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PAPER

A rapid and facile method for the general synthesis of 3-aryl substituted 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines and their ring fused analogues†

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We report a general and facile method that provides rapid entry into 3-aryl substituted 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines and their ring fused analogues in one-pot under palladium–copper catalysis. The methodology utilises simple and easily available substrates of broad range. The applicability of this reaction for the synthesis of optically active products has been demonstrated. A plausible reaction mechanism has also been proposed.

Introduction

The thermal cycloaddition between azides and acetylenes studied by Huisgen[1a–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 pioneered independently by Sharpless[2a] and Meldal[2b] which ensured dramatic acceleration of the reaction rate and lowering of the reaction temperature. Subsequently, exclusive formation of 1,5-substituted 1,2,3-triazoles, the other regio-isomer, was also achieved by Fokin and co-workers[2c–e] through judicious employment of a Ru(II) catalyst.[2c,d] In addition, the synthesis of fully decorated (1,4,5-substituted) triazoles has also been achieved.[2f]

Metal catalysed cycloaddition reactions, popularly known as 'click reactions', have found numerous applications in various fields ranging from medicinal chemistry[3a–d] to materials science.[3e–h] Despite such advancements, most of the applications for these have been reported for intermolecular reactions, while examples involving intramolecular versions are relatively limited possibly due to the constraint of structural requirements. In principle, intramolecular reactions should constitute powerful methods for the synthesis of diverse analogues including fused triazoles difficult to obtain through intermolecular reactions. In actual practice, most of such substrates require high temperature and long reaction times to undergo thermal cycloaddition; survival of the labile protecting group(s) also becomes difficult. With this background, the development of elegant methods for the synthesis of fused triazoles[4] remains a real challenge in organic synthesis.

It may be pointed out that 1,2,3-triazoles are of particular interest due to their wide array of biological effects[5] including anti-HIV,[5a] anticancer,[5b] antibacterial,[5c] antiallergic,[5d] and antihaemagglutination[5e] among others.[5f–h] Fused 1,2,3-triazoles have also been equally important due to their broad spectrum of activities including antitumor,[6a] anticancer,[6b] antiviral,[6c] glycosidase inhibitory,[6d] and 5-$HT_{1A/B/D}$ receptor antagonistic activity.[6e]

On the other hand piperazines fused with specific nitrogen heterocycles (*e.g.* pyrrole, triazole *etc.*) are found in a number of biologically active natural products, synthetic agents, and drugs. Notable among the pyrrolo-piperazines are phakellstatins (antineoplastic and anticancer alkaloids),[7] longamide and longamide B (antibacterial compounds isolated from marine organisms),[8] and antileishmanial agents.[9] Besides, 1,2,3-triazolo[1,5-*a*]quinoxaline[10] **1** (Fig. 1) has also been shown to elicit good affinity toward benzodiazepine and adenosine receptors.[10a,b]

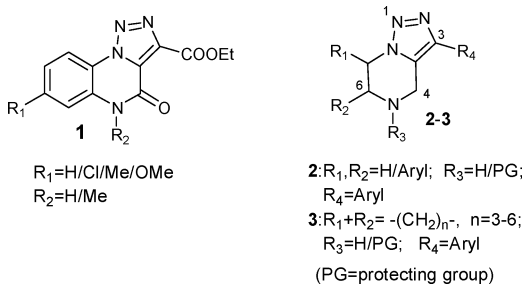

Fig. 1 Some important triazolo-piperazine derivatives.

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 **3** (Fig. 1) could be novel pharmacophores or important building blocks. Only a few methods

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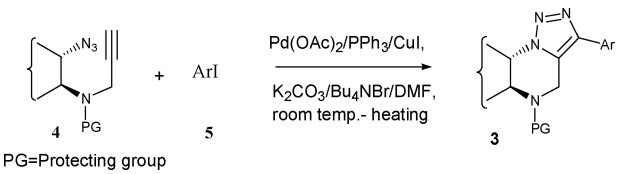
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and copies of spectra. CCDC reference numbers 804536 and 804692. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05255a

are available in the literature for the synthesis of compounds of type **2**[11] (R_4 = H/alkyl) and of its 6-keto derivatives.[12] The majority of the syntheses used the conventional intramolecular cycloaddition between azide and terminal alkyne, limiting the diversity of substitutions at C-3 of the product. Regarding fused analogues **3**, only a few specific examples ($n = 4$, R_4 = H/alkyl) of this class have been prepared,[11b] employing classical cycloaddition reactions.

In continuation of our interest in the development of palladium catalysed synthetic methods,[13] we felt it desirable to develop a facile and general means for rapid access to 3-substituted 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines **2** and of their ring fused analogues **3** through palladium–copper catalysis. We report herein the results obtained in this direction (Scheme 1).



Scheme 1 Synthesis of the fused analogues **3** of 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines.

