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THESIS TITLE

Intramolecular 1,3-dipolar cycloaddition: a powerful tool to synthetize fused heterocycles.

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i. Glossary of Abbreviations, Acronyms and Simbols

1,3-DC	1,3-dipolar cycloaddition
Ar	generic aromatic substituent
DCM	dichloromethane
DG	directing group
DIPEA	N,N-Diisopropylethylamine
DMSO	dimethylsulfoxide
dr	*diastereomeric ratio*
FG	functional group
HRMS	high-resolution mass spectrometry
NMR	nuclear magnetic resonance
R	generic group
rr	*regioisomeric ratio*
RSM	recovered starting material
TBDPSCl	tert-Butyldiphenylsilyl chloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
X, Y	generic atom or substituent

1. Introduction

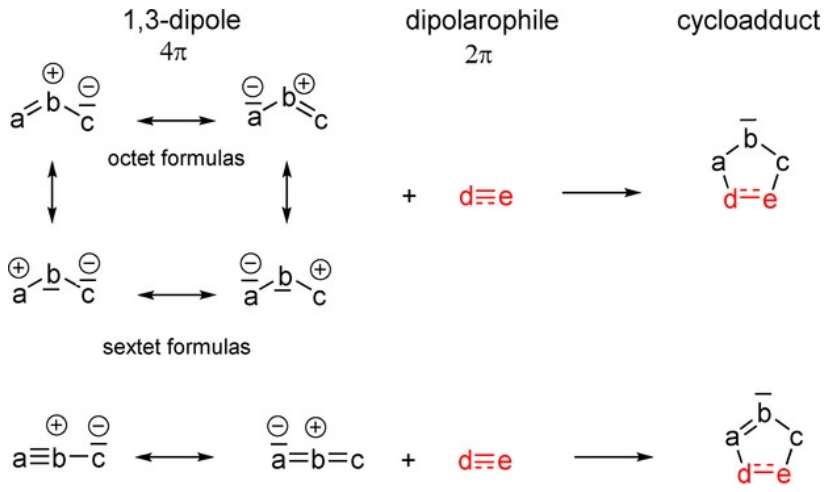
The [4+2] cycloaddition, also known as the Diels–Alder reaction, is probably one of the most studied and most utilized reactions in organic synthesis. The Diels-Alder is a concerted, pericyclic reaction between a 2 π-electrons system (dienophile) and a 4 π-electrons system (diene), in which the driving force is the formation of new σ-bonds, (energetically more stable than the π-bonds).

Diels-Alder reactions represent a powerful tool in heterocyclic chemistry for the generation of polycyclic scaffolds, essentially due to their associated rapidity and atom-economy. Since its discovery in 1928, the Diels–Alder reaction has been deeply investigated for over more than eighty years. This monumental investigation provided information about all the factors that influence the mechanism of addition, such as steric and electronic effects, allowing a better understanding that led to the development of many different versions of inter- and intramolecular cycloadditions, including the 1,3-dipolar cycloaddition.

Discovered in 1960 by Rolf Huisgen, the 1,3-dipolar cycloaddition has soon become a fundamental organic reaction for its ability to rapidly increase molecular complexity and to increase functionality. Its high utility spreads in every aspect of chemistry, from natural product synthesis to drug discovery.

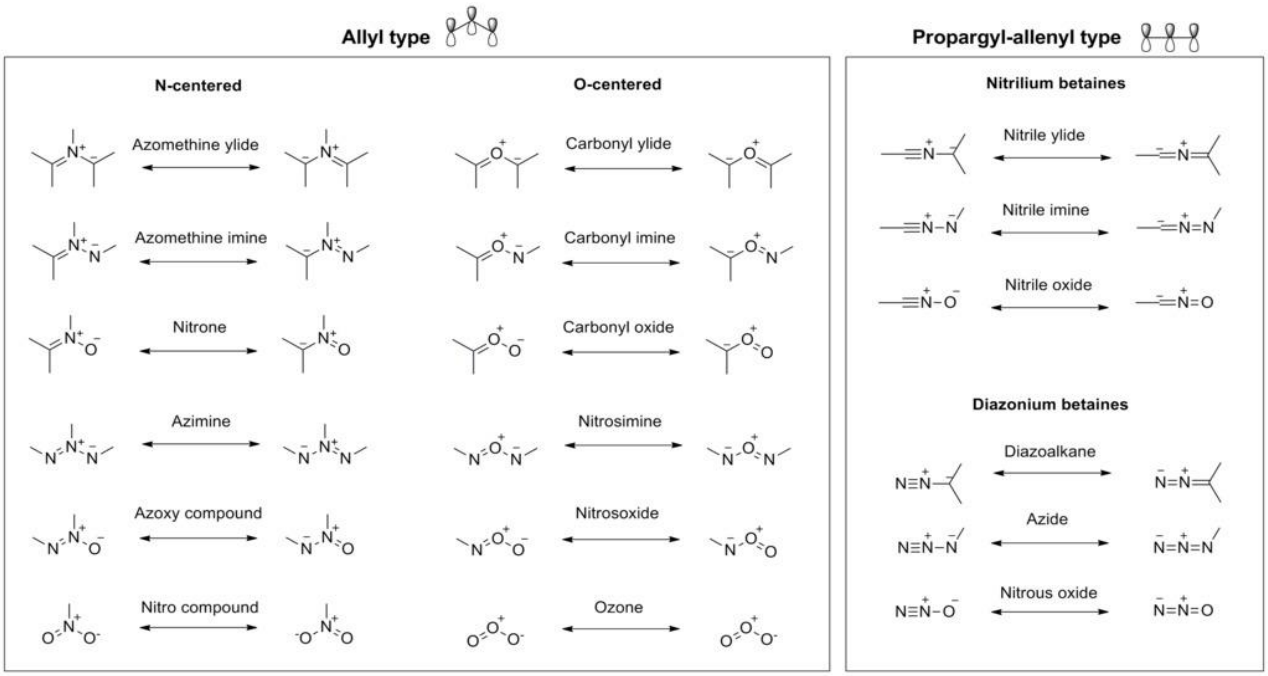
In analogy to the Diels–Alder reaction, a 1,3-dipole reacts (as a 4π system with the general formula "a-b-c") with a dipolarophile "d-e" (delivering 2π electrons) in a (3+2) cycloaddition to give five-membered products[1]. In his seminal work, Huisgen defined the 1,3-dipole as an "a-b-c" structure, which cannot be described by neutral octet formulas but only by zwitterionic resonance structures. Four different formulas are shown in Scheme 1, reflecting the ambivalent character of 1,3-dipoles, with both nucleophilic and electrophilic properties. The two octet formulas bear a positive charge at the central atom "b", while the two sextet formulas show neutral "b" (explaining the choice of the name 1,3-dipole for these compounds).

The combination of a 1,3-dipole with a 2π-electron component (dipolarophile "d-e") provides a 1,3-dipolar cycloaddition[2].



Scheme 1*: Resonance structures of 1,3-dipoles and (3+2) Cycloadditions of 1,3-dipoles "a-b-c" to dipolarophiles "d-e" to give five-membered heterocycles.*

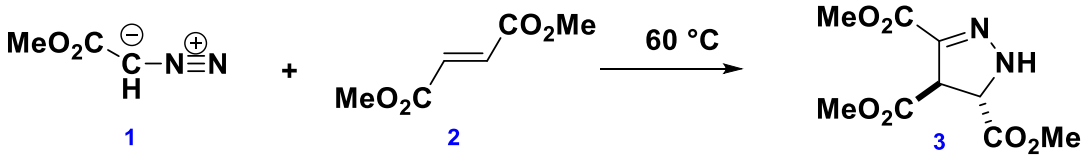
In his work, Huisgen and co-workers have classified the 1,3 dipoles "a-b-c" in two main types: 1) the allyl anion type is characterized by four electrons in three parallel p_z orbitals perpendicular to the plane of the dipole; for this type, the central atom "b" can be oxygen or nitrogen; 2) allenyl-propargyl type contains a triple bond; the second π-orbital orthogonally located causes the linear structure, but it is not involved in the cycloaddition; for this type, only nitrogen is possible as the central atom.



Scheme 2: *types of 1,3-dipoles*

Throughout the years, a considerable number of these hetero-allyl or hetero-propargyl dipoles systems has been extensively explored and their reactions with a variety of double- and triple-bond systems have been studied, to provide five-membered cycloadducts.[3]

The history of 1,3-dipoles goes back to Curtius[4], who discovered in 1883 ethyl diazoacetate, the very first diazoalkane. Five years later Buchner studied the reaction of diazoacetic ester with unsaturated carboxylic acid esters and described the reaction of methyl diazoacetate with dimethyl fumaric acid, the first 1,3 cycloaddition.



***Scheme 3**: the first 1,3-dipolar cycloaddition of methyl diazoacetate with fumaric acid diester*

The unique reactivity of 1,3-dipolar cycloaddition for the synthesis of aromatic or partially saturated heterocycles was proven on a vast number of heterocycle systems, such as isoxazole, pyrrole, pyrrolidine, pyrazole, and triazole derivatives.

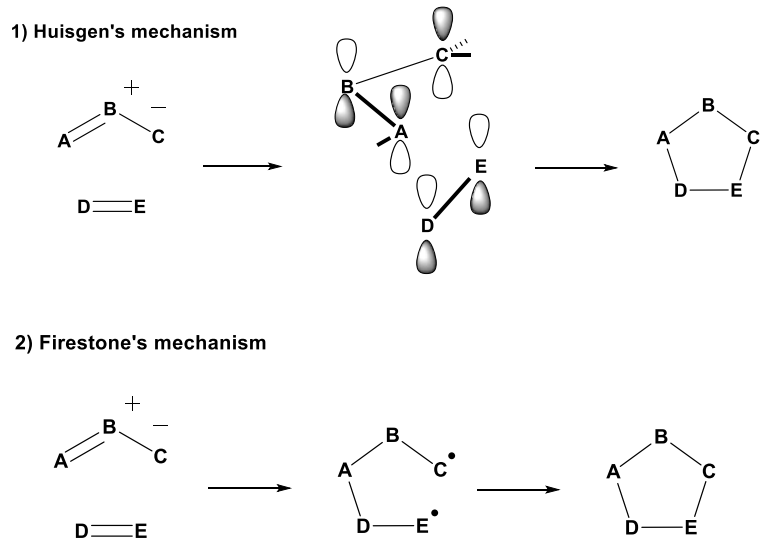
All the 1,3-dipoles discovered during the years have been employed in many applications for the synthesis of natural and pharmaceutical products.

In 1977 Rebek Jr. reported his work on the synthesis of the pyrrole derivative "Münchnone" starting from l-hydroxyproline[5], while Stork and McMurry explored nitrile oxide–alkyne cycloaddition to synthesize a specifically substituted isoxazole, an aldol–equivalent building block for the synthesis of steroid derivatives[6]. In 1979 Tufariello applied nitrone–alkene cycloadditions for the synthesis of alkaloids[7], whereas Stevens investigated nitrile oxide group in his studies on vitamin B12[8].

