Intramolecular azide-alkyne [3 + 2] cycloaddition: versatile route to new heterocyclic structural scaffolds†

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Investigating the relatively unexplored intramolecular version of the azide-alkyne [3 + 2] cycloaddition, the present studies demonstrate the utility of the above reaction in the synthesis of a variety of as yet unreported heterocyclic structural scaffolds. The approach involved initial installation of strategic azide and alkyne moieties on a common structural framework, followed by their intramolecular cycloaddition studies. The pivotal azidoalkyne intermediates were efficiently accessed from a variety of easily available starting materials such as olefins, epoxides, amino acids, amino alcohols, ketones *etc.* The key reactions for incorporation of the azide functionality into the desired framework involved azidolysis of epoxides, displacement of hydroxy groups with azide nucleophiles, and diazo transfer on amine. Attachment of the desired alkyne functionalities was accomplished by either *N*-, or, *O*-alkylation with appropriate propargylic halides. The azidoalkynes thus prepared underwent smooth intramolecular cycloaddition, resulting in a variety of novel triazolooxazine and triazolopyrazine derivatives. Interestingly, unlike in the intermolecular version, metal catalysis was not necessary for the performance of the above cycloadditions. It is expected that the results from the present studies and its further extension will provide a potentially fertile pathway to a variety of unique chemical entities of structural and biological significance.

Introduction

Initially studied by Huisgen in the 1960's,[1] the 1,3-dipolar cycloaddition of azides and alkynes is the most efficient pathway for the synthesis of 1,2,3-triazoles (Fig. 1).[2] In recent years, the chemistry of the above class of heterocycles has gained new significance due to their varied applications in chemical, biological, medicinal and materials science. 1,2,3-Triazole-containing compounds are variously used as chemotherapeutic agents, synthetic intermediates for bioactive compounds, agrochemicals, optical brighteners, photostabilizers, corrosion inhibitors, and metal chelators *etc.*[2]

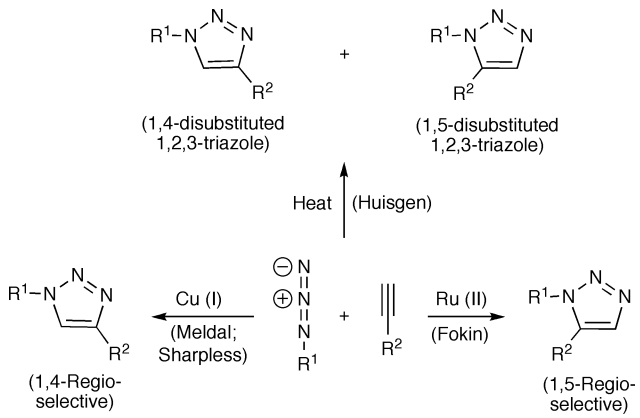

Fig. 1 1,3-Dipolar azide-alkyne cycloaddition.

During 2001–2002, a pioneering discovery of a copper catalyzed version of the azide-alkyne cycloaddition, made independently by the research groups of Meldal and Sharpless,[3,4] facilitated a more efficient and regioselective performance of the cycloaddition. Unlike in the uncatalyzed reaction, the Cu(I) catalyzed 1,3-dipolar cycloaddition results in a highly regioselective formation of the 1,4-disubstituted triazole (Fig. 1), while also dramatically accelerating the reaction rate and lowering the reaction temperature. Subsequently, in another remarkable development complementary to the Cu-catalyzed method, Fokin and coworkers reported a Ru(II) catalyzed azide-alkyne cycloaddition,[5] leading to the exclusive formation of the corresponding 1,5-disubstituted regioisomeric 1,2,3-triazoles (Fig. 1).

A prototypical 'click reaction', the efficiency and versatility of the metal catalyzed azide-alkyne 1,3-dipolar cycloadditions have resulted in an exponential growth in publications describing various applications of this reaction in organic synthesis, drug discovery efforts, bioconjugation, polymer chemistry, and materials science disciplines.[6]

However, in spite of this widespread utility, a large majority of the contemporary investigations and related publications on the azide-alkyne 1,3-dipolar cycloadditions involve the *intermolecular version* of the reaction,[6] whereas, studies directed at the corresponding *intramolecular version*[7] remains relatively limited.[8] Additionally, among the various instances of intramolecular azide-alkyne cycloadditions, majority of the reported studies were focused on the synthesis of specific target molecules, rather than on a systematic general investigation of the potential and application of the intramolecular variant of this cycloaddition in organic synthesis.[7]

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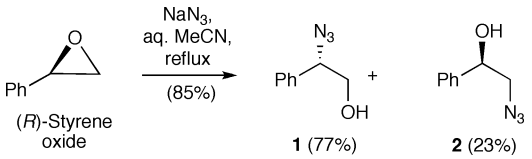
The untapped potential of the intramolecular azide-alkyne cycloadditions in the rapid construction of unique heterocyclic compounds renders exploration of this reaction a worthwhile endeavor. Accordingly, the present research reports the results of a systematic investigation involving the largely unexplored intramolecular azide-alkyne 1,3-dipolar cycloaddition. Details of these studies, leading to the synthesis of several novel molecular scaffolds/new chemical entities, are described herein.

Results and discussion

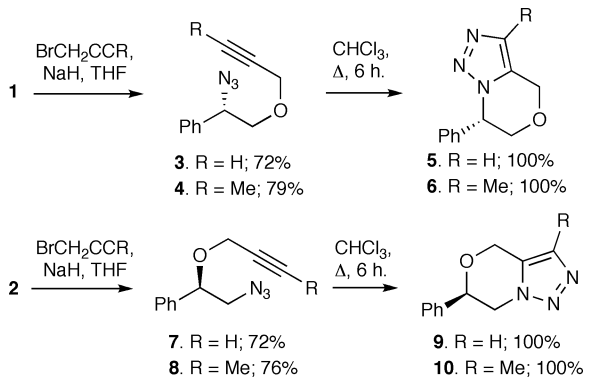
To ascertain the feasibility of the proposed plan, general strategies for initial construction of appropriately functionalized intramolecular cycloaddition precursors, containing strategically located azide and alkyne functionalities on the same structural framework were investigated. The approach entailed conversion of easily available starting materials, such as epoxides, olefins, and ketones *etc.* to variously substituted 'azido-alkyne' intermediates, and their subsequent utilization as probes to study the desired intramolecular 1,3-dipolar cycloaddition.

Ring opening of epoxides with azide nucleophiles is among the most frequently used reactions for the formation of vicinal azido alcohols (azidohydrins).[9] Accordingly, it was decided to employ the above reaction protocol to synthesize the initial azido-alkyne precursors for the intended studies. Thus, when (*R*)-styrene oxide was subjected to ring opening with sodium azide in aqueous acetonitrile, the corresponding regioisomeric 1,2-azidoalcohol derivatives **1** and **2** (Scheme 1) were isolated as the major and minor (approximately 3:1) products respectively. Although possible,[9] regioselective azidolysis of the epoxide ring was not pursued at this juncture, as it was intended to use both the regioisomeric products for the subsequent studies. The spectral and analytical data of **1**and **2** were in good agreement with the literature reported values,[10] confirming the assigned structures and stereochemical integrity.