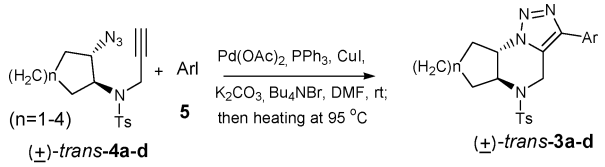
Results and discussion

At the outset, we were keen to find out the optimised reaction conditions using **4a** and **5a** as substrates. Thus, a variety of reaction conditions were screened, varying palladium catalyst, base, solvent, temperature *etc.* (see electronic supplementary information for details about optimisation studies). In each case, a competing self cycloaddition of substrate **4a** took place; however, employment of $Pd(OAc)_2/PPh_3$ as catalyst and CuI as cocatalyst along with K_2CO_3 as base allowed the reaction to proceed to completion within a few hours, affording exclusively the desired product **3aa** with good yield (68%; Table 1, entry 1).

With the optimised reaction conditions in hand, we became interested to explore the scope and generality of the reaction. This was tested with different *trans*-azido-alkynes **3a–d** and a range of aryl/heteroaryl iodides **5a–m** (Table 1). As can be seen from Table 1, various substitutions (*e.g.* methyl, methoxy, carbomethoxy, fluoro, trifluoromethyl, nitro *etc.*) in the aryl iodide **5** were well tolerated under the reaction conditions. We also employed aryl di-iodides (**5f**, **5l**) in this reaction with a view to testing the feasibility of bis-heteroannulation in one pot. To our delight, reactions using 1,4-diiodobenzene (**5f**) and 4,4′-diiodobiphenyl (**5l**) led to the isolation of bis-heteroannulated products **3af** (44%) and **3cl** (71%), respectively (Table 1, entry 6 and 15). Thus, this method is amenable to the synthesis of polyheteroannulated frameworks also. It is noteworthy that immediate heating without stirring at room temperature for the requisite time resulted in lower yields of the desired products. Interestingly, the time period of heating to effect the cycloaddition was found to be relatively shorter in the cases of seven-/eight-membered substrates **4c–d** compared to those of five-/six-membered compounds **4a–b** (Table 1, entries 11–17 *vs.* entries 1–10).

Some of the synthesised compounds (**3aa**, **3ae** and **3bc**) were examined to assess the viability of the deprotection of the *N*-tosyl

Table 1 Synthesis of the fused analogues **3** of 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazines under palladium-copper catalysis[a]



a) **3a**, **4a**: n=1; b) **3b**, **4b**: n=2; c) **3c**, **4c**: n=3; d) **3d**, **4d**: n=4

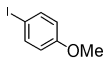
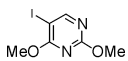
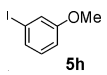
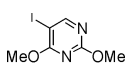
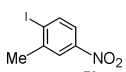
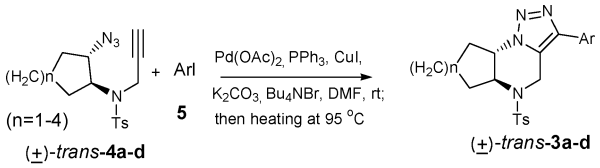
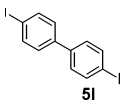
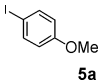
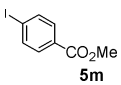
Entry	Azide-alkyne[b]	Aryl iodide **5**	Time[c] (h) (rt + heating)	Product	Yield[d] (%)
1	**4a**	 **5a**	1.25 + 1.0	**3aa**	68
2	**4a**	 **5b**	1.5 + 4.0	**3ab**	47
3	**4a**	 **5c**	1.5 + 3.0	**3ac**	71
4	**4a**	 **5d**	1.5 + 0.75	**3ad**	50
5	**4a**	 **5e**	1.5 + 4.0	**3ae**	61
6	**4a**	 **5f**	1.5 + 3.0	**3af**	44
7	**4b**	 **5g**	1.0 +2.5	**3bg**	47
8	**4b**	 **5c**	1.5 + 2.5	**3bc**	77
9	**4b**	 **5h**	1.5 + 4.0	**3bh**	60
10	**4b**	 **5i**	1.0 + 2.0	**3bi**	53
11	**4c**	 **5d**	0.75 + 0.75	**3cd**	55
12	**4c**	 **5g**	2.0 + 0.75	**3cg**	52
13	**4c**	 **5j**	0.75 + 1.25	**3cj**	51
14	**4c**	 **5k**	3.0 + 0.75	**3ck**	48

Table 1 *(Contd.)*



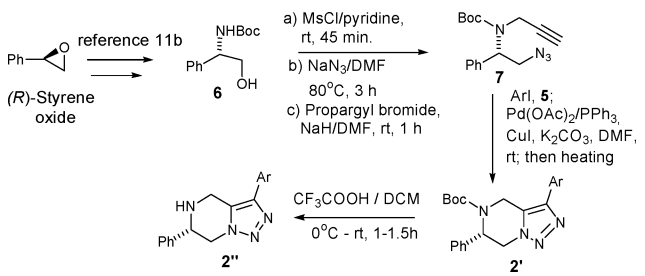
a) **3a**, **4a**: n=1; b) **3b**, **4b**: n=2; c) **3c**, **4c**: n=3; d) **3d**, **4d**: n=4