1.1 Mechanism of 1,3-dipolar cycloaddition

In 1963 Huisgen developed a detailed rationale for the concerted mechanism of this reaction. According to the Woodward-Hoffmann theory[9], he proposed a model for the transition state of the 1,3-dipolar reactions, involving 4 π electrons from the dipole and 2 π electrons from the dipolarophile. The orbital illustration (*Scheme 4*) shows the three p_z orbitals of the 1,3-dipole and the two p_z orbitals

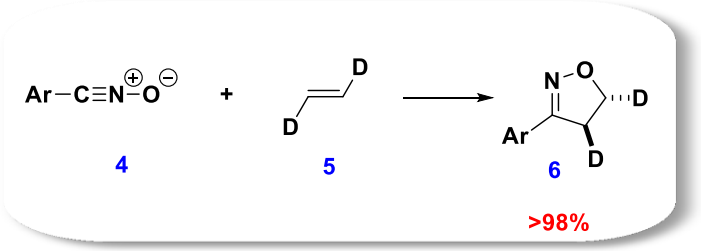
of the dipolarophile approaching each other suprafacially, in two parallel planes to achieve a thermally allowed overlap of the π-systems[10].



***Scheme 4**: postulated mechanism for 1,3-dipolar cycloadditions.*

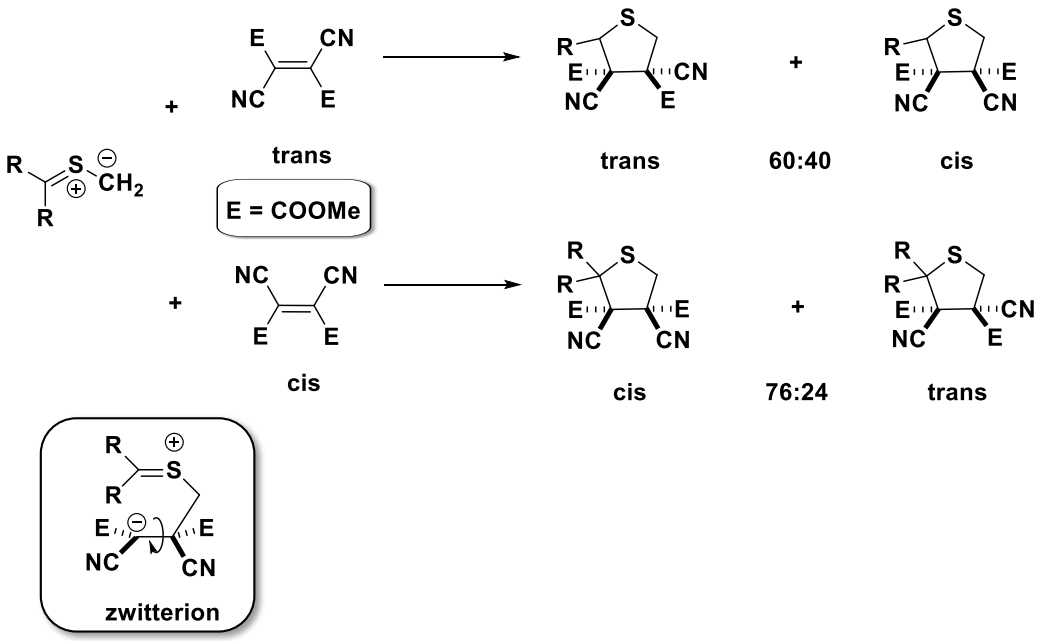
However, the concerted reaction mechanism became quite a controversial subject: in 1968 Firestone published a report in which he considered the 1,3-DC reaction proceeding in a stepwise process with a singlet diradical intermediate. Both sides in the debate based their arguments on a number of experimental observations, such as solvent effect, byproducts, regioselectivity and stereospecificity[11]. The pros and cons of the two mechanisms were expressed during a long-lasting and fervid debate. The great interest aroused around this matter, triggered many additional experimental and theoretical studies in order to clarify the reaction mechanism.

As an example, the 1,3-DC reaction of benzonitrile oxide with trans–dideuterated ethylene gave exclusively the trans–isoxazoline[12] (*Scheme 5*).



Scheme 5: *stereospecificity of the Concerted 1,3-DC reaction between benzonitrile oxide and trans–dideuterated ethylene*

A diradical intermediate would allow for a 180° rotation of the terminal bond and would thus be expected to yield a mixture of the cis and trans isomers[13]. Based on the stereospecificity of the 1,3-DC reaction, the controversy was solved in favour of the concerted mechanism. However, in 1986 Huisgen turned the tables by reporting the first well-documented example of a stepwise 1,3-dipolar cycloaddition involving a zwitterionic intermediate[14]. The report described the reaction of a thiocarbonyl ylide sterically hindered on one side with extremely electrophilic dipolarophiles, and a clear violation of the stereospecificity was recorded, probably due to the steric hindrance of the substituents R, CO_2Me.



Scheme 6: *Cycloadditions of a thiocarbonyl ylide with cis/trans-isomeric dipolarophiles: the first two-step 1,3-dipolar cycloaddition with a zwitterionic intermediate.*

Nevertheless, recent kinetic studies involving aryl diazoalkanes show further strong evidence of the concerted nature of this reaction[15].

In 1971 Sustman[16] stated that the frontier molecular orbitals (FMO) of the substrates control the transition state of the concerted 1,3-DC reaction. The reaction involves either a $LUMO_{dipole}/HOMO_{dipolarophile}$ interaction or a $HOMO_{dipole}/LUMO_{dipolarophile}$ interaction depending on the nature of the dipole and the dipolarophile. However, if the frontier molecular orbital energies of the dipole and the dipolarophile are very similar, a combination of both interactions can happen.

On the basis of the relative FMO energies, Sustman classified the 1,3-DC reactions in three types: in type I, the dominant FMO interaction is $HOMO_{dipole}/LUMO_{dipolarophile}$. This interaction is typical for substrates such as azomethine ylides and azomethine imines; in type II 1,3-DC reactions, the FMO energies of the dipole and dipolarophile are very similar: it implies that both HOMO-LUMO interactions are important. Reactions of nitrones are classified as type II; reactions of nitrile oxides could be classified as type II too, but since nitrile oxides have relatively low-lying HOMO energy, it is more correct to classify them as borderline to type III. Type III reactions are dominated by the

interaction between the $LUMO_{dipole}/HOMO_{dipolarophile}$; in type III, reactions of ozone and nitrous oxide are included. However, the introduction of electron-donating or electron-withdrawing substituents on the dipole or the dipolarophile can alter the FMO energies, and therefore the reaction type[17,18].

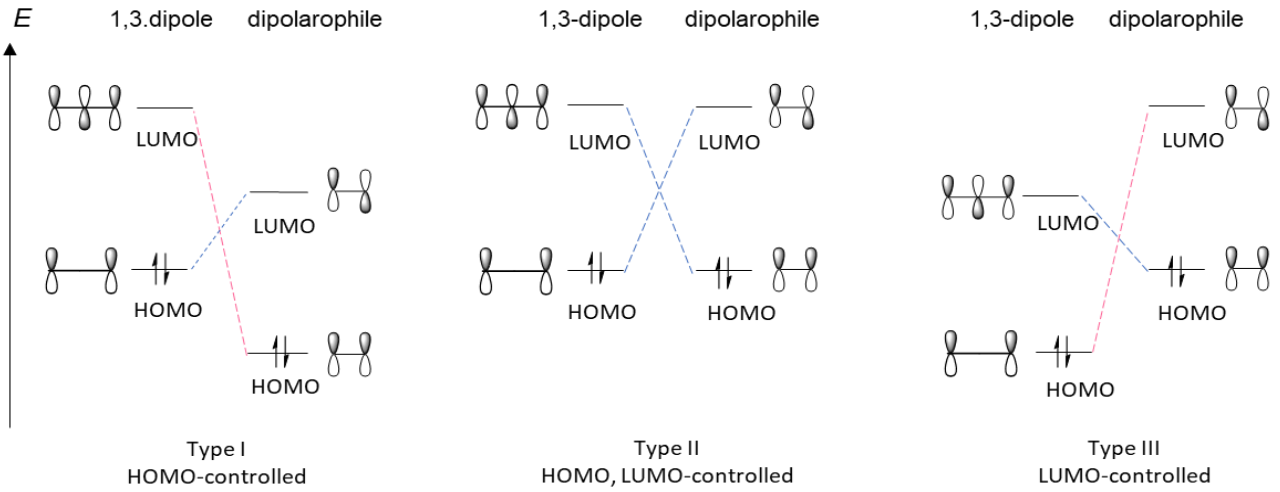


***Fig. 1**: Classification of (3+2) cycloadditions according to the dominant interaction in the frontier molecular orbitals of the 1,3-dipole.*

The HOMO-LUMO interactions can discriminate the approach toward one of the faces of the alkene or the 1,3-dipole, leading to a diastereoselective reaction. This type of selectivity will be referred to as diastereofacial selectivity or as either endo/exo selectivity. Endo- transition state is stabilized by small secondary π interactions while exo- transition state lacking such a stabilization. Structure of the substrates or the catalyst can also be important factors to control the endo/exo selectivity.

Metal catalyst, such as Lewis acids, have been applied successfully to catalyse a vast number of reactions, including 1,3-DC. The increase in reactivity of the 1,3- dipole and the dipolarophile in the presence of metal catalysts is due to a change of the FMO energy of the substrate interacting with the catalyst. In particular, the Lewis acid catalyst lower the LUMO energy of one of the reacting species. The result is a decrease in the energy difference between HOMO and LUMO of the dipole and the dipolarophile, leading to an increased reactivity[19].

$$\Delta E \propto \frac{cHOMOcLUMO}{EHOMO - ELUMO}$$

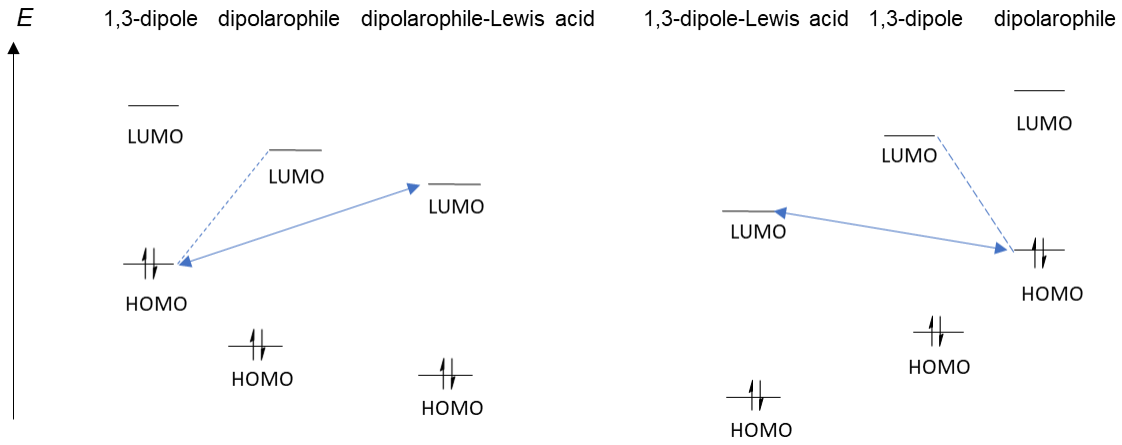


Fig. 2: *the change in frontier orbitals by coordination of a Lewis acid.*

Furthermore, the Lewis acid may also have influence on the selectivity of the 1,3-DC reaction, since both regio-, diastereo-, and enantioselectivity can be controlled by the presence of a metal-ligand complex.