Scheme 1

Installation of the alkyne functionality on the azidoalcohol **1** was achieved by standard base mediated *O*-alkylation with appropriate propargylic bromides, leading to efficient formation of the pivotal azido-alkynes **3** and **4** respectively (Scheme 2). Having obtained the appropriate substrates for our desired intramolecular cycloaddition studies, thermally induced cyclization of these azido-alkynes was next investigated. Gratifyingly, in refluxing chloroform, both **3** and **4** underwent facile [3 + 2] intramolecular cycloaddition, resulting in the expected ring-fused bicyclic triazolooxazines **5** and **6** in quantitative yields. Unlike in the intermolecular azide-alkyne 1,3-dipolar cycloadditions, the strategic intramolecular positioning of the two reacting functionalities eliminated the need of any metal catalysis, and the present cycloaddition could be efficiently performed at a moderate reaction temperature. Interestingly, the cycloaddition was found to work equally well with the mono-substituted alkyne **3** (R = H)

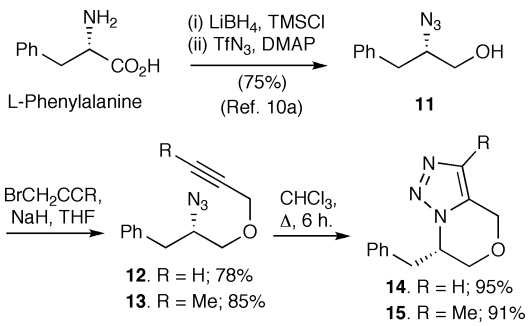


Scheme 2

as well as with the alkyne **4** (R = Me) with a terminal substituent. Another noteworthy feature of the above reaction was the clean and complete conversion of the starting azido-alkynes to the corresponding cyclized products (crystalline solids after solvent removal), thereby avoiding the need for any further purification.

Following a similar sequence of reactions as above, *O*-alkylation of the secondary hydroxyl functionality of azidoalcohol **2** to the corresponding azido-alkynes **7** and **8** (Scheme 2), followed by their thermal cyclization under the described conditions resulted in the clean formation of the respective triazolooxazines **9** and **10**.

Employing a representative amino acid as a chiral pool starting material, its application in the stereodefined formation of bicyclic triazolooxazines was next investigated. Trifluoromethanesulfonyl azide mediated diazo transfer to amines is an efficient and convenient method for the conversion of amines to azides.[11] Accordingly, following a reported method,[10a] L-phenylalanine was converted to the corresponding enantiopure azidoalcohol derivative **11** (Scheme 3) in good yield. Formation of the propargylic ether derivatives **12** and **13** *via O*-alkylation and subsequent cyclization in refluxing chloroform yielded the respective triazolooxazines **14** and **15** in good overall yields.



Scheme 3

Since a large number of natural and non-natural amino acids are readily available, the above method can provide a versatile route towards the stereoselective synthesis of variously substituted triazolooxazine derivatives.

To extend the scope of the above method, reactions of cyclic azido alcohols were next investigated. Accordingly, azidolysis of the cyclohexene-derived epoxide **17** (also available commercially) provided the *trans*-1,2-azido alcohol derivative **18** (Scheme 4). Subsequent *O*-alkylative installation of the propargylic functionalities, forming the desired azido-alkyne intermediates **19** and

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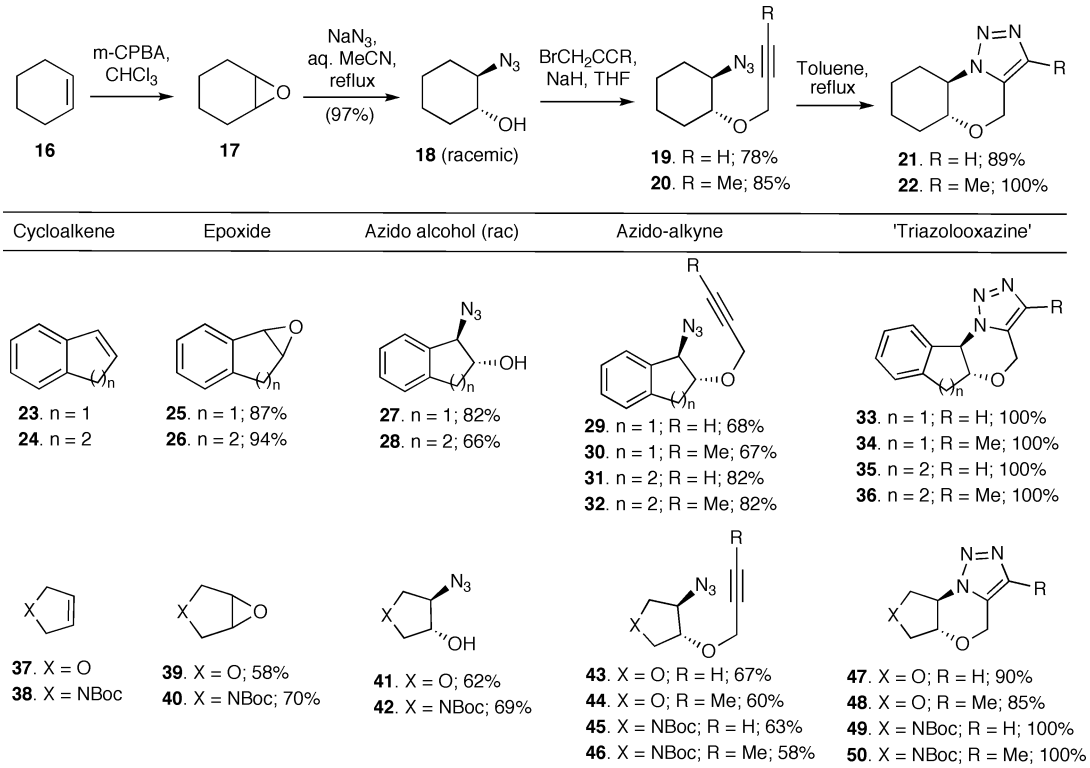
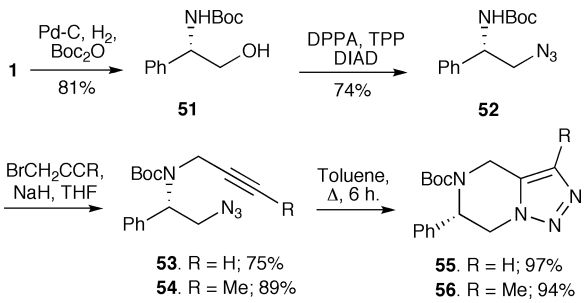


Scheme 4

20, and cycloaddition in refluxing toluene provided the corresponding tricyclic triazolooxazine derivatives **21** and **22** in high yields. The above method was equally successful with the azidoalkynes **29–32**, derived from the bicyclic olefins indene (**23**) and 1,2-dihydronaphthalene (**24**) respectively, leading to the construction of the corresponding tetracyclic triazolooxazine derivatives **33–36** (Scheme 4) in good overall yields. It is to be noted that, employing standard asymmetric epoxidation protocols (Jacobsen-Katsuki, Shi, Yamamoto *etc.*),[12] enantiopure versions of the above cyclic epoxides can also be obtained easily, allowing access to the corresponding triazolooxazine products in a stereoselective manner.

