[1,5-a]pyrazine-5(4H)-carboxylate 12c: Colourless oil; yield, 81%; R<sub>y</sub> = 0.52 (8/2, hexane/ethyl acetate); δ<sub>α</sub><sup>13</sup>C = +26.9 (c 0.13, CHCl<sub>3</sub>); IR (neat, cm<sup>-1</sup>): 3437, 1776, 1434, 1265, 1082, 763, 671; δ<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.33-7.23 (m, 5H), 4.40-4.10 (m, 3H), 3.59-3.50 (m, 1H), 3.25-3.21 (m, 1H), 1.44 (s, 9H), 1.27 (d, 3H, <i>J</i> = 4.7 Hz) ppm; δ<sup>1</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 154.6, 131.6, 128.9, 128.2, 127.8, 126.0, 122.9, 81.7, 60.0, 56.0, 34.6, 28.5, 14.0 ppm; MS (ESI): m/z = 315
General experimental procedure or the synthesis of 14b: To an ice cooled solution of compound 13b (1 equiv.) in dry DCM (10 mL), Ph$_3$P=CHCO$_2$Et (1.3 equiv.) was added. The reaction mixture was stirred at room temperature for 2h. After completion of the reaction, the solvent was evaporated and the residue was chromatographed over silica gel to furnish 14b as colourless oil.

(S,E)-ethyl 4-((tert-butoxycarbonyl) amino)-5-phenylpent-2-enate 14b: Colourless oil; yield, 89%; R$_f$ 0.50 (8/2, hexane/ethyl acetate); [α]$^0_{D}$ = +9.81 (c 0.15, CHCl$_3$); IR (neat, cm$^{-1}$): 3280, 3160, 1721, 1521, 1452, 1381, 1311, 1291, 1270, 1235, 1154, 1112, 1091, 1072, 1015, 986, 948, 791, 683; NMR (75 MHz, CDCl$_3$) δ 7.23-7.15 (3H, m, 3H), 7.09 (d, 2H, $J=5.2$ Hz), 5.78 (d, 1H, $J=12.6$ Hz), 4.56 (s, 2H), 4.12~4.07 (m, 2H), 2.85-2.80 (m, 2H), 1.31 (s, 9H), 1.90 (t, 3H, $J=128.4$ Hz), 5.21 (d, 1H, $J=6.0$ Hz), 1.35 (s, 9H), 1.18 (s, 2H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 154.4, 143.1, 138.7, 129.7, 126.9, 80.9, 66.2, 58.8, 46.9, 37.7, 29.7, 28.1 ppm; MS (ESI): m/z 320 [M+H$^+$]; Anal. Calcd for C$_{13}$H$_{25}$NO$_2$: C, 67.61; H, 7.92; N, 16.30.

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Notes and references


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