1.2 Click chemistry.

In 2001 K. B. Sharpless introduced, for the first time, the concept of "click chemistry". In his famous work Sharpless described a "click reaction" as a stereospecific, modular reaction, which should provide libraries of compounds in high yields from a variety of starting materials and generate only inoffensive by-products[20]. It must be easy to perform, be insensitive to oxygen or water, and use only readily available reagents. Reaction work-up and product isolation must be simple, without requiring chromatographic purification. It is intuitive that to achieve these required characteristics, "click reactions" need a high thermodynamic driving force, usually greater than 20 kcal mol^{-1}.

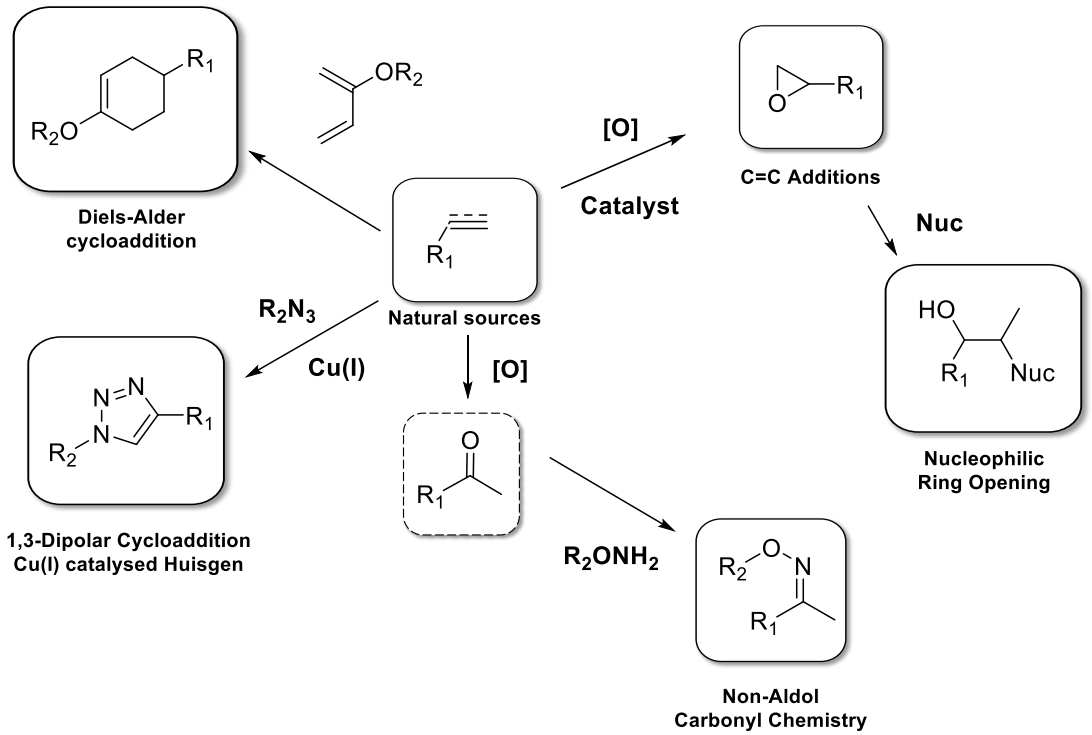
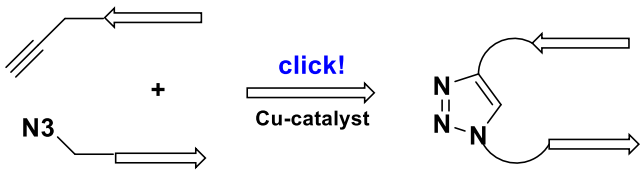


***Fig. 3**: a selection of reactions that match the "click chemistry" criteria.*

Although all the reactions shown in figure 3 are good candidates to represent the concept of "click chemistry", the 1,3-dipolar cycloaddition of azides and alkynes has emerged as the most popular click reaction by far[21]. The great success of Sharpless's reports on copper catalyzed azide–alkyne cycloadditions[22] paved the way for the "click chemistry" in the following years. The two concepts go hand-in-hand, so much so that they can be inter-changeble. The catalyzed Huisgen 1,3-dipolar

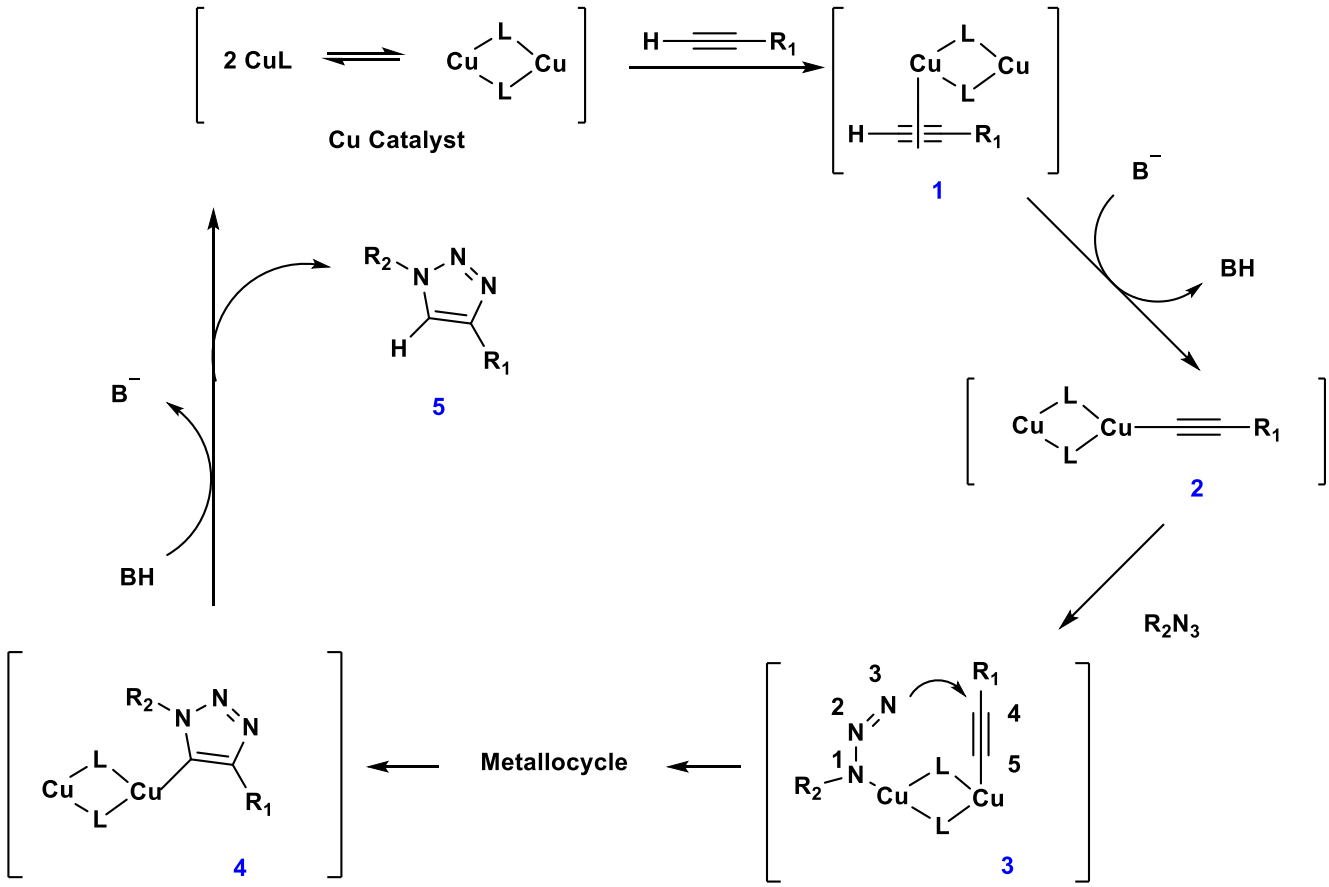
cycloaddition has found numerous applications across a wide variety of disciplines, including materials research, polymer chemistry and, obviously, pharmaceutical sciences. It has proven to be a powerful tool in biomedical research, ranging from combinatorial chemistry and bioconjugation strategies to lead discovery in drug design[23].



***Scheme 7**: Copper-catalyzed click reaction of organic azides with terminal alkynes to give 1,4-disubstituted 1,2,3-triazoles.*

The use of the 1,3-dipolar cycloaddition reaction between azides and alkynes, in combination with classical organic chemistry, has led to the synthesis of a huge variety of synthetic structures. Azides and alkynes are easy to install, and despite being among the most energetic species known, they are also among the least reactive functional groups in organic chemistry.

In 2005 Sharpless reported the seminal work on the mechanism of copper catalyzed azide–alkyne cycloadditions[24]. If 1,3-DC generally proceed through a concerted mechanism, experimental kinetic data and computational studies performed on copper catalyzed reaction seem to favour a stepwise reaction pathway.

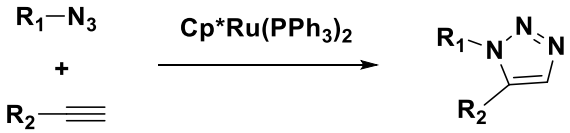


***Scheme 8**: proposed mechanism for the copper catalyzed azide–alkyne cycloadditions.*

The sequence begins with the coordination of the alkyne to the Cu^{I} dimer. Then deprotonation of the terminal hydrogen occurs to convert the alkyne to a Cu-acetylide. The π complexation of Cu^{I} lowers the pKa of the terminal alkyne to 9. 8 pH units, allowing deprotonation to occur in an aqueous solvent without the addition of a base. If a non-basic solvent such as acetonitrile is used, then addition of a base, (e.g., DIPEA), is necessary. In the next step the azide replaces one of the ligands and binds to the copper atom via the nitrogen proximal to carbon. The azide is now "activated" for nucleophilic attack. The distal nitrogen of the azide in **3** attacks the C2 carbon of the acetylide, forming a six-membered copper (III) metallacycle. Then the lone pair of electrons of N1 attacks C5 to form the respective triazole **4** and the attached Cu dimer immediately complexes to a second terminal alkyne.