Subjecting the heterocyclic olefins **37** and **38** to the above reaction sequence resulted in the expected formation of the corresponding tri-heterocyclic ring-fused products **47–50** (Scheme 4). While this work was in progress, Pericàs and coworkers reported a strategically similar synthetic route, leading to the tricyclic triazoles **49** and **50** in enantiopure form.[7a] Interestingly, some of the above class of tricyclic triazoles, as synthesized by Pericàs, exhibited nanomolar range affinity for the physiologically important sigma-1 receptor.[7a]

Aiming further diversification of product structural features, syntheses of the corresponding 'all-aza' heterocyclics were next investigated. Accordingly, a one-pot hydrogenation and *in situ* Boc-protection of the azido alcohol **1** provided the corresponding *N*-Boc amino alcohol **51** (Scheme 5) in high yield. *N*-Boc amino alcohols similar to **51** can also be easily obtained by carboxylic acid reduction and amine protection of the corresponding enantiopure amino acids.[13] Displacement of the hydroxy group of **51** to provide the corresponding azide **52** was accomplished by a modified Mitsunobu protocol.[14]



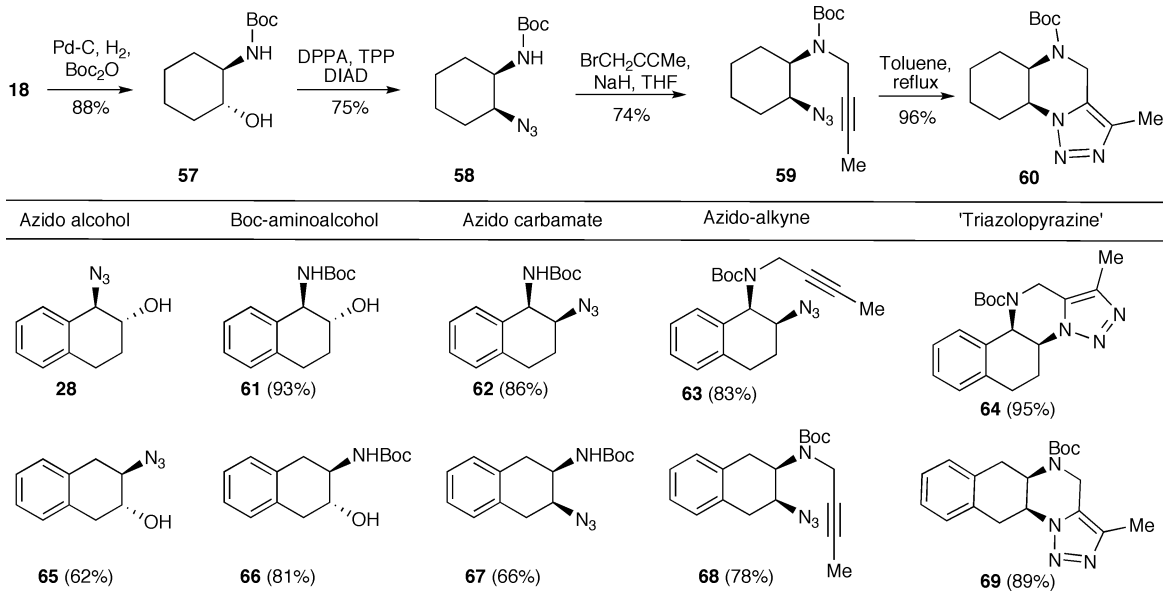
Scheme 5

Subsequent base mediated *N*-alkylation of **52** with propargyl bromide and 1-bromo-2-butyne respectively, afforded the corresponding *N*-Boc-azidoalkynes **53** and **54**. Gratifyingly, thermal cyclization of **53** and **54** resulted in the clean formation of the desired triazolopyrazine derivatives **55** and **56** in high yields.

A noteworthy feature of the above triazolopyrazines is the presence of an additional amino functionality (*N*-Boc) in the molecule, which provides opportunities for further derivation at this site *via* easy deprotection and subsequent reactions (acylation, alkylation *etc.*) of the amine.

Continuing with the studies, the cyclohexene-derived azidoalcohol **18** was similarly converted to the *N*-Boc-aminoalcohol derivative **57** (Scheme 6), followed by its transformation to the corresponding azide **58**. Attachment of alkyne substituent on the carbamate nitrogen, forming the *cis*-azidoalkyne **59**, and subsequent intramolecular cycloaddition yielded the tricyclic triazolopyrazine **60**.

It is to be noted that, unlike in the *trans*-fused tricyclic triazolooxazine class of compounds as described earlier (Scheme 4),

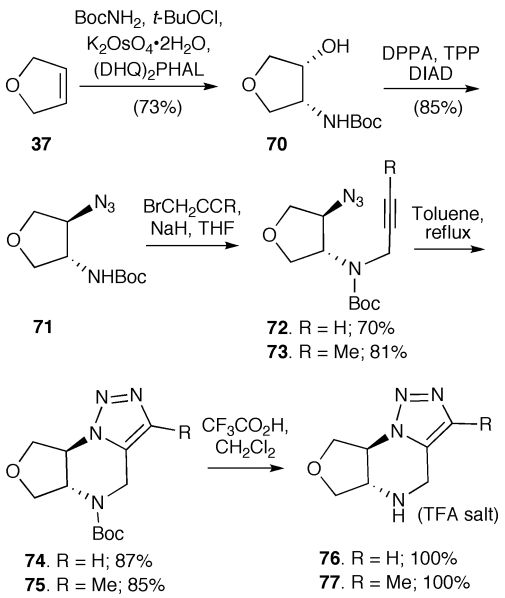


Scheme 6

the above triazolopyrazines are made up of a *cis*-fused bicyclic structural framework.

Extending the above protocol to the bicyclic azidoalcohols **28** and **65**, their initial conversion to the corresponding 1,2-azidocarbamates **62** and **67** (Scheme 6) was followed by formation of the *cis*-azido-alkynes **63** and **68** respectively. The azidoalkynes underwent smooth [3 + 2] cycloaddition, culminating in the corresponding tetracyclic ring-fused triazolopyrazines **64** and **69**.

In subsequent studies directed at stereoselective syntheses of triazoloheterocyclic products, Sharpless asymmetric aminohydroxylation (SAAH) was employed to form the pivotal 1,2-aminoalcohol precursors in enantiopure form.[15] Thus, standard SAAH of commercially available 2,5-dihydrofuran (**37**) provided the expected *cis*-1,2-aminoalcohol derivative **70** (Scheme 7) with high stereocontrol.[16] Conversion of the hydroxy group of



Scheme 7

70 to the corresponding azide **71** under Mitsunobu conditions, and *N*-alkylation of the carbamoyl functionality with propargylic bromides yielded the *trans*-1,2-azidoalkyne intermediates **72** and **73**.