Entry	Azide-alkyne[b]	Aryl iodide **5**	Time[c] (h) (rt + heating)	Product	Yield[d] (%)
15	**4c**	 **5l**	0.75 + 1.0	**3cl**	71
16	**4d**	 **5a**	0.75 + 0.75	**3da**	46
17	**4d**	 **5m**	0.75 + 0.75	**3dm**	54

[a] Azido-alkyne **4** (1.1 equiv), iodide **5** (1.0 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.2 equiv), CuI (0.1 equiv), K_2CO_3 (2.0 equiv), Bu_4NBr (0.05 equiv) in dry DMF stirred at rt for requisite time followed by heating at 95 °C. [b] Substrates **4a–d** are all racemic mixture. [c] Time required for the consumption of starting materials/intermediate based on TLC. [d] Yields of the products isolated after column chromatographic purification.

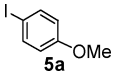
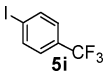
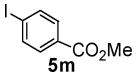
group; indeed, treatment with sodium/naphthalene afforded the corresponding detosylated amines with good yields (61–72%) (see electronic supplementary information for details).

We next applied this method for the synthesis of optically active 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines **2**. Toward this objective, we prepared azido-alkyne **7** from *R*-styrene oxide *via* (*S*)-amino alcohol **6**,[11b] using a reaction sequence involving mesylation and azide addition followed by *N*-propargylation (Scheme 2). When substrate **7** was allowed to react with aryl iodide **5** under the optimised reaction conditions, the expected 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazine **2′** was formed with moderate to good yields (Scheme 2 and Table 2). Finally, the removal of the Boc group could easily be carried out by the treatment of trifluoroacetic acid, resulting in the formation of the corresponding amines **2″** (81–98%). The free amine functionality of product **2″** may serve as a diversification site in combinatorial synthesis.



Scheme 2 Synthesis of the optically active 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines **2′** and **2″**.

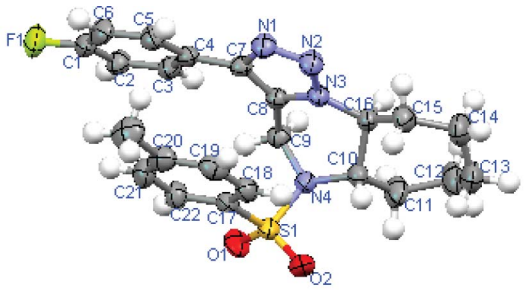
Table 2 Synthesis of optically active products[a,b] **2′** and **2″**

Entry	Aryl iodide **5**	Time (h)[c] (rt + heating)	Product **2′** (yield %)[d]	Product **2″** (yield %)[d]
1	 **5a**	0.75 + 1.0	**2′a** (43)	**2″a** (98)
2	 **5c**	0.75 + 1.0	**2′c** (74)	**2″c** (89)
3	 **5i**	0.75 + 1.0	**2′i** (57)	**2″i** (81)
4	 **5j**	0.75 + 1.5	**2′j** (55)	**2″j** (88)
5	 **5m**	0.75 + 1.0	**2′m** (60)	**2″m** (96)
6	 **5n**	0.75 + 0.75	**2′n** (50)	**2″n** (91)

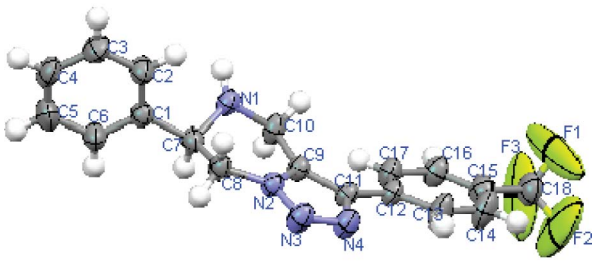
[a] Compound **7** (0.55 mmol), iodide **5** (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.1 mmol), CuI (0.05 mmol) in dry DMF (3.0 mL) stirred at rt for requisite time followed by heating at 95 °C. [b] Product **2′** (0.25 mmol), TFA (0.5 mL) in dry DCM (3 mL) stirred at 0 °C to rt during 1–1.5 h. [c] Time required for the synthesis of product **2′** as determined through TLC. [d] Yields of the purified products.

The structures of the products were determined based on spectral (NMR, IR, mass) and analytical data. The *trans* stereochemistry of the tricyclic scaffolds **3** was deduced from the large (~9–12 Hz) coupling constant (*J*) between the methine protons observed in the ^{1}H-NMR spectra. The structural deduction was further supported by a single crystal X-ray analysis of product **3cj** (Fig. 2).[14a] Careful examination of the ^{1}H-NMR spectra of amines **2″** revealed an interesting feature of their structures. The vicinal H–H coupling constants (*J*) in the piperazine ring of products **2″** appeared to be large (~10–12 Hz), suggesting the orientation of the phenyl ring as equatorial. Single crystal X-ray study of **2″i** was in conformity with this conclusion (Fig. 2).[14b]