However, this second alkyne cannot undergo a cycloaddition due to the unfavorable structure of the complex, and it dissociates to reform **4**. One final protonation releases the Cu^{I} catalyst from the 1,2,3-triazole product **5**.

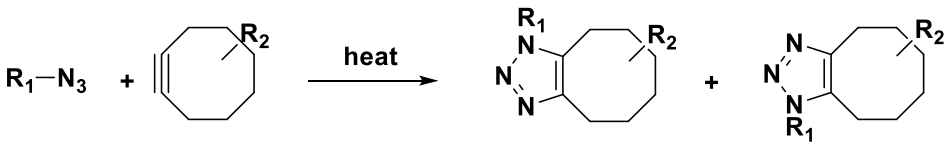
Since this work, considerable efforts have been made to increase number of methods to generate the active catalyst for the "click reaction". One of the most common techniques is to reduce Cu^{II} salts, such as $CuSO_4 \cdot 5H_2O$, *in situ* to form Cu^{I} salts[25]. This method requires a reducing agent, usually sodium ascorbate. Another procedure to create the catalyst is to directly add Cu^{I} salts. Examples include CuBr, CuI, $CuOTf \cdot C_6H_6$, $[Cu(NCCH_3)_4][PF_6]$, etc. In this case reducing agent is not required, but anhydrous environment and organic solvent are necessary. In order to find a replacement for copper as the catalyst, different transition metals were investigated by Golas[26] group: $NiCl_2$, $PtCl_2$, and $PdCl_2$ were tested in the polymerization reaction between propargyl ether and azide-terminated polystyrene. They could catalyse the reaction, althought less efficiently than CuBr. In 2005, ruthenium complexes (Cp*Ru), such as $Cp^*RuCl(PPh_3)_2$, were discovered as novel catalysts for click chemistry[27]. It is noteworthy that this catalyst, unlike copper, allows the reaction between internal alkynes and azides. Contrary to all previously mentioned catalysts, Cp*Ru complexes afford only 1,5-substituted 1,2,3-triazoles (as shown in Scheme 9).



Scheme 9: *ruthenium complexes as 1,3-DC catalyst*

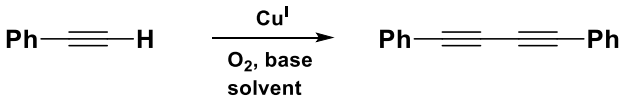
In the process of optimizing the 1,3-dipolar cycloaddition, Li *et al*. have shown that catalyst is not always required for the cycloaddition to proceed[28]. If an electron-deficient internal or terminal alkyne is used, the 1,3-dipolar cycloaddition reaction can proceed readily, without any catalysts, at ambient conditions. This procedure is fully compatible with *in vivo* applications. However, electron deficient alkynes are very reactive toward biological nucleophiles.

Other studies have shown that the cycloaddition of azides and alkyne incorporated into an eight-member ring (cyclooctyne derivatives) occurs readily under physiological conditions in the absence of auxiliary reagents [29]. Cyclooctynes are very unstable, due to a high degree of ring strain (18 kcal/mol). This destabilization causes them to react with azides with a dramatic acceleration rate compared to unstrained alkynes. However, a racemic mixture of regioisomers is obtained. While this method leaves no side products and requires no cytotoxic catalysts, connecting the alkyne of interest to an eight-member ring can be a very challenging task.



***Scheme 10**: cycloaddition of azides and cyclooctyne derivative*

Although Huisgen 1,3-dipolar cycloaddition of terminal alkynes and azides can be easily applied to generate heterocycles with outstanding reliability and efficiency, a number of limitations do exist. The first challenge involves biocompatibility: alkyne–azide cycloaddition has limited applicability in biological systems due to the requirement of elevated temperatures (or pressures). Another obvious disadvantage is the necessity of a metal catalyst. Excessive intake of metals like copper can lead to generation of free radicals. This condition of oxidative stress triggers several human diseases, such as neurological disorders, kidney diseases, and Alzheimer's disease . Therefore, in order for the click reaction to find in vivo applications, the copper catalyst must be completely removed. Another important limitation is linked to reactivity: azide binding may prove problematic for highly electron-deficient azides or for electron rich dienophile. Furthermore, alkyne can react with a second alkyne instead of the azide in a reaction of homocoupling. Most of these side reactions reactions can be minimized by using a sterically bulky base. Smaller bases, such as pyridine and triethylamine, can lead frequently to alkyne homocoupling.



Scheme 11: *reaction of alkyne homocoupling*

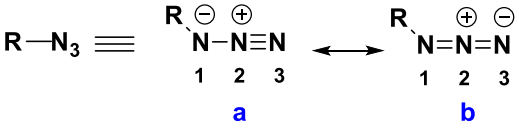
A less common problem is CuI saturation[30]: If the CuI-acetylide complex intermediate is surrounded by terminal alkynes, they will chelate with the complex, "saturating" it and preventing the reaction.

The stability of some azides may also be a limitation but it will be discussed in next paragraph.

1.3 Azides

The chemistry of azides has attracted the attention of chemists since the discovery of the first organic azide, phenyl azide, by Peter Grieß over 100 years ago. A few years later Curtius developed hydrogen azide and discovered the rearrangement of acyl azides to the corresponding isocyanates. However, organic azides gained new popularity in 1950s, when new applications in chemistry were discovered. Applications in industrial, agricultural, and pharmaceutical fields for the synthesis of heterocycles such as triazoles and tetrazole caused the extensive development of organic azide[31].

Structurally, azides consist of three nitrogen atoms in linear form. The angles N1–N2–N3 and R–N1N2N3 are approximately 172.58 and 115.28 respectively (calculated for methyl azide, R = CH3).



Scheme 12: *structure and resonance forms of organic azides*

The polar resonance structures *b* explains the strong IR absorption at ~2114 cm^{-1} (for phenyl azide) and the UV absorption (287 nm and 216 nm for alkyl azides). Organic azides can react very differently under various reaction conditions: the N1 atom can work as a nucleophile with electron-deficient compounds while N3 position nitrogen atom shows electrophilic reactivity[32]

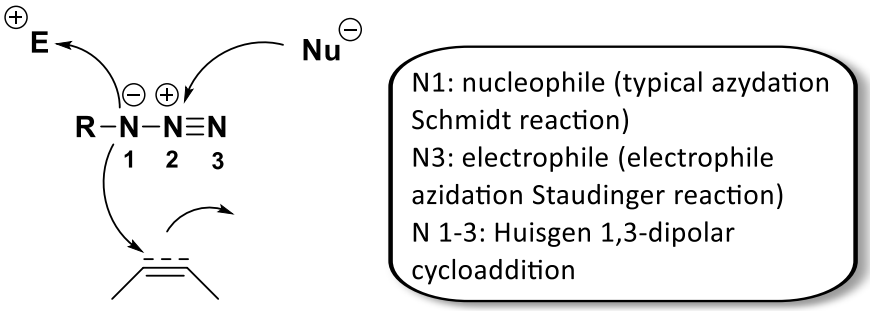


Fig. 4: *properties of organic azides*

In aromatic substitution reactions the azide group acts as an ortho- and para-directing substituent.

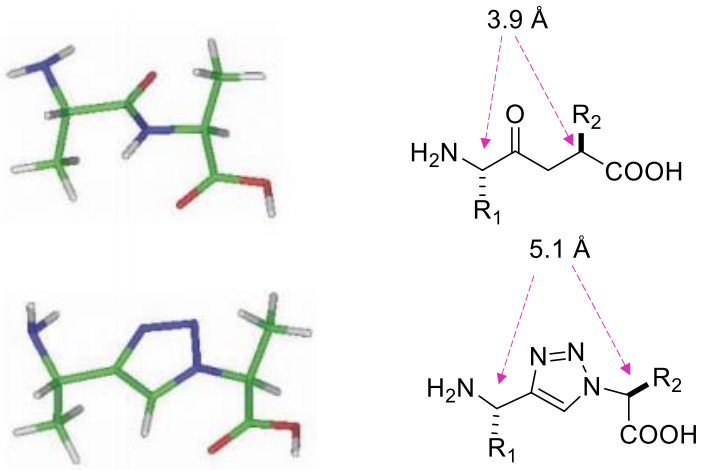
While ionic azides such as sodium azide are relatively stable, most other azides are explosive substances. They can easily evolve nitrogen gas in many reactions through the slightest input of external energy, especially pressure or heating conditions[33]. For organic azides to be relatively safe or nonexplosive, the ratio of nitrogen atoms to carbon atoms in an organic molecule should follow the rule: $(nC + nO)/nN \geq 3$ (n = number of atoms)[34]. Sodium azide is toxic and can be absorbed through the skin. It reacts vigorously with water or Brønsted acids to release highly toxic hydrogen azide. Other organic and covalent azides are classified as toxic[35] (e.g., inorganic azides are considered neurotoxins while azide ions behave as COX inhibitors) or highly explosive[36], such as solid iodoazide. However, despite their less attractive properties, organic azides are valuable intermediates in organic synthesis. The specific efficiency of organic azides is its character as 1,3-dipolar and this provides 1,3-DC with unsaturated bonds to give triazolines, triazoles and tetrazoles.

The reaction of organoazides with alkynes and olefins has been a focus in chemical biology and it is illustrated with several examples. The addition takes place at different rates depending on the dipolarophile. Whereas strained olefins or alkynes such as cyclooctyne[37] react readily, terminal alkenes react extremely slowly while many olefins are totally unreactive.

1.4 Triazoles

This work, where mild conditions led to high yields and a total regioisomeric selectivity to form 1,4-disubstituted 1,2,3-triazole derivatives, enlightened the importance of the azide–alkyne cycloadditions. This type of "click reaction" allows the connection of two different and quite complex molecules, for example, proteins with fluorescence markers, azido-substituted carbohydrate derivatives with cell surfaces or building blocks leading to new polymers. The newly gained popularity of organic azides, despite their less attractive properties such as toxicity or explosiveness, proved to be a rebirth for this compound class in synthetic organic chemistry.

The advent of click chemistry propelled the application of triazoles in drug design. 1, 2, 3-Triazoles are planner five membered heterocyclic systems with two carbon and three nitrogen atom in the 1-, 2- and 3,-position[38]. Structurally, triazoles possess a strong dipole moment and hydrogen bond accepting properties, that display stability towards metabolic degradation. The hydrogen-bonding strengths, responsible for binding target molecules, and the hydrophilicity, which improve solubility, make its synthesis highly desirable for drug development.



F***ig. 5****: molecular dimensions of the 1,4-disubstituted 1,2,3- triazoles are similar to amide bonds in terms of distance and*

Triazoles are reported to exhibit a wide range of biological activities; this motif is present in a vast number of bioactive compounds, such as antifungal [39], antimicrobial [40], anti-inflammatory [41], analgesic[42] and anticancer[43].