Subsequent cyclization in refluxing toluene completed the synthesis of the unique tricyclic heterocyclics **74** and **75** in high yields. As evident, the above aminohydroxylation protocol leads to a *cis*-1,2-disubstituted aminoalcohol adduct **70**, which on subsequent Mitsunobu reaction forms the corresponding *trans*-1,2-disubstituted 'azido-amine' intermediate **71**, consequently providing access to the *trans*-fused triazolopyrazine product. The epoxide-based synthetic route (Scheme 6) and the aminohydroxylation-based route (Scheme 7) are thus complementary to each other, leading to the synthesis of the corresponding *cis*-fused and *trans*-fused cyclic products respectively. To ascertain the viability of *N*-Boc deprotection, **74** and **75** were treated with trifluoroacetic acid under standard conditions, resulting in the clean formation of the free amino derivatives **76** and **77** (as their trifluoroacetate salts). As mentioned previously, the availability of the free amine functionalities in these triazolopyrazine derivatives provide an additional diversification site, an attractive feature for possible applications in the synthesis of combinatorial libraries.

An interesting extension of the above approach resulted in the rapid construction of a polyazaheterocycle mimic of the tetracyclic structural scaffold as present in various steroidal compounds. Thus, Sharpless asymmetric aminohydroxylation of 1,2-dihydronaphthalene (**24**)[17] to the corresponding *cis*-1,2-aminoalcohol adduct **78** (Scheme 8) was followed by its conversion to the *trans*-azidocarbamate derivative **79**. A subsequent sequence of reactions involving *N*-alkylation with 1-bromo-2-butyne, followed by cycloaddition of the resulting azidoalkyne intermediate yielded the tetracyclic triazolopyrazine derivative **80** in good overall yield. Finally, Boc-deprotection provided the free amine derivative **81** in quantitative yield. It is expected that, the above synthetic route can be easily manipulated to incorporate various substituents at positions 11- and 17- (steroid numbering),

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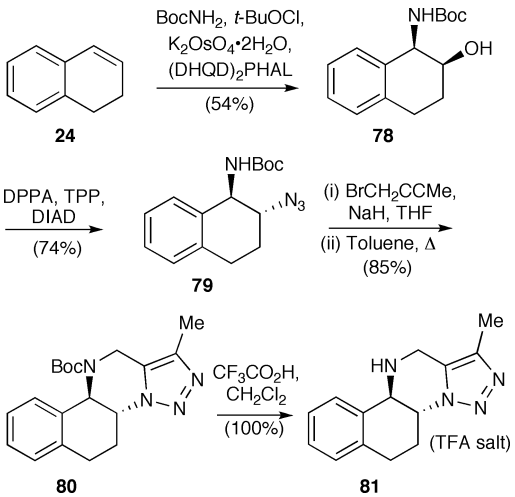
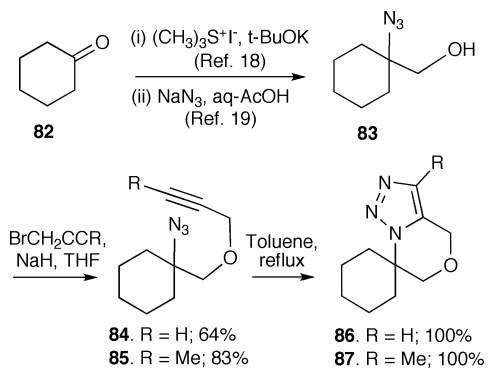


Scheme 8

via *N*(11)-alkylation and use of appropriate propargylic halides respectively, allowing access to a unique class of steroid mimic compounds of potential biochemical and medicinal significance.

To further expand the utility of the present intramolecular azide-alkyne cycloaddition protocol in the synthesis of new structural scaffolds, the viability of ketone-derived epoxides as azidoalkyne precursor was next investigated. Accordingly, in a representative reaction, following reported procedures, initial conversion of cyclohexanone (**82**) to the corresponding spirocyclic epoxide[18] and its subsequent azidolysis provided the known azidoalcohol derivative **83** (Scheme 9).[19] Subsequent *O*-alkylation with the respective propargylic halides resulted in the corresponding azidoalkyne intermediates **84** and **85**. Finally, thermal cycloaddition under described conditions yielded the spirocyclic triazolooxazine derivatives **86** and **87** in high yields.



Scheme 9

Potential extension of the above method to the large pool of easily available cyclic and acyclic ketones can provide ready access to a wide variety of the corresponding spirocyclic or, *gem*-disubstituted triazolooxazines respectively.

Conclusions

The present studies, involving a systematic investigation of the intramolecular version of [3 + 2]-azide-alkyne cycloaddition, allowed rapid access to a variety of novel heterocycles. In an important deviation from the contemporary intermolecular version of the above reaction, in the present intramolecular reactions, metal catalysis was not required to perform the cycloaddition. A majority of the polycyclic products synthesized during this study represent heterocyclic structural scaffolds as yet unknown in the literature. Some of the other notable features of the present strategy and approach are, (i) formation of the pivotal 1,2-azidoalkyne (or, 1,2-aminoalkyne) intermediates from a large pool of readily available starting materials such as olefins, epoxides, amino acids, ketones *etc.* (ii) application of the method in the stereoselective formation of various end products, *via* utilization of easily available chiral starting materials, or employment of standard asymmetric synthetic protocols, (iii) simple, robust, and versatile reactions, leading to relatively short-step synthetic routes to polycyclic and polyfunctional heterocycles, (iv) formation of drug-like products with high local density of H-bond donor acceptor heteroatoms, (v) formation of products with various diversification sites, with potential application in combinatorial library synthesis.

The above results complements and extends the scope, versatility, and utility of the azide-alkyne dipolar cycloaddition reactions. As new chemical entities continue to be a major focus of contemporary drug discovery endeavors, it is expected that the present studies and their further extension will provide a potentially fertile source of a variety of structurally unique compounds of chemical and medicinal significance.

Experimental

General procedure for olefin epoxidation

To an ice-cooled solution of the olefin (1 equiv) in chloroform (5% solution) was added an equal volume of saturated aq. $NaHCO_3$ solution. To this stirred mixture was added m-CPBA (77%) (1 equiv) in small portions over 10 min. After stirring for 5 hours at room temperature, the reaction mixture was once again cooled to 0 °C, followed by portion wise addition of m-CPBA (0.5 equiv). The mixture was stirred at room temperature till the disappearance of starting material (tlc monitoring). The organic layer was separated, washed sequentially with saturated sodium thiosulfate solution and water, and dried over anhydrous sodium sulfate. After removal of solvent, the crude product was purified by flash column chromatography over silica gel using ethyl acetate/hexane as eluent.