A plausible reaction mechanism can be envisaged (Scheme 3) through control experiments and known features of palladium chemistry. Based on the evidence,[15] we believe that the intermediate internal alkyne **D** is formed through the conventional copper-assisted Sonogashira pathway. Thus the oxidative addition of aryl iodide **5** to Pd(0), formed *in situ* through the interaction of palladium acetate and triphenyl phosphine,[16] affords σ-aryl-palladium(II) complex **A** which undergoes transmetalation with copper-acetylide **B** to generate arylalkynylpalladium complex **C**.[17] This on reductive elimination of palladium(0) affords the intermediate C-arylated internal alkyne **D**. Palladium(0) may then activate the triple bond of intermediate **D** through a π-complex **E**, in which palladium is stabilised by the nitrogen in proximity.[18] Next, insertion of palladium into the triple bond possibly leads to the vinylidene like transition state **F**. Presumably, the increase of electron density in the dipolarophile due to the palladium insertion accelerates the cycloaddition through a

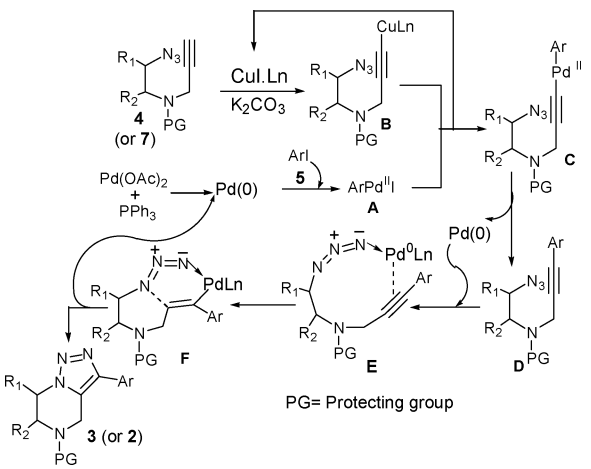


ORTEP representation of **3cj**



ORTEP representation of **2''i**

Fig. 2 X-ray crystal structure of products **3cj** and **2''i**.



Scheme 3 Plausible reaction mechanism.

$HOMO_{(dipolarophile)}$–$LUMO_{(dipole)}$ interaction[19] leading to the formation of the desired cycloadduct **3** (or **2**) with concurrent regeneration of palladium(0). Further evidence in favour of the proposed mechanism for the conversion of **D** to the final product **3** (or **2**) was clinched by control experiments.[20]

Conclusions

In conclusion we have developed an efficient and general method that provides rapid access to 4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyrazines and their fused analogues with moderate to excellent yields. The methodology utilises easily accessible substrates of broad range. A variety of functional groups can easily be accommodated without affecting the outcome. This protocol is successfully utilised for the formation of one C–C and two C–N bonds in one pot. The method is also suitable for synthesising optically active compounds which may be of possible biological significance. It thus promises to be of interest to practitioners of both organic and medicinal chemistry.

Experimental section

General procedure for the synthesis of product 3

A mixture of $Pd(OAc)_2$ (9.6 mg, 0.043 mmol, 5 mol%) and PPh_3 (44.8 mg, 0.171 mmol, 20 mol%) in dry DMF (1 mL) was stirred at room temperature for 10 min under argon atmosphere. Aryl iodide **5** (0.855 mmol), K_2CO_3 (236 mg, 1.709 mmol) and tetrabutylammonium bromide (13.8 mg, 0.043 mmol, 5 mol%) were then added successively and the whole reaction mixture was allowed to stir at room temperature for another 10 min. A solution of azido-acetylene **4** (0.940 mmol) in dry DMF (2 mL) was added dropwise, followed by the addition of CuI (16.3 mg, 0.085 mmol, 10 mol%). The resulting mixture was flushed with argon carefully and stirred for the specified time (Table 1) at room temperature. After disappearance of starting materials (monitored by TLC), the reaction mixture was allowed to heat at 95 °C for the requisite time period (Table 1). Upon completion of the reaction (TLC), the solvent was removed *in vacuo*; the residue was mixed with water (10 mL) and then extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried (anhydrous Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting residue was purified through silica gel (100–200 mesh) column chromatography (ethyl acetate–petroleum ether).

(±)-*trans*-(5a,8a)-3-(4-Methyl-phenyl)-5-(toluene-4-sulfonyl)-5,5a,6,7,8,8a-hexahydro-4*H*-cyclopenta[*e*][1,2,3]triazolo[1,5-*a*]-[1,4]pyrazine (3aa). Yield: 68%; white solid, m.p.: 231–233 °C; IR (KBr): ν_{max} 3434, 2960, 1614, 1505, 1327, 1303, 1251, 1157, 1089, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.93–1.98 (m, 2H), 2.09–2.12 (m, 1H), 2.22–2.25 (m, 1H), 2.39–2.42 (m, 1H), 2.42 (s, 3H), 2.67–2.72 (m, 1H), 2.84 (ddd, J = 6.4, 9.7, 11.5 Hz, 1H), 3.87 (s, 3H), 4.19 (ddd, J = 7.4, 10.2, 10.2 Hz, 1H), 4.36 (d, J = 15.6 Hz, 1H), 5.18 (d, J = 15.6 Hz, 1H), 7.01 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.6, 21.5, 23.9, 27.4, 45.1, 55.3, 62.3, 62.4, 114.3, 123.0, 125.3, 127.5, 127.6, 130.1, 133.1, 142.0, 144.6, 159.4; ESI-MS: m/z 424.98 $[M + H]^+$, 446.98 $[M + Na]^+$, 460.07 $[M + K]^+$; HRMS Calcd. for $C_{22}H_{25}N_4O_3S$ $[M + H]^+$ 425.1647, found 425.1666.