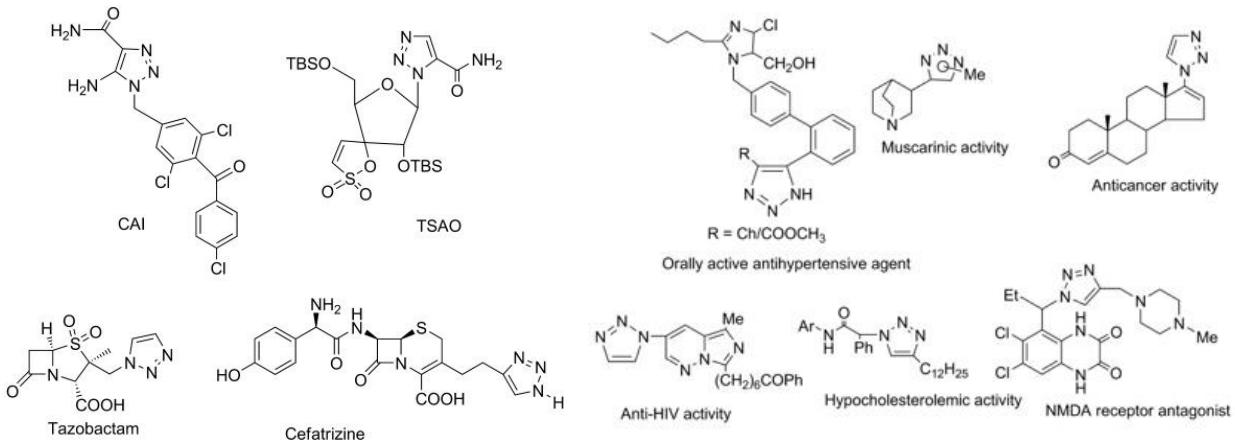
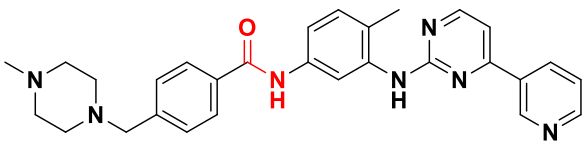
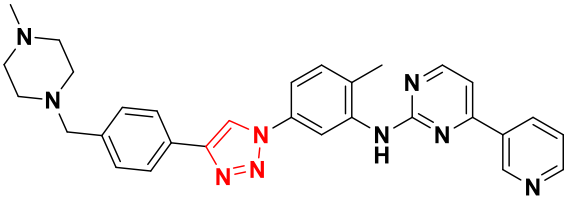


***Fig. 6**: potential pharmaceuticals based on 1,2,3-triazoles[44]*

In recent years, triazoles have gained interesting pharmaceutical applications as replacement for amide groups[45]. As bioisosters, triazoles introduce conformational restrictions and reduce the intrinsic instability of peptidic bond; also, in some cases, the replacement of the amide bonds results in enhanced activity as seen in the anticancer drug, imatinib[46], which shows an IC_{50} value of 0.38 µM against the K562 cancer cell line.



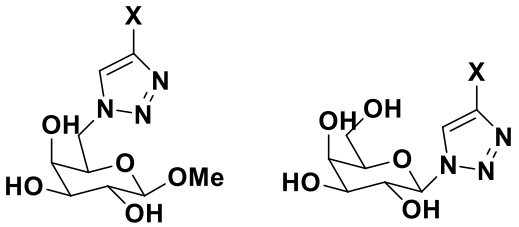
Imatinib (IC_{50} = 0.38 µM)



Imatinib triazole analogue (IC_{50} = 0.03 µM)

Fig. 7: *IC_{50} value of anticancer drug imatinib and its triazole analogue*

Triazoles also behave as attractive linker units, allowing the connection of two pharmacophores to form innovative bifunctional drugs[47]. They are good ligands for carbohydrates, organic molecules, polymers, dendrimers, and labeling agents. For example, Carvalho *et al.* synthesized a library of sugar 1,2,3-triazoles galactose derivatives[48].



X = alkyl side-chains

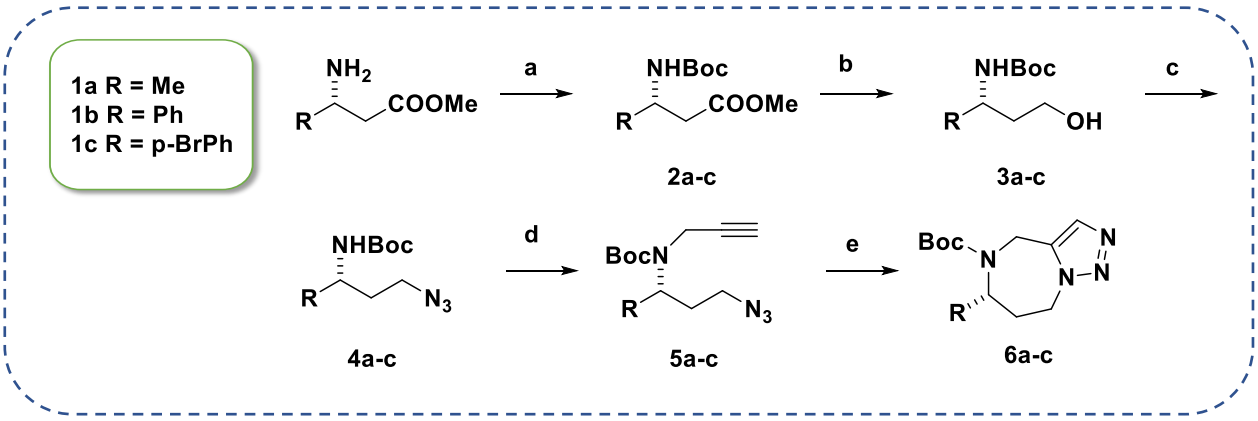
Fig. 8

2. Project aims.

"Click chemistry" offers a unique approach to create new molecular entities from simple starting materials. In fact, azides and alkynes can be easily introduced into a molecule and they are relatively stable under various reaction conditions. In this work we will focus on intramolecular "click" reactions which are known to proceed with higher diastereoselectivity than the intermolecular variant, due to more restricted flexibility of the reactants. Also, due to a favored entropy term compared to the intermolecular variant, the reactivity of the intramolecular reactions is higher in general. In next chapter it will be provided an effective application of "click chemistry" into chiral (S)-β-amino acid substrates in order to synthesize 1,2,3-triazole-fused bicyclic compounds as novel pharmacophores or building blocks for natural product synthesis.[49].

3. Results and Discussion

The synthesis of the required substrates for 1,3-dipolar cycloaddition reaction began with (S)-β-amino acid methyl esters 1a–c, which were Boc protected on primary amines to give **2a–c**. Ester reduction to **3a–c** was followed by mesyl protection of primary alcohols, then the SN2 reaction of the corresponding mesylates with NaN_3 provided the azido substrates **4a-c**. The IR spectra showed a peak at νmax ~2100 cm^{-1} a clear indication of the presence of the azido group. Amino acid-derived azides were treated with NaH and propargyl bromide in dry DMF at 0 °C. Finally, intramolecular "click reaction" was performed under catalyst-free conditions by heating a 0.5 M chloroform solution of the azido-alkyne 5a–c at 60 °C for 72 h. All products were obtained in good yields (as shown in Table 1).



Scheme 13: *reagents and conditions:* ***a****:*$(Boc)_2O$, Na_2CO_3, *dioxane, 16 h;* ***b****: NMM, isobutyl chloroformate,* $NaBH_4$, *THF, MeOH, 2 h;* ***c****: MsCl,* Et_3N, NaN_3, CH_2Cl_2, *DMF, 6 h;* ***d****: propargyl bromide, NaH, DMF, 0 °C, 3.5 h;* ***e****:* $CHCl_3$ *reflux, 72 h*

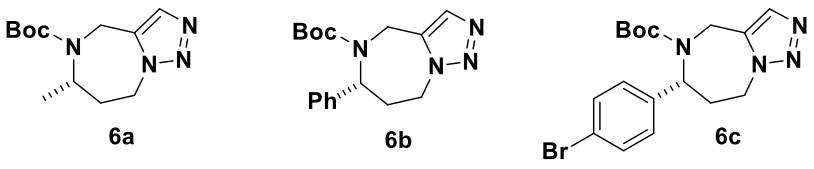
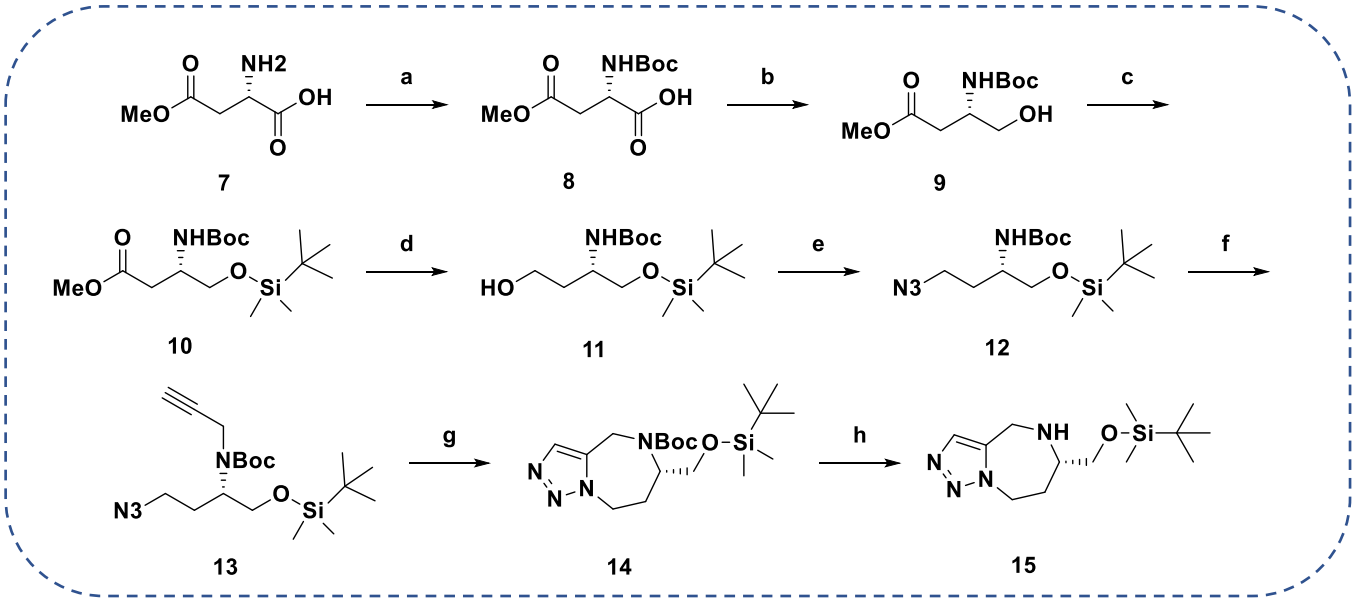


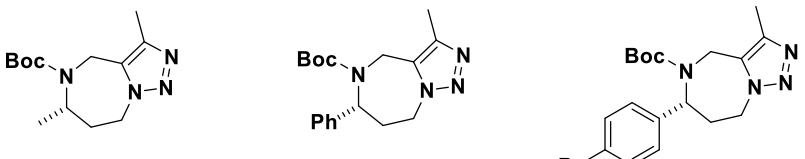
Table 1

Aiming to introduce a second functionalized group in the final product, a similar pathway was adopted for the synthesis of the cycloadduct obtained from L-aspartic acid. Firstly, the primary amine was BOC protected **8** then the carboxylic group was reduced to **9** and the primary alcohol was protected with TBSCl. Ester reduction was followed by mesylation and reaction with NaN_3. The high temperature condition of this step caused a partial loss of the silyl group; however, the deprotected azide was collected and then reprotected, restoring the final yield of the reaction. The azido substrate **12** was treated with NaH, propargyl bromide and a large excess of 15-crown-5 in dry DMF at –30 °C for 1.5 h. After different attempts, 15-crown-5 proved to be necessary to increase the yield of the reaction (which passed from 15 to ~90%). The 1,3-dipolar cycloaddition was carried out under catalyst-free conditions in a 0.5 M chloroform solution at 60° C for 72 h, affording product **14**. Finally, the N-Boc protection was removed using TFA in dry dichloromethane to provide an additional opportunity for diversity-oriented synthesis and derivatization.