(*R*)-Styrene oxide and the cyclohexene epoxide **17** are available commercially. The spectral and analytical data of the known epoxides **25**, **26**, **39**, and **40** were in good agreement with the reported values.[20]

General procedure for the azidolysis of epoxides

To a stirred solution of the epoxide (1 equiv) in acetonitrile (10% solution) an equal volume of water was added, followed by addition of sodium azide (3 equiv) in one portion. The resulting mixture was stirred at 80 °C till the disappearance of starting material (tlc monitoring). After completion of reaction, the organic layer was separated and the aqueous layer was extracted with diethyl ether (three times). The combined organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. After removal of solvent, the crude product was purified

by flash chromatography over silica gel using ethyl acetate/hexane as eluent.

The spectral and analytical data of the azidoalcohols thus synthesized (**1**, **2**, **27**, **28**, **41**, **42** and **65**) were in good agreement with the literature reported values.[10,21]

General procedure for conversion of azide to the corresponding *N*-Boc derivative

The azido compound (1 equiv) was dissolved in anhydrous EtOAc (5% solution), to which 10% Pd-C (approximately 0.3 g of catalyst/1g of azido compound) was added followed by di-*tert*-butyldicarbonate (1.4 equiv) and Et_3N (20 μL, catalytic). The reaction was allowed to stir under hydrogen atmosphere at room temperature overnight. The mixture was then filtered and the residue washed thoroughly with EtOAc. The combined filtrate was concentrated under vacuum and the crude residue was purified by flash chromatography using ethyl acetate/hexane as eluent.

The spectral and analytical data of the known *N*-Boc aminoalcohols **51**, **57**, **61**, and **66** were in good agreement with the reported values.[22]

General procedure for hydroxy to azide conversion

To an ice-cooled solution of the hydroxy compound (1 equiv) in anhydrous THF (5% solution) was added diisopropylazodicarboxylate (1.4 equiv) and triphenylphosphine (1.4 equiv), followed by dropwise addition of diphenylphosphoryl azide (1.4 equiv). After completion of addition, the reaction mixture was brought to room temperature and then stirred 50 °C for 6–8 hours (tlc monitoring). Excess solvent was removed under vacuum and the residue was purified by flash column chromatography using ethyl acetate/hexane as eluent.

The spectral and analytical data of the azide derivatives thus synthesized (**52**, **58**, and **62**) were in good agreement with the corresponding literature reported values.[23]

General procedure for the Sharpless asymmetric aminohydroxylation

To a magnetically stirred room temperature solution of *tert*-butyl carbamate (3.63 g, 31.0 mmol) in *n*-propyl alcohol (40 mL) was added an aqueous solution of NaOH (1.22 g, 30.5 mmol in 75 mL of H_2O), followed by a freshly prepared solution of *tert*-butyl hypochlorite (3.31 g, 30.5 mmol, *ca.* 3.5 mL). Subsequently, a solution of the appropriate ligand [$(DHQ)_2PHAL$, or, $(DHQD)_2PHAL$] (400 mg, 0.5 mmol, 5 mol%) dissolved in *n*-propyl alcohol (35 mL) was added to the reaction mixture and stirred until homogenous (approx. 10 min). The olefinic substrate (10.0 mmol) and the osmium catalyst $K_2OsO_2(OH)_4$ (147 mg, 0.4 mmol, 4 mol%) was then added sequentially to the mixture and stirring continued for 1 h. The reaction mixture was diluted with EtOAc (70 mL), the organic layer separated, and the aqueous layer was extracted with EtOAc (3 times). The combined organic extracts were washed with water and brine, dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by flash column chromatography using ethyl acetate/hexane as eluent.

General procedure for *O*-alkylation

To an ice-cooled suspension of sodium hydride (60% dispersion in mineral oil) (1.5 equiv) in anhydrous THF (5 mL) was added a solution of the hydroxy compound (1 equiv) in THF (10% solution) dropwise, followed by stirring at the same temperature for 30 min. Propargyl bromide or 1-bromo-2-butyne (1.3 equiv) was then added to the reaction mixture dropwise. After stirring at 0 °C for 30 min, the reaction was allowed to attain room temperature and stirred overnight. The reaction was quenched by careful addition of saturated ammonium chloride solution, followed by extraction of the resulting mixture with ethyl acetate (three times). The extracts were combined, washed with brine and dried over anhydrous sodium sulfate. After removal of solvent, the crude product was purified by flash chromatography over silica gel using ethyl acetate/hexane as eluent. Some of the above azidoalkynes were found to undergo cyclization/decomposition on storage, therefore, these compounds were generally subjected to the next reaction immediately after purification.

General procedure for *N*-alkylation

To an ice-cooled suspension of sodium hydride (60% dispersion in mineral oil) (1.5 equiv) in anhydrous DMF (5 mL) was added a solution of the Boc-amino compound (1 equiv) in DMF (10% solution) dropwise, followed by stirring at the same temperature for 30 min. Propargyl bromide or 1-bromo-2-butyne (1.3 equiv) was then added to the reaction mixture dropwise. After stirring at 0 °C for 30 min, the reaction was allowed to attain room temperature and stirred for another 2–3 h (tlc monitoring). After quenching the reaction with saturated ammonium chloride solution, the mixture was extracted with diethyl ether (five times). The extracts were combined, washed with brine and dried over anhydrous sodium sulfate. After removal of solvent, the crude product was purified by flash chromatography over silica gel using ethyl acetate/hexane as eluent. As several of the above azidoalkynes were found to undergo cyclization/decomposition on storage, these compounds were generally subjected to the next reaction immediately after purification.

General procedure for the intramolecular azide-alkyne cycloaddition

A 10% solution of the azidoalkyne derivative in chloroform (or toluene) was refluxed between 6 h–overnight (tlc monitoring). After completion of reaction, excess solvent was removed under vacuum and the residual solid triturated with CH_2Cl_2–Et_2O to afford the pure product.

General procedure for Boc-deprotection

The Boc-protected compound was dissolved in CH_2Cl_2–CF_3CO_2H (1:2, 10% solution) and stirred at room temperature for 1 h. After removal of solvent under vacuum, the residue was triturated with dichloromethane to afford the pure product as the corresponding TFA salt.

Representative characterization Data

(*S*)-(1-Azido-2-(prop-2-ynyloxy)ethyl)benzene (3). Colorless oil; $[\alpha]_D$ 71.6 (*c* 1.1, $CHCl_3$); IR (thin film) 2359, 2341 cm^{-1};

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^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.35 (m, 5H), 4.77 (dd, J = 8.6, 4.2 Hz, 1H), 4.26 (dd, J = 8.4, 2.4 Hz, 2H), 3.80 (dd, J = 10.1, 4.2 Hz, 1H), 3.74 (dd, J = 10.1, 8.6 Hz, 1H), 2.48 (t, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 136.4, 128.9, 128.8, 128.1, 127.1, 127.0, 79.1, 75.1, 73.5, 65.1, 58.6. HRMS (ESI, m/z) calculated for $C_{11}H_{12}N_3O$ (MH^+) 202.0980, found 202.0938.