(±)-*trans*-(5a,8a)-5-(Toluene-4-sulfonyl)-3-*p*-tolyl-5,5a,6,7,8,8a-hexahydro-4*H*-cyclopenta[*e*][1,2,3]triazolo[1,5-*a*][1,4]pyrazine (3ae). Yield: 61%; off-white solid, m.p.: 239–241 °C; IR (KBr): ν_{max} 3434, 2968, 1597, 1507, 1452, 1383, 1349, 1303, 1166, 1115, 1090, 1036, 1005 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.95–2.00 (m, 2H), 2.08–2.12 (m, 1H), 2.20–2.26 (m, 1H), 2.38–2.40 (m, 1H), 2.41 (s, 3H), 2.42 (s, 3H), 2.67–2.72 (m, 1H), 2.84 (ddd, J = 6.1, 10.0, 11.5 Hz, 1H), 4.19 (ddd, J = 7.6, 10.2, 10.2 Hz, 1H), 4.38 (d, J = 15.6 Hz, 1H), 5.20 (d, J = 15.6 Hz, 1H), 7.28 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.5, 21.2, 21.4, 23.8, 27.3, 45.1, 62.1, 62.2, 125.6, 126.0, 127.5, 129.5, 130.0, 133.0, 137.8, 142.0, 144.5; MS (FAB+): m/z 409 $[M + H]^+$; HRMS Calcd. for $C_{22}H_{25}N_4O_2S$ $[M + H]^+$ 409.1698, Found 409.1679.

(±)-*trans*-(5a,9a)-3-(4-Trifluoromethyl-phenyl)-5-(toluene-4-sulfonyl)-4,5,5a,6,7,8,9,9a-octahydro[1,2,3]triazolo[1,5-*a*]quinoxaline (3bi). Yield: 53%; white solid, m.p.: 196–198 °C; IR (KBr): ν_{max} 2938, 2864, 1621, 1452, 1325, 1161, 1117, 1068, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.34–1.67 (m, 3H), 1.93–2.04 (m, 3H), 2.36 (s, 3H), 2.36–2.44 (m, 1H), 2.98–3.02 (m, 1H), 3.28 (ddd, J = 2.4, 10.9, 10.9 Hz, 1H), 3.96 (ddd, J = 3.3, 10.3, 10.3 Hz, 1H), 4.74 (d, J = 17.1 Hz, 1H), 5.33 (d, J = 16.8 Hz, 1H), 7.11 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.75–7.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 23.6, 25.2, 29.9, 30.3, 43.8, 59.2, 62.3, 125.8, 125.9, 126.4, 126.8, 127.4, 127.5, 129.8, 134.1, 136.8, 140.4, 144.3; ESI-MS: m/z 477.22 $[M + H]^+$, 499.19 $[M + Na]^+$; HRMS Calcd. for $C_{23}H_{24}F_3N_4O_2S$ $[M + H]^+$ 477.1572, found 477.1579.

(±)-*trans*-(5a,9a)-3-(3-Methoxy-phenyl)-5-(toluene-4-sulfonyl)-4,5,5a,6,7,8,9,9a-octahydro[1,2,3]triazolo[1,5-*a*]quinoxaline (3bh). Yield: 60%; off-white solid, m.p.: 192–194 °C; IR (KBr): ν_{max} 2944, 2867, 1580, 1495, 1449, 1349, 1292, 1158, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.36–1.39 (m, 1H), 1.45–1.48 (m, 1H), 1.57–1.61 (m, 1H), 1.92–1.98 (m, 3H), 2.35 (s, 3H), 2.43–2.46 (m, 1H), 2.96–2.98 (m, 1H), 3.25 (ddd, J = 3.2, 11.1, 11.1 Hz, 1H), 3.88 (ddd, J = 4.2, 10.8, 10.8 Hz, 1H), 3.90 (s, 3H), 4.75 (d, J = 16.8 Hz, 1H), 5.29 (d, J = 16.8 Hz, 1H), 6.94 (ddd, J = 0.6, 2.5, 8.2 Hz, 1H), 7.09 (d, J = 7.8 Hz, 2H), 7.13 (dt, J = 1.2, 7.2 Hz, 1H), 7.29 (dd, J = 1.2, 2.4 Hz, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.5, 23.6, 25.3, 29.9, 30.6, 43.9, 55.4, 59.0, 62.3, 111.8, 113.9, 118.6, 126.7, 126.8, 129.8, 129.9, 131.9, 136.7, 141.6, 144.2, 160.0; ESI-MS: m/z 439.13 $[M + H]^+$, 461.12 $[M + Na]^+$; Anal. Calcd. for $C_{23}H_{26}N_4O_3S$: C, 62.99; H, 5.98; N, 12.78. Found: C, 62.95; H, 6.02; N, 12.74%.