Scheme 14: *reagents and conditions:* ***a****: $(Boc)_2O$, Na_2CO_3, dioxane, 16 h;* ***b****: NMM, isobutyl chloroformate, $NaBH_4$, THF, MeOH, 2h;* ***c****: TBDMSCl, NMM, DMAP, CH_2Cl_2, 16 h;* ***d:*** *$LiBH_4$, THF, 16 h;* ***e:*** *MsCl, Et_3N, NaN_3, DCM, DMF, 6h;* ***f****: propargyl bromide, NaH, 15-crown-5, DMF, –30°C, 1.5 h;* ***g****: CH_3Cl reflux, 72 h;* ***h:*** *TFA, DMF, 2 h.*

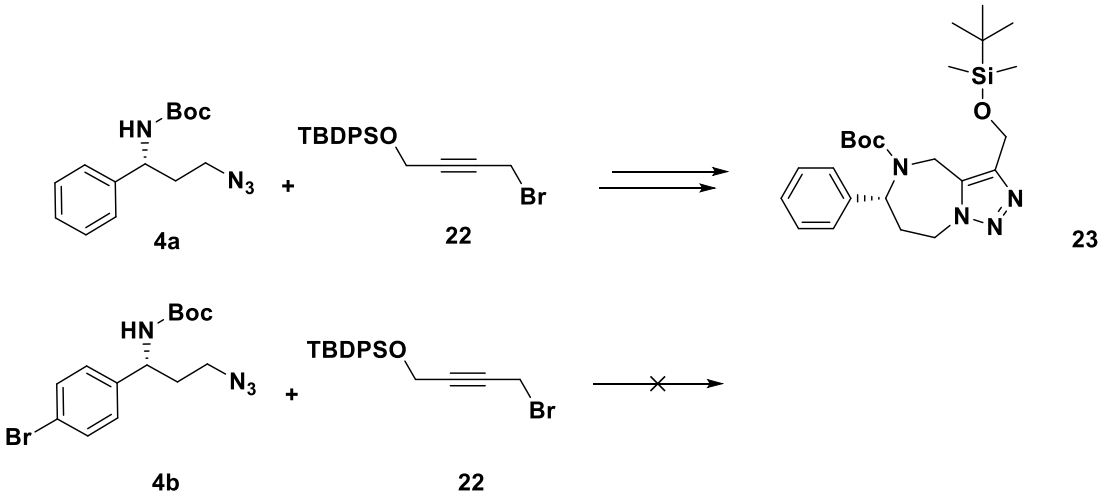
In order to expand our compounds library, different alkyne groups were explored: commercially available 1-bromo-2-butyne allowed to introduce a methyl substituent on the triazole ring (compounds **16**, **18**, **20**), affording products **17**, **19** and **21** in moderate to excellent yield.



Yield of the final step

Table 2

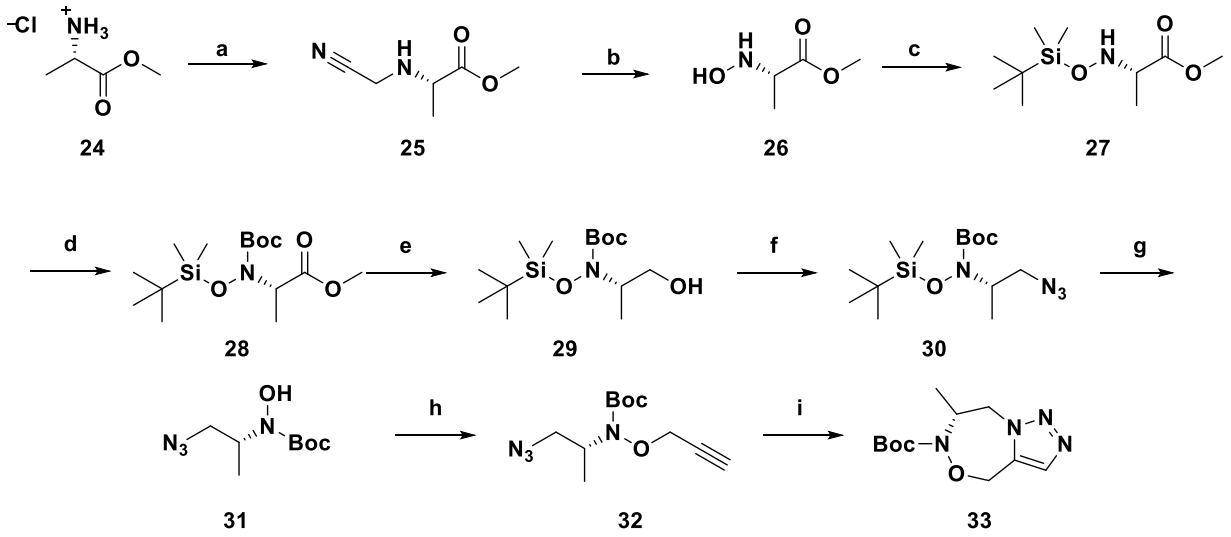
Another interesting type of alkyne, that can increase diversity on the triazole ring, is the (4-bromobut-2-yn-1-yl) oxy) (tert-butyl) diphenylsilane, which can be easily synthetized from monosylilation and subsequent bromuration of but-2-yne-1,4-diol. Only one example of 1,3-dipolar cycloadduct was performed using this particular alkyne.



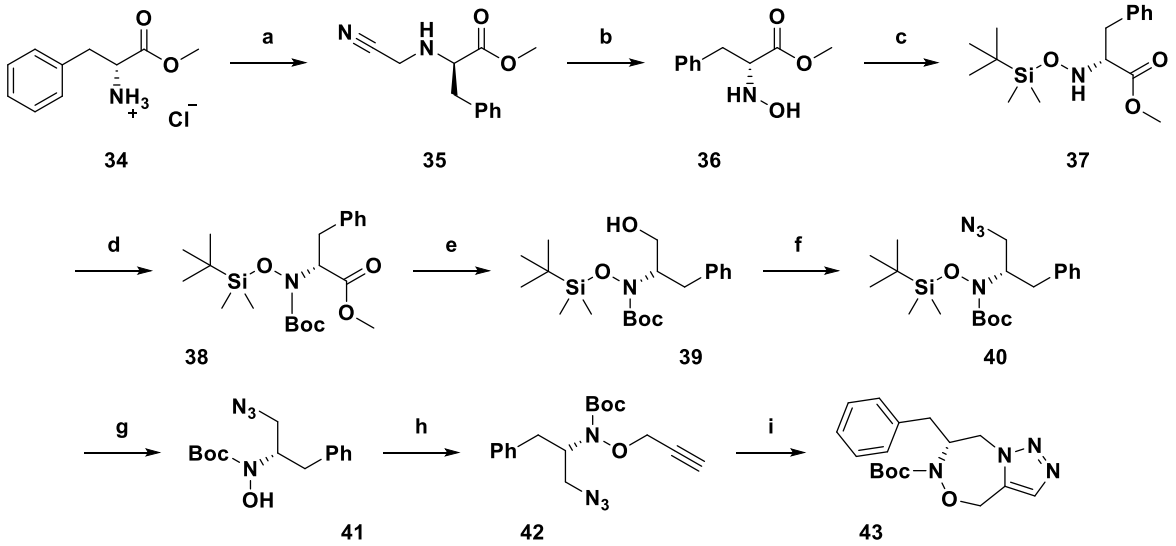
Scheme 15*: reagents and conditions****:*** *$CHCl_3$, reflux, 72 h.*

Fused heterocycles bearing a N-O bond occur in a vast number of natural products and pharmacologically active compounds, such as asiaticumine and phyllantidine[50]. Despite this, methods that form N–O bonds remain rare[51]. Among the strategies, the use of commercially available α-hydroxylamine as building blocks represents an attractive approach for the construction of seven membered scaffold containing N–O bond.

The synthetic pathways started with the Fukuyama[52] procedure for selective monocyanomethylation of primary amines with bromoacetonitrile in presence of a Hünig's base and subsequent oxidation of cyanomethylamines with m-CPBA. The Fukuyama protocol has proven to be a remarkably robust approach to the synthesis of primary hydroxylamines and it is readily executed on a variety of reaction scales and substrates. The afforded nitrones were treated with a large excess of hydroxylamine hydrochloride in MeOH leading to the desired N-monoalkylhydroxylamines **26-36**. Both primary alcohol and amine were protected, respectively with TBSCl and $(Boc)_2$, and ester reduction was followed by mesylation and conversion to azide **30-40**. Then, alcoholic function was deprotected to be alkylated by propargyl bromide and to react in a classical 1,3-intramolecular dipolar cycloaddition.