(*S*)-(1-Azido-2-(but-2-ynyloxy)ethyl)benzene (4). Colorless oil; $[\alpha]_D$ 97.2 (c 1.4, $CHCl_3$) IR (thin film) 2241, 2098 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.35 (m, 5H), 4.76 (dd, J = 8.8, 4.4 Hz, 1H), 4.27–4.19 (m, 2H), 3.77 (dd, J = 10, 8.8 Hz, 1H), 3.70 (dd, J = 10, 8.8 Hz, 1H), 1.87 (t, J = 2.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 136.6, 129.0, 128.8, 128.6, 127.1, 127.0, 83.2, 74.5, 733, 65.2, 59.1, 3.7. HRMS (ESI, m/z) calculated for $C_{12}H_{14}N_3O$ (MH^+) 2216.1137, found 216.1124.

(*S*)-7-Phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (5). White solid; mp. 90–91 °C; $[\alpha]_D$ 67.9 (c 1.2, $CHCl_3$); IR (thin film) 2359, 2343 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (s, 1H), 7.42–7.35 (m, 3H), 7.17–7.14 (m, 2H), 5.66 (t, J = 5.0 Hz, 1H), 5.10 (d, J = 15.1 Hz, 1H), 5.04 (d, J = 15.1 Hz, 1H), 4.30 (dd, J = 12.1, 4.3 Hz, 1H), 4.08 (dd, J = 12.1, 5.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 136.6, 131.3, 129.0, 128.9, 128.8, 128.1, 127.0 (2C), 70.6, 62.6, 59.8. HRMS (ESI, m/z) calculated for $C_{11}H_{12}N_3O$ (MH^+) 202.0980, found 202.0925.

(*S*)-3-Methyl-7-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (6). White solid; mp. 101–103 °C; $[\alpha]_D$ 77.1 (c 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.31 (m, 3H), 7.13–7.10 (m, 2H), 5.56 (t, J = 4.5 Hz, 1H), 4.96 (d, J = 14.8 Hz, 1H), 4.89 (d, J = 14.8 Hz, 1H), 4.20 (dd, J = 12.1, 4.3 Hz, 1H), 3.99 (dd, J = 12.1, 5.5 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 135.5, 135.4, 135.2, 134.5, 128.5, 127.6,127.4,127.2, 68.8, 61.2, 58.5, 8.0. HRMS (ESI, m/z) calculated for $C_{12}H_{14}N_3O$ (MH^+) 216.1137, found 216.1126.

(*R*)-6-Phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (9). White solid; mp. 136–137 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (s, 1H), 7.51–7.43 (m, 5H), 5.27 (d, J = 15.2 Hz, 1H), 5.03 (d, J = 15.2 Hz, 1H), 4.91 (dd, J = 10.6, 3.4 Hz, 1H), 4.76 (dd, J = 13.1, 3.3 Hz, 1H), 4.33 (dd, J = 13.1, 10.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 136.9, 130.4, 129.1, 129.0, 128.8, 128.2, 126.3, 126.1, 75.7, 62.3, 51.1. HRMS (ESI, m/z) calculated for $C_{11}H_{12}N_3O$ (MH^+) 202.0980, found 202.0980.

(*R*)-3-Methyl-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine (10). White solid; mp. 100–102 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33–7.31 (m, 3H), 7.13–7.10 (m, 2H), 5.56 (t, J = 4.5 Hz, 1H), 4.96 (d, J = 14.8 Hz, 1H), 4.89 (d, J = 14.8 Hz, 1H), 4.20 (dd, J = 12.1, 4.3 Hz, 1H), 3.99 (dd, J = 12.1, 5.5 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 135.5, 135.4, 135.2, 134.5, 128.5, 127.6, 127.4, 127.2, 68.8, 61.2, 58.5, 8.0. HRMS (ESI, m/z) calculated for $C_{12}H_{14}N_3O$ (MH^+) 216.1137, found 202.1126.

5a,6,7,8,9,9a-Hexahydro-4*H*-benzo[*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazine (21). As the precursor azidoalkyne **19** was found to undergo partial cyclization during chromatographic purification, it was subjected directly to the cycloaddition reaction step to afford the product **21** as a white solid; mp. 102–104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (s, 1H), 5.11 (d, J = 15.0 Hz, 1H), 4.91 (d, J = 15.0 Hz, 1H), 4.02–3.94 (m, 1H), 3.45 (ddd, J = 11.0, 9.4, 4.0 Hz, 1H), 3.08–3.01 (m, 1H), 2.22–2.15 (m, 1H), 2.00–1.90 (m, 2H), 1.70–1.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 130.8, 128.3, 78.6, 62.3, 61.1, 30.4, 28.1, 24.0, 23.9. HRMS (ESI, m/z) calculated for $C_9H_{14}N_3O$ (MH^+) 180.1137, found 180.1133.

3-Methyl-4,5a,6,10b-tetrahydroindeno[2,1-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazine (34). White solid; mp. 168–170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (d, J = 6.9 Hz, 1H), 7.39–7.34 (m, 3H), 5.22 (d, J = 14.7 Hz, 1H), 5.21 (d, J = 5.0 Hz, 1H), 5.05 (d, J = 14.7 Hz, 1H), 4.08 (ddd, J = 11.0, 6.6, 5.0 Hz, 1H), 3.27 (dd, J = 14.0, 6.6 Hz, 1H), 3.10 (dd, J = 14.0, 11.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 137.5, 135.1, 129.6, 128.7, 127.8, 127.2, 125.6, 125.2, 83.0, 64.2, 64.1, 33.6, 10.2. HRMS (ESI, m/z) calculated for $C_{13}H_{14}N_3O$ (MH^+) 228.1137, found 228.1125.

5a,6,7,11b-Tetrahydro-4*H*-naphtho[2,1-*b*][1,2,3]triazolo[1,5-*d*]-[1,4]oxazine (35). As the precursor azidoalkyne **31** was found to undergo partial cyclization during chromatographic purification, it was subjected directly to the cycloaddition reaction step to afford the product **35** as a white solid; mp. 121–122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (t, J = 3.4 Hz, 1H), 7.61 (s, 1H), 7.35–7.28 (m, 2H), 7.27–7.18 (m, 1H), 5.33 (d, J = 9.4 Hz, 1H), 5.18 (d, J = 14.8 Hz, 1H), 4.93 (d, J = 14.8 Hz, 1H), 3.90 (m, 1H), 3.18–3.07 (m, 2H), 2.48–2.36 (m, 1H), 2.18–2.07 (m, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 135.6, 132.3, 132.0, 128.5, 128.2, 128.1, 127.7, 126.5, 62.7 (2C), 61.5, 27.4, 26.2. HRMS (ESI, m/z) calculated for $C_{13}H_{14}N_3O$ (MH^+) 228.1137, found 228.1133.