(±)-*trans*-(5a,10a)-3-(2,4-Dimethoxy-pyrimidin-5-yl)-5-(toluene-4-sulfonyl)-5,5a,6,7,8,9,10,10a-octahydro-4*H*-cyclohepta[*e*][1,2,3]-triazolo[1,5-*a*][1,4]pyrazine (3cd). Yield: 55%; light yellow solid, m.p.: 134–135 °C; IR (KBr): ν_{max} 3428, 2931, 2865, 1611, 1560, 1477, 1386, 1342, 1280, 1161, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.70–1.79 (m, 4H), 1.91–1.94 (m, 2H), 2.02–2.08 (m, 2H), 2.34 (s, 3H), 2.41–2.45 (m, 1H), 3.11–3.14 (m, 1H), 3.84 (ddd, J = 3.4, 9.7, 9.7 Hz, 1H), 3.96 (ddd, J = 3.0, 9.7, 9.7 Hz, 1H), 4.09 (s, 3H), 4.10 (s, 3H), 4.60 (d, J = 17.4 Hz, 1H), 4.92 (d, J = 17.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 8.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.5, 24.4, 24.7, 24.9, 29.7, 33.1, 41.1, 54.2, 55.2, 59.9, 61.6, 106.0, 126.5, 129.5, 129.6, 135.0, 135.9, 144.1, 158.2, 165.2, 166.9; MS (FAB+): m/z 485 $[M + H]^+$; Anal. Calcd. for $C_{23}H_{28}N_6O_4S$: C, 57.01; H, 5.82; N, 17.34. Found: C, 56.97; H, 5.88; N, 17.31%.

(±)-*trans*-(5a,11a)-3-(4-Methoxycarbonyl-phenyl)-5-(toluene-4-sulfonyl)-4,5,5a,6,7,8,9,10,11,11a-decahydrocycloocta[*e*][1,2,3]-triazolo[1,5-*a*][1,4]pyrazine (3dm). Yield: 54%; white solid, m.p.: 222–224 °C; IR (KBr): ν_{max} 3415, 2930, 2860, 1718, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.55–1.57 (m, 1H),1.61–1.75 (m, 5H), 1.81–1.88 (m, 3H), 2.04–2.12 (m, 2H), 2.33 (s, 3H), 2.85–2.89 (m, 1H), 3.97 (s, 3H), 4.23 (ddd, J = 5.1, 10.5, 5.1 Hz, 1H), 4.40 (ddd, J = 5.2, 5.2, 10.9 Hz, 1H), 4.54 (d, J = 17.4 Hz, 1H), 5.22 (d, J = 16.8 Hz, 1H), 7.00 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 8.16 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 21.5, 22.6, 23.1, 26.5, 26.7, 31.7, 33.8, 38.1, 52.3, 55.0, 56.8, 126.1, 126.6, 128.3, 129.6, 129.7, 130.4, 134.8, 135.6, 141.2, 144.1, 166.7; MS (FAB+): m/z 495 $[M + H]^+$, 517 $[M + Na]^+$; HRMS Calcd. for $C_{26}H_{31}N_4O_4S$ $[M + H]^+$ 495.2066, found 495.2091.

General procedure for preparation of optically active 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazines 2′

A mixture of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%) and PPh_3 (26.2 mg, 0.1 mmol, 20 mol%) in dry DMF (3 mL) was stirred at room temperature for 10 min under argon atmosphere. Iodo-compound **5** (0.5 mmol), K_2CO_3 (138 mg, 1.0 mmol) and tetrabutylammonium bromide (8.0 mg, 0.025 mmol, 5 mol%) were then added successively. The whole reaction mixture was allowed to stir at room temperature for another 10 min under argon atmosphere. A solution of azido-acetylene **7** (165.0 mg, 0.55 mmol) in dry DMF (2 mL) was added dropwise, followed by the addition of CuI (9.5 mg, 0.05 mmol). The resulting mixture was flushed with argon carefully and stirred at room temperature for specified time (as shown in Table 2). After disappearance of starting materials (TLC), the whole mixture was allowed to heat at 95 °C for the requisite time period (as shown in Table 2). Upon completion of the reaction (TLC), the solvent was removed *in vacuo*; the residue was mixed with water (10 mL) and then extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified through silica gel (100–200 mesh) column chromatography (ethyl acetate-petroleum ether) to afford the desired product.