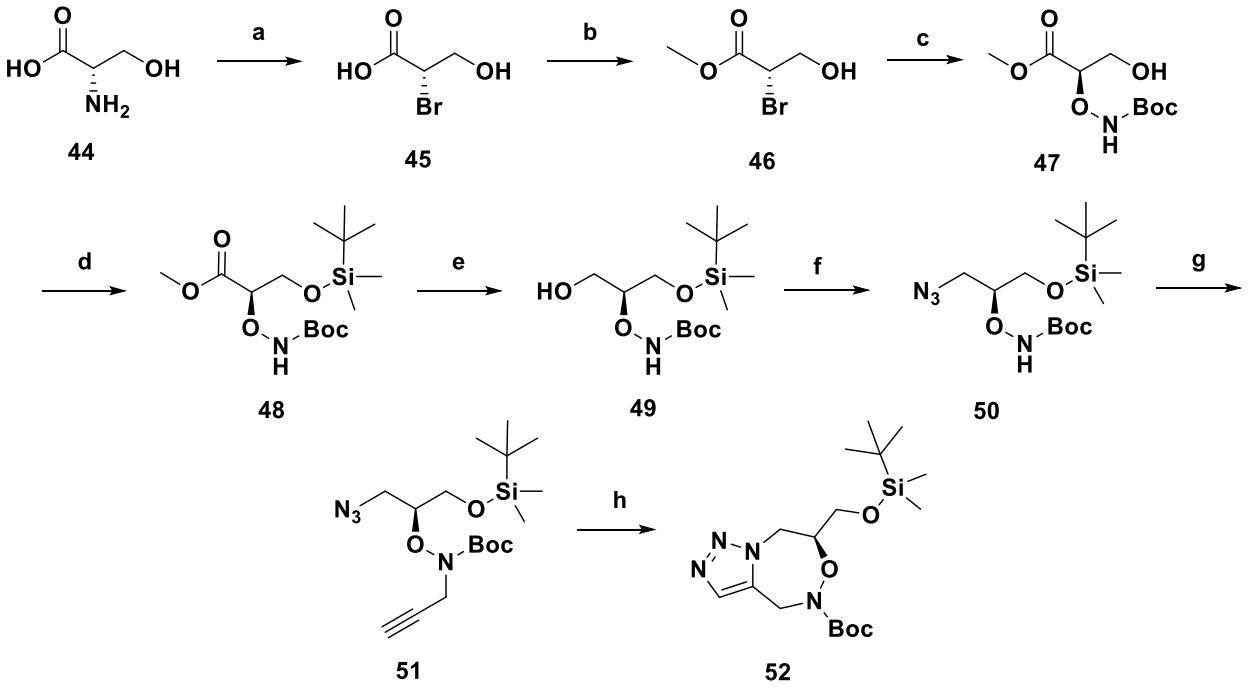


Scheme 16: *reagents and conditions:* ***a****: DIPEA, $BrCH_2CN$, ACN dry, 12 h;* ***b****: m-CPBA, NH_2OH HCl, DMC dry, MeOH, 16 h;* ***c****: imidazole, TBDMSCl, DCM dry, 16 h;* ***d****: $(Boc)_2O$, DMAP, ACN dry, 16 h;* ***e****: $LiBH_4$, THF dry, 16 h;* ***f****: Et_3N, MsCl, DCM dry, NaN_3, DMF dry, 6 h;* ***g****: $Bu_4N^+F^-$, THF, 1 h;* ***h****: propargyl bromide, NaH, DMF, 1.5;* ***i****: $CHCl_3$ reflux, 72 h*

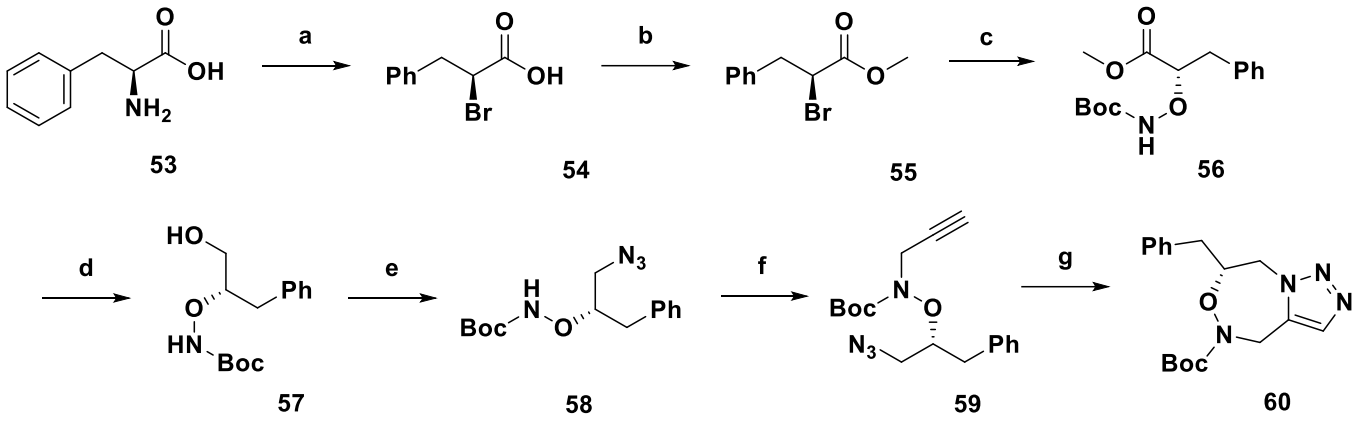


Scheme 17*: reagents and conditions:* ***a****: DIPEA, $BrCH_2CN$, ACN dry, 12h;* ***b****: m-CPBA, NH_2OH HCl, DMC dry, MeOH, 16 h;* ***c****: imidazole, TBDMSCl, DCM dry, 16 h;* ***d****: $(Boc)_2O$, DMAP, ACN dry, 16 h;* ***e****: $LiBH_4$, THF dry, 16 h;* ***f****: Et_3N, MsCl, DCM dry, NaN_3, DMF dry, 6 h;* ***g****: $Bu_4N^+F^-$, THF, 1h;* ***h****: propargyl bromide, NaH, DMF, 1.5 h;* ***i****: $CHCl_3$ reflux, 72 h*

With this successful preparation in our hand, we next evaluated a different synthetic route[53]. As shown in scheme **18-19**, α-bromoacids **45-54** were prepared by nitrous deamination of commercially available L-serine and L-phenylalanine, followed by acetylation and reaction with N-Boc hydroxylamine to give **47-56**. The reaction occurred with inversion of the configuration. Then the conventional pathway was adopted: primary alcohol was protected with TBSCl (**48)** and ester reduction was followed by mesylation and conversion to azide **50-58**. Ammine function was Boc-deprotected to be alkylated by propargyl bromide and final 1,3-intramolecular dipolar cycloaddition afforded products **52-60**.

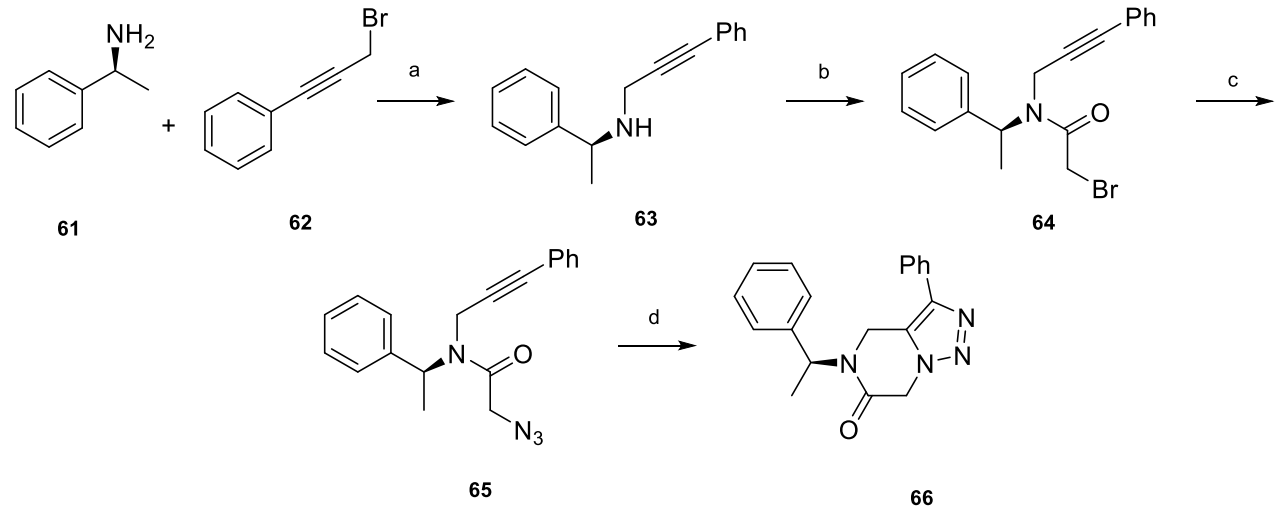


Scheme 18: *reagents and conditions:* ***a****: KBr, H_2SO_4 1.25 M, $NaNO_2$, ACN dry, 12 h;* ***b****: Acetyl chloride, MeOH dry, reflux 4 h;* ***c:*** *N-Boc hydroxylamine, DBU, ACN dry, 16 h;* ***d****: TBDMSCl, imidazole, DCM dry, 16 h;* ***e****: $LiBH_4$, THF dry, 16 h;* ***f****: Et_3N, MsCl, DCM dry, NaN_3, DMF dry, 6 h;* ***g****: 8. propargyl bromide, NaH, DMF, 1.5 h;* ***h****: $CHCl_3$ reflux, 72 h*

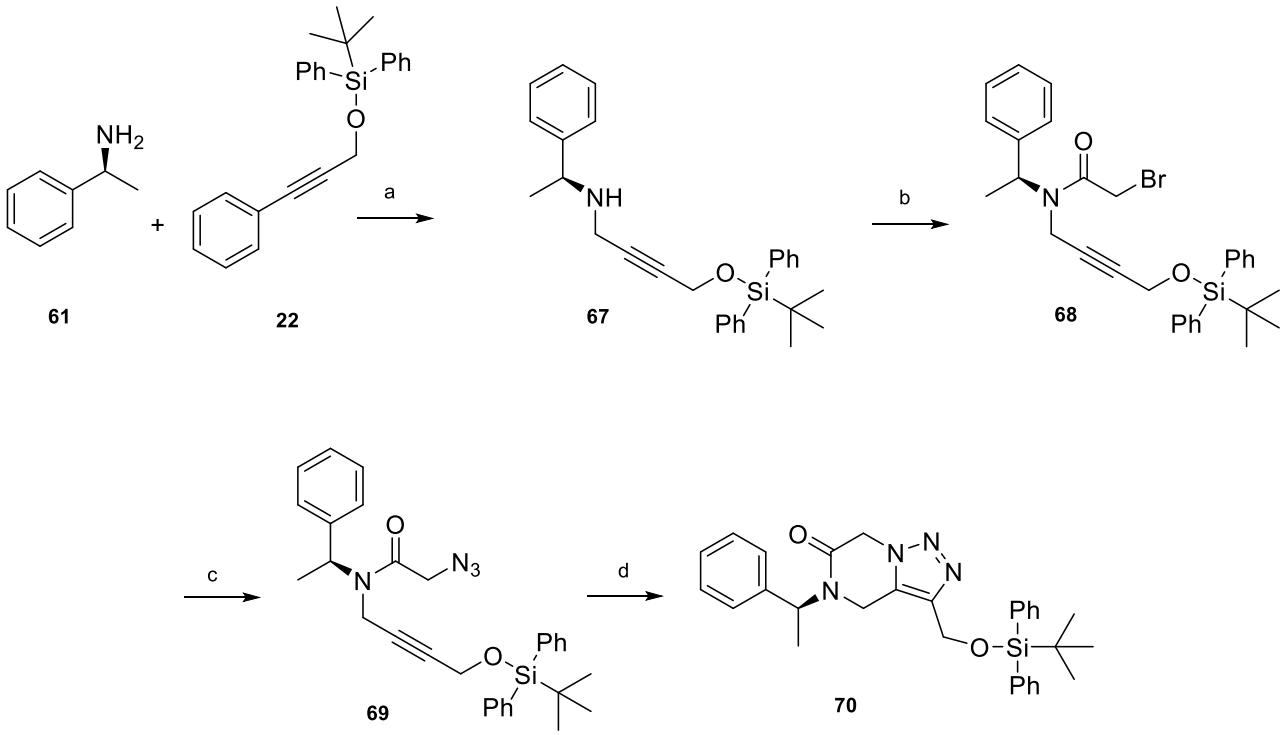


Scheme 19: *reagents and conditions:* ***a****: KBr, H_2SO_4 1.25M, $NaNO_2$, ACN dry, 12h;* ***b****: Acetyl chloride, MeOH dry, reflux 4 h;* ***c****: N-Boc hydroxylamine, DBU, ACN dry, 16h;* ***d****: $LiBH_4$, THF dry, 16h;* ***e****: Et_3N, MsCl, DCM dry, NaN_3, DMF dry, 6h;* ***f****. propargyl bromide, NaH, DMF, 2 h;* ***g****: $CHCl_3$ reflux,72 h*