5a,6,8,8a-Tetrahydro-4*H*-furo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]-oxazine (47). Low melting solid; IR (thin film) 2359, 2341 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.59 (s, 1H), 5.32 (d, J = 15.2 Hz. 1H), 5.11 (d, J = 15.2 Hz, 1H), 4.72 (dd, J = 8.0, 7.28 Hz, 1H), 4.43 (td, J = 9.6, 7.4 Hz, 1H), 4.22 (t, J = 7.3 Hz, 1H), 4.10 (m, 2H), 3.86 (dd, J = 10.0, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 130.7, 128.9, 79.6, 65.9, 65.6, 64.3, 60.0. HRMS (ESI, m/z) calculated for $C_7H_{10}N_3O$ (MH^+) 168.0733, found 168.0756.

***tert*-Butyl 3-methyl-5a,6,8,8a-tetrahydropyrrolo[3,4-*b*][1,2,3]triazolo[1,5-*d*][1,4]oxazine-7(4*H*)-carboxylate (50).** White solid; mp. 178–179 °C. ^{1}H NMR ($CDCl_3$, 400 MHz; rotameric mixture) δ 5.20 (d, J = 15.3 Hz, 1H), 5.00 (d, J = 15.3 Hz, 1H), 4.41 (dd, J = 9.9, 7.5 Hz, 1H), 4.32–4.23 (m, 1H), 3.99–3.89 (m, 2H), 3.54 (t, J = 10.3 Hz, 1H), 3.40–3.35 (m, 1H), 2.30 (s, 3H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz; rotameric mixture) δ 154.3, 137.9, 127.0, 80.7, 77.6, 63.8, 58.2, 45.6, 45.3, 28.4, 10.2. HRMS (ESI, m/z) calculated for $C_{13}H_{21}N_4O_3$ (MH^+) 281.1614, found 281.1602.

***tert*-Butyl 3-methyl-5a,6,7,8,9,9a-hexahydro-[1,2,3]triazolo[1,5-*a*]quinoxaline-5(4*H*)-carboxylate (60).** As the precursor azidoalkyne **59** was found to undergo partial cyclization during chromatographic purification, it was subjected directly to the cycloaddition reaction step to afford the product **60** as a white solid; mp. 166–167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz, rotameric mixture) δ 5.23 (br s, 1H), 4.37 (s, 1H), 4.17 (d, J = 13.2 Hz, 1H), 3.11 (d, J = 11.4 Hz, 1H), 2.22 (s, 3H), 1.81–1.70 (m, 1H), 1.69–1.55 (m, 2H), 1.53–1.47 (m, 1H), 1.45 (s, 9H), 1.40–1.01 (m, 4H); ^{13}C NMR ($CDCl_3$, 125.8 MHz, rotameric mixture) δ 154.2, 138.2, 126.3, 81.2, 56.0, 52.2, 50.7, 37.2, 29.7, 28.4, 27.3, 24.6, 24.2, 19.1, 10.2. HRMS (ESI, m/z) calculated for $C_{15}H_{25}N_4O_2$ (MH^+) 293.1977, found 293.1978.

***tert*-Butyl 1-methyl-5,6,10b,12-tetrahydrobenzo[*f*][1,2,3]triazolo-[1,5-*a*]quinoxaline-11(4a*H*)-carboxylate (64).** As the precursor azidoalkyne **63** was found to undergo partial cyclization during chromatographic purification, it was subjected directly to the cycloaddition reaction step to afford the product **64** as a white solid; mp. 161–163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 7.25–7.14 (m, 3H), 7.03 (br s, 2H), 5.95 & 5.74 (d, J = 3.8 Hz, 1H), 5.10 & 4.91 (d, J = 16.7 Hz, 1H), 4.82 (br s, 1H), 3.79 & 3.68 (d, J = 16.9 Hz, 1H), 3.35–3.17 (m, 1H), 2.78–2.52 (m, 2H), 2.35–2.24 (m, 1H), 2.17 (s, 3H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz, mixture of rotamers) δ 154.9, 137.7, 130.7, 129.4, 127.9, 127.2, 126.9, 126.8, 81.8, 54.1, 52.4, 36.4, 28.4, 25.0, 23.1, 10.1. HRMS (ESI, m/z) calculated for $C_{19}H_{25}N_4O_2$ (MH^+) 341.1977, found 341.1967.

***tert*-Butyl 3-methyl-5a,6,11,11a-tetrahydrobenzo[*g*][1,2,3]tria-zolo[1,5-*a*]quinoxaline-5(4*H*)-carboxylate (69).** As the precursor azidoalkyne **63** was found to undergo partial cyclization during chromatographic purification, it was subjected directly to the cycloaddition reaction step to afford the product **69** as a white solid; mp. 172–174 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, mixture of rotamers) δ 7.39–7.15 (m, 4H), 5.22 (d, J = 15.8 Hz, 1H), 4.44–4.37 (m, 1H), 4.18 (d, J = 15.8 Hz, 1H), 4.05 (dd, J = 16.4, 5.0 Hz, 1H), 3.89–3.80 (m, 1H), 3.68–3.53 (m, 2H), 3.15–3.06 (m, 1H), 2.36 (s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz, rotameric mixture) δ 154.8, 138.4, 137.9, 133.9, 133.5, 131.9, 129.9, 127.8, 127.0, 126.2, 126.1, 81.5, 61.3, 56.9, 56.5, 43.9, 37.2, 35.0, 32.3, 29.7, 28.4, 27.8, 26.1, 10.1. $C_{19}H_{25}N_4O_2$ (MH^+) 341.1977, found 341.1988.

***tert*-Butyl (3*R*,4*R*)-4-hydroxytetrahydrofuran-3-ylcarbamate (70).** Viscous oil; $[\alpha]_D$ −2.7 (*c* 0.7 $CHCl_3$); IR (thin film) 3410, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.01 (br s, 1H), 4.39 (br s, 1H), 4.25 (br s, 1H), 4.12–3.97 (m, 2H), 3.80 (d, J = 8.0 Hz, 1H), 3.52 (d, J = 7.7 Hz, 1H), 2.12 (d, J = 4.4 Hz 1H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 155.8, 80.1, 74.5, 70.9, 70.4, 53.6, 28.4. HRMS (ESI, m/z) calculated for $C_9H_{17}NO_4Na$ (MNa^+) 226.1055, found 226.1065.

***tert*-Butyl (3*S*,4*S*)-4-azidotetrahydrofuran-3-ylcarbamate (71).** White solid; mp. 86–87 °C; $[\alpha]_D$ −4.2 (*c* 1.1 $CHCl_3$); IR (thin film) 2099, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.74 (br s, 1H), 4.25–4.00 (m, 4H), 3.74 (d, J = 8.2 Hz, 1H), 3.67 (d, J = 9.7 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 154.9, 80.4, 71.5, 71.1, 66.3, 57.2, 28.3. HRMS (ESI, m/z) calculated for $C_9H_{17}N_4O_3$ (MH^+) 229.1301, found 229.1313.