(6*S*)-*tert*-Butyl-6-phenyl-3-(4-trifluoromethyl-phenyl)-6,7-dihydro-4*H*-[1,2,3]triazolo[1,5-*a*]pyrazine-5-carboxylate (2′i). Yield: 57%; white solid, m.p.: 179–180 °C; $[\alpha]_D^{20}$ +6.03 (c 0.24, $CHCl_3$); IR (KBr): ν_{max} 2978, 1696, 1620, 1454, 1405, 1323, 1245, 1171, 1122, 1071, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56 (s, 9H), 4.20 (d, J = 17.1 Hz, 1H), 4.69 (dd, J = 4.6, 13.3 Hz, 1H), 5.26 (d, J = 13.8 Hz, 1H), 5.35 (d, J = 17.1 Hz, 1H), 5.99 (br, 1H), 7.11 (d, J = 5.4 Hz, 2H), 7.28 (br, 3H), 7.66 (d, J = 7.8 Hz, 2H), 7.80 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3, 37.9, 47.9, 51.1, 82.2, 122.2, 125.7, 125.8, 126.0, 126.3, 127.3, 128.4, 129.2, 129.8, 134.2, 135.8, 140.3, 154.1; MS (FAB+): m/z 445 $[M + H]^+$; HRMS Calcd. for $C_{23}H_{23}F_3N_4O_2Na$ $[M + Na]^+$ 467.1671, found 467.1645.

(6*S*)-*tert*-Butyl-3-(4-fluoro-phenyl)-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[1,5-*a*]pyrazine-5-carboxylate (2′j). Yield: 55%; white solid, m.p.: 202–204 °C; $[\alpha]_D^{20}$ +10.52 (c 0.13, $CHCl_3$); IR (KBr): ν_{max} 2983, 1700, 1516, 1452, 1397, 1372, 1300, 1238, 1161, 1095, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56 (s, 9H), 4.17 (d, J = 17.1 Hz, 1H), 4.67 (dd, J = 2.4, 13.5 Hz, 1H), 5.23 (d, J = 13.8 Hz, 1H), 5.29 (d, J = 18.6 Hz, 1H), 5.98 (br, 1H), 7.11 (br, 4H), 7.28 (br, 3H), 7.64 (br, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3, 37.8, 47.8, 51.1, 82.1, 115.7, 115.9, 126.0, 126.3, 126.9, 127.6, 127.7, 128.3, 129.1, 135.9, 140.8, 154.1, 160.6, 163.9; ESI-MS: m/z 395.04 $[M + H]^+$, 417.01 $[M + Na]^+$; HRMS Calcd. for $C_{22}H_{24}FN_4O_2$ $[M + H]^+$ 395.1883, found 395.1861.

(6*S*)-*tert*-Butyl-3-(4-methoxycarbonyl-phenyl)-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[1,5-*a*]pyrazine-5-carboxylate (2′m). Yield: 60%; white solid, m.p.: 259–261 °C; $[\alpha]_D^{20}$ +17.04 (c 0.15, $CHCl_3$); IR (KBr): ν_{max} 2976, 1718, 1690, 1614, 1442, 1403, 1363,

1281, 1243, 1174, 1114, 1003 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56 (s, 9H), 3.92 (s, 3H), 4.21 (d, J = 17.1 Hz, 1H), 4.69 (dd, J = 4.6, 13.3 Hz, 1H), 5.26 (d, J = 13.8 Hz, 1H), 5.36 (d, J = 17.1 Hz, 1H), 5.99 (br, 1H), 7.11 (d, J = 5.1 Hz, 2H), 7.26–7.28 (m, 3H), 7.76 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3, 37.9, 47.9, 51.1, 52.2, 82.2, 125.7, 126.7, 127.3, 128.4, 129.2, 130.2, 135.1, 135.8, 137.7, 140.7, 154.2, 166.7; MS (FAB+): m/z 435 $[M + H]^+$; HRMS Calcd. for $C_{24}H_{27}N_4O_4$ $[M + H]^+$ 435.2032, found 435.1997.

General procedure for Boc-deprotection

To a solution of Boc-protected product **2″** (0.135 mmol) in dry DCM (2 mL) was added trifluoroacetic acid (0.1 mL, 1.35 mmol) at 0 °C under argon atmosphere. The reaction mixture was allowed to reach to room temperature during 1–1.5 h. After completion of the reaction (TLC), the solvent was evaporated to dryness. The residue was treated with saturated $NaHCO_3$ solution followed by extraction with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), then dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified through silica gel (100–200 mesh) column chromatography (ethyl acetate–petroleum ether) to afford the purified product **2″**.

(6*S*)-3-(4-Methoxy-phenyl)-6-phenyl-4,5,6,7-tetrahydro[1,2,3]-triazolo[1,5-*a*]pyrazine (2″a). Yield: 98%; yellow solid, m.p.: 127–129 °C; $[\alpha]_D^{20}$ +111.68 (*c* 0.2, $CHCl_3$); IR (KBr): ν_{max} 3289, 2929, 2102, 1680, 1611, 1556, 1501, 1457, 1296, 1247, 1177, 1113, 1030 cm^{-1}; ^1H NMR (pyridine-d_5, 600 MHz): δ 3.74 (s, 3H), 4.18 (dd, J = 3.9, 10.5 Hz, 1H), 4.29 (t, J = 11.4 Hz, 1H), 4.39 (d, J = 15.6 Hz, 1H), 4.65 (d, J = 15.6 Hz, 1H), 4.79 (dd, J = 3.9, 12.3 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 8.01 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.5, 52.7, 55.3, 57.1, 114.3, 123.9, 126.8, 127.1, 127.4, 128.7, 129.1, 138.8, 141.3, 159.2; ESI-MS: m/z 307.18 $[M + H]^+$, 329.15 $[M + Na]^+$; HRMS Calcd. for $C_{18}H_{18}N_4ONa$ $[M + Na]^+$ 329.1378, found 329.1380.