An interesting group of six-membered fused triazoles were synthetized starting from L(-)-alpha-Methylbenzylamine. Firstly, alkyne **62** was prepared, starting from the corresponding alcohol. Then, methylbenzylamine reacted with alkyne **62-22** to form propargylic derivatives **63-67**. Next step led to bromoacetamido derivatives by reaction with bromoacetyl chloride, which were converted into the corresponding azides **65-69**. General procedure for 1,3-intramolecular dipolar cycloaddition was applied, affording products **66-70**.



Scheme 20: *reagents and conditions: a: NaH, DMF, 2 h; b: Bromo acetyl chloride, Et_3N, DCM dry, 16 h; c Et_3N, NaN_3, DMF dry, 6h; d: $CHCl_3$ reflux,72 h*



Scheme 21: *reagents and conditions: a: NaH, DMF, 2 h; b: Bromo acetyl chloride, Et_3N, DCM dry, 16 h; c Et_3N, NaN_3, DMF dry, 6h; d: $CHCl_3$ reflux,24 h*

4. Conclusions

In summary, we have developed a general and efficient multistep method for the synthesis of triazole-fused heterocyclic compounds exploiting the unique reactivity of intramolecular 1,3-dipolar cycloaddition under catalyst free conditions. The absence of a metal catalyst makes the approach "greener" and more advantageous in terms of conditions, despite longer reaction times. The optimization process went along with the expansion of the scope.

5. Future work

There are three main points to work on in this project: first, the molecular library should be expanded, providing further examples with different α-amino acids as starting material. Derivatisation and late-stage functionalisation of the final products should be attempted after deprotection of the hydroxyl group or the secondary amine. Finally, these groups can represent a useful vector to include the products into peptidomimetic oligomers, scaffolds that can mime protein bioactive conformation and modulate PPI interactions[54].

Synthesis of 1,4-dioxane from oxetan-3-ols as versatile substrates

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Supervisors: Prof. James A. Bull

Department of Chemistry

Imperial College London

Molecular Science Research Hub

2020

5. Introduction

5.1 Structural Features of Oxetane

The oxetane is a small, four-membered heterocyclic compound composed of three carbon atoms and one oxygen atom. The ring adopts an essentially planar structure (that minimize ring strain) with a puckering angle of only 8.7° at 140 K (10.7° at 90 K)[55].

Lone pairs of electrons on the oxygen are exposed due to the strained C-O-C bond angle, making the oxetane an excellent hydrogen-bond acceptor and Lewis Base, forming more effective H-bonds than other cyclic ethers[56].

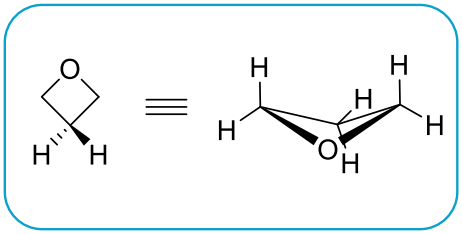


Figure 1 *Oxetane Structure and Ring Puckering*

Marketed drugs containing the oxetane ring are derived from one family of natural products. The natural products which contain the oxetane ring (Figure 1) possess important biological activity which often relies on the ring. Taxol was first isolated from the bark of Taxus brevifolia and is used in cancer chemotherapy[57]. It acts by interfering with the breakdown of microtubules during cell division. Oxetanocin A was first isolated from the soil bacterium Bacillus megaterium. It inhibits the reverse transcriptase enzyme of HIV, by mimicking adenosine, preventing in vivo replication [58]. Thromboxane A2 is predominantly synthesized in platelets which cause vasoconstriction, platelet aggregation and bronchoconstriction. The oxetane has a short half-life in the body due to the acetal functionality[59]. Maoyecrystal I and mitrephorone A were shown to be cytotoxic to a variety of cancer cell lines[60]. Oxetin was found to elicit herbicidal and antibacterial effects[61].

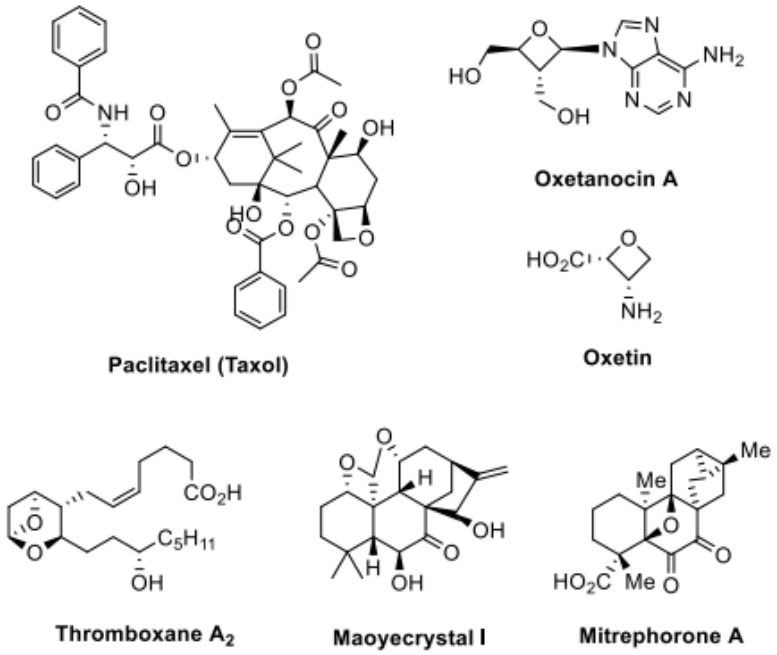


Fig 2.: *Valuable dioxane-containing compounds.*

Physicochemical and pharmacokinetic properties of compounds are investigated early in drug discovery, and their optimization is addressed in parallel to target affinity and selectivity. This multidimensional approach to optimization has allowed successful transition from lead discovery to early *in vivo* studies on potential drug candidates[62]. Yet optimizing compound property remains a challenge medicinal chemistry. Molecular scaffolds which can easily incorporate small molecular entities to alter the properties of the compound in distinct and predictable ways are of high interest. Oxetanes can serve to function as such a scaffold. Over the past decade, there have been several advances describing the ability of oxetanes to enhance physicochemical parameters such as solubility, lipophilicity, basicity, and metabolic stability. In recent years, oxetanes have received enormous interest, due to their medicinal chemistry properties and their use as synthetic intermediates.

In 2006, Carreira and co-workers proposed oxetanes as replacement groups for *gem*-dimethyl and carbonyl groups with improved physicochemical properties[63].

gem-Dimethyl groups are often used to metabolically protect vulnerable methylene sites from chemical or metabolic modification. However, this group leads to a substantial lipophilicity increase. Oxetanes have a similar van-der-Waals volume than gem-dimethyl groups, but due to their higher polarity, they do not entail the disadvantages associated with methyl groups.

Oxetanes have proved to be excellent isosteres also for carbonyl groups, due to similar dipoles and H-bonding properties. Moreover, while carbonyl groups are vulnerable to enzymatic attack, oxetanes provide a superior metabolic stability, due to the lack of reactivity of the sp2 carbon centre.

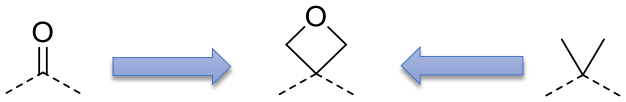
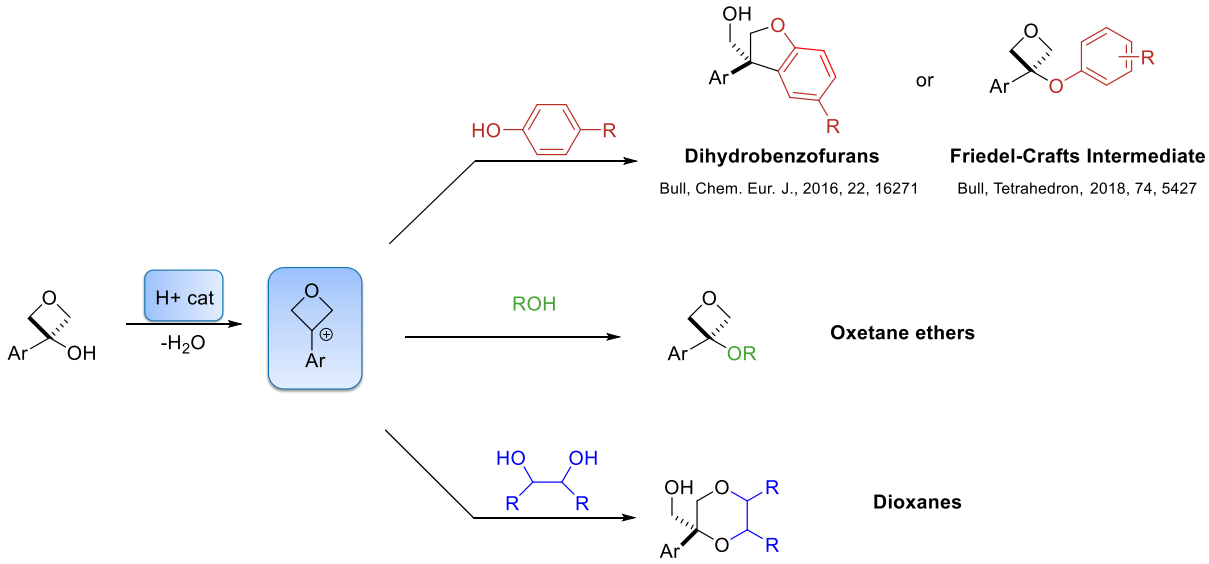


Figure 3 *Oxetane as gem-Dimethyl and carbonyl potential replacements*

The fact that