***tert*-Butyl (3*S*,4*S*)-4-azidotetrahydrofuran-3-yl(but-2-ynyl)car-bamate (73).** Colorless oil; IR (thin film) 2224, 2104, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.40–4.35 (m, 2H), 4.16 (dd, J = 9.8, 6.4 Hz, 1H), 4.15–3.93 (m, 4H), 3.67 (dd, J = 9.8, 4.3 Hz, 1H), 1.83 (t, J = 2.4 Hz, 3H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 154.4, 81.3, 79.4, 75.3, 71.8, 68.9, 65.1, 63.3, 35.8, 28.4, 3.5. HRMS (ESI, m/z) calculated for $C_{13}H_{20}N_4O_3Na$ (MNa^+) 303.1433, found 303.1432.

(5a*S*,8a*S*)-*tert*-Butyl 3-methyl-5a,6,8,8a-tetrahydrofuro[3,4-*e*]-[1,2,3]triazolo[1,5-*a*]pyrazine-5(4*H*)-carboxylate (75). White solid; mp. 157–158 °C; $[\alpha]_D$ −31.3 (*c* 1.1 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.76 (d, J = 16.6 Hz, 1H), 4.69 (t, J = 7.8 Hz, 1H), 4.62 (d, J = 16.6 Hz, 1H), 4.60–4.52 (m, 1H), 4.50 (dd, J = 10.0, 7.4 Hz, 1H), 4.19 (dd, J = 9.8, 8.5 Hz, 1H), 4.14 (t, J = 9.4 Hz, 1H), 3.63 (dd, J = 10.2, 6.8 Hz, 1H), 2.33 (s, 3H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 154.5, 138.8, 127.9, 82.2, 69.3, 65.3, 60.6, 60.0, 41.7, 28.3, 10.2. HRMS (ESI, m/z) calculated for $C_{13}H_{21}N_4O_3$ (MH^+) 281.1614, found 281.1624.

(5a*S*,8a*S*)-3-Methyl-4,5,5a,6,8,8a-hexahydrofuro[3,4-*e*][1,2,3]-triazolo[1,5-*a*]pyrazine TFA salt (77). Light yellow solid; ^{1}H NMR (MeOD, 400 MHz) δ 4.86 (d, J = 16.2 Hz, 1H), 4.80–4.72 (m, 2H), 4.64 (d, J = 16.2 Hz, 1H), 4.33 (t, J = 7.5 Hz, 1H), 4.14–4.03 (m, 2H), 3.96 (dd, J = 10.4, 7.9 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 139.4, 125.3, 65.7, 64.6, 58.2, 57.0, 40.9, 8.3. HRMS (ESI, m/z) calculated for $C_8H_{13}N_4O$ (free amine) (MH^+) 181.1089, found 181.1094.

***tert*-Butyl (1*R*,2*S*)-2-hydroxy-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (78).** White solid; mp. (CH_2Cl_2–hexane) 111–112 °C; $[\alpha]_D$ 20.7 (*c* 1.2 $CHCl_3$). IR (thin film) 3400, 1711, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, rotameric mixture) δ 7.36–7.32 (m, 1H), 7.25–7.20 (m, 2H), 7.16–7.11 (m, 1H), 4.96 (br s, 2H), 4.19 (d, J = 8.6 Hz, 1H), 3.05–2.90 (m, 1H), 2.85–2.75 (m, 2H), 2.08–1.90 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz, rotameric mixture) δ 157.1, 136.4, 134.8, 129.4, 128.7, 127.7, 126.5, 80.2, 69.6, 53.0, 28.4, 26.8, 26.2. HRMS (ESI, m/z) calculated for $C_{15}H_{21}NO_3Na$ (MNa^+) 286.1419, found 286.1411.

***tert*-Butyl (1*R*,2*R*)-2-azido-1,2,3,4-tetrahydronaphthalen-1-ylcarbamate (79).** White solid; mp. 81–82 °C; $[\alpha]_D$ 29.5 (*c* 0.8 $CHCl_3$); IR (thin film) 2095, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, rotameric mixture) δ 7.36–7.28 (m, 1H), 7.26–7.21 (m, 2H), 7.14–7.10 (m, 1H), 4.80–4.74 (m, 2H), 3.88 (br s, 1H), 3.02–2.80 (m, 2H), 2.19–2.12 (m, 1H), 2.06–1.95 (m, 1H), 2.20–2.10 (m, 1H), 2.04–1.94 (m, 1H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 125.8 MHz, rotameric mixture) δ 154.4, 134.8, 129.1, 127.8, 127.7, 126.7, 125.7, 79.1, 60.3, 52.3, 27.4, 25.0, 24.1. HRMS (ESI, m/z) calculated for $C_{15}H_{20}N_4O_2Na$ (MNa^+) 311.1484, found 311.1482.

(4a*R*,10b*R*)-1-Methyl-4a,5,6,10b,11,12-hexahydrobenzo[*f*]-[1,2,3]triazolo[1,5-*a*]quinoxaline TFA salt (81). Light yellow solid; mp. 272 °C (decomp); ^{1}H NMR (MeOD, 400 MHz) δ 7.57 (d, J = 6.5 Hz, 1H), 7.40–7.31 (m, 3H), 4.94–4.85 (m, 2H), 4.69 (d, J = 16.0 Hz, 1H), 4.60 (dd, J = 11.4, 2.9 Hz, 1H), 3.35–3.24 (m, 1H), 3.23–3.12 (m, 2H), 2.31 (s, 3H), 2.28–2.16 (m, 1H); ^{13}C NMR (MeOD, 125.8 MHz) δ 139.4, 136.0, 129.8, 129.1, 128.3, 126.7, 123.9, 123.7, 57.7, 56.3, 39.1, 26.7, 24.2, 8.2. HRMS (ESI, m/z) calculated for $C_{14}H_{17}N_4$ (MH^+) 241.1453, found 241.1446.

1-Azido-1-((prop-2-ynyloxy)methyl)cyclohexane (84). Color-less oil; IR (thin film) 2106 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.21 (d, J = 2.4 Hz, 2H), 3.50 (s, 2H), 2.45 (t, J = 2.4 Hz, 1H), 1.76–1.38 (m, 9H), 1.33–1.23 (m, 1H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 80.1, 76.6, 74.7, 63.2, 58.7, 31.8, 31.5, 25.5, 22.3, 21.8. HRMS (ESI, m/z) calculated for $C_{10}H_{16}N_3O$ (MH^+) 194.1293, found 194.1302.

4,6-Dihydrospiro[[1,2,3]triazolo[5,1-*c*][1,4]oxazine-7,1′-cyclo-hexane] (86). White solid; mp. 78–79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (s, 1H), 4.89 (s, 2H), 3.94 (s, 2H), 2.36–2.27 (m, 2H), 1.95–1.85 (m, 4H), 1.78–1.70 (m, 1H), 1.53–1.40 (m, 3H); ^{13}C

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NMR ($CDCl_3$, 125.8 MHz) δ 130.0, 127.8, 70.3, 69.7, 60.3, 34.1, 34.0, 25.0, 22.5, 22.3. HRMS (ESI, *m/z*) calculated for $C_{10}H_{16}N_3O$ (MH^+) 194.1293, found 194.1300.

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