(6*S*)-3-(4-Methoxycarbonyl-phenyl)-6-phenyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazine (2″m). Yield: 96%; light yellow solid, m.p.: 193–195 °C; $[\alpha]_D^{20}$ +190.56 (*c* 0.2, $CHCl_3$); IR (KBr): ν_{max} 3318, 2945, 1718, 1680, 1442, 1277, 1184, 1105, 1006 cm^{-1}; ^1H NMR (pyridine-d_5, 600 MHz): δ 3.86 (s, 3H), 4.23 (dd, J = 3.6, 10.8 Hz, 1H), 4.33 (t, J = 11.4 Hz, 1H), 4.42 (d, J = 16.2 Hz, 1H), 4.70 (d, J = 16.2 Hz, 1H), 4.82 (dd, J = 3.9, 12.3 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.65 (d, J = 7.8 Hz, 2H), 8.13 (d, J = 8.4 Hz, 2H), 8.28 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 42.6, 52.1, 52.8, 57.0, 125.7, 126.8, 128.8, 128.9, 129.0, 129.1, 130.2, 135.7, 138.6, 140.4, 166.8; ESI-MS: m/z 335.16 $[M + H]^+$, 357.14 $[M + Na]^+$; HRMS Calcd. for $C_{19}H_{18}N_4O_2Na$ $[M + Na]^+$ 357.1327, found 357.1351.

(6*S*)-3-(4-Bromo-phenyl)-6-phenyl-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyrazine (2″n). Yield: 91%; white solid, m.p.: 195–197 °C; $[\alpha]_D^{20}$ +88.05 (*c* 0.5, $CHCl_3$); IR (KBr): ν_{max} 3298, 3036, 2878, 1478, 1322, 1233, 1073, 1001 cm^{-1}; ^1H NMR (pyridine-d_5, 600 MHz): δ 4.19 (dd, J = 3.9, 10.5 Hz, 1H), 4.30 (t, J = 11.4 Hz, 1H), 4.36 (d, J = 16.2 Hz, 1H), 4.63 (d, J = 16.2 Hz, 1H), 4.80 (dd, J = 3.6, 12.0 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.5 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 42.5, 52.8, 57.0, 121.6, 126.8, 127.5, 128.1, 128.8, 129.1, 130.2, 132.0, 138.6, 140.4; MS (FAB+): m/z 355 and 357 $[M + H]^+$, 377 and 379 $[M + Na]^+$; HRMS Calcd. for $C_{17}H_{15}BrN_4$ $[M^+]$ 354.0480, found 354.0502.

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15 In a control experiment, the acyclic intermediate **D** [R_1+ R_2 = -$(CH_2)_3$-, PG = -$SO_2C_6H_4$Me-*p*, Ar = -C_6H_4OMe-*p*], the precursor intermediate compound of product **3aa**, was isolated with 65% yield by the reaction between azido-alkyne **4a** and iodide **5a** under the optimised reaction conditions except that no heating was performed and stirring was done at rt for 1.0 h. Interestingly, the elimination of CuI from this reaction afforded the intermediate **D**, albeit only with 16% yield even after stirring at rt for 14 h. This underlines the crucial role of CuI in these reactions. Thus, this situation is somewhat different from our earlier observations (see reference 13b) dealing with *O*-propargylated systems.

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20 Heating of acyclic intermediate **D** [R_1+R_2 = -$(CH_2)_3$-, PG = -$SO_2C_6H_4$Me-*p*, Ar = -C_6H_4OMe-*p*] at 95 °C in DMF without any catalyst yielded the cycloadduct **3aa** only in 21% yield even after 13 h, along with recovery of the starting material (78%). However, the desired cycloaddition affording the product **3aa** occurred when intermediate **D** was heated at 95 °C in DMF in the presence of 5 mol% $Pd(OAc)_2$ and 20 mol% PPh_3 for 1.5 h (91% yield) or in the presence of 5 mol% $Pd(OAc)_2$ alone for 3 h (93% yield). In the latter case with phosphine free system, preactvation of Pd(II) to Pd(0) might occur while heating $Pd(OAc)_2$ in presence of trace amount of dimethylamine (see: I. P. Beletskaya, and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009) which is being produced from the decomposition of DMF at elevated temperature or as contaminant in the DMF (see: K. K. Balasubramanian, S. Selvaraj and P. S. Venkataramani, *Synthesis*, 1980, 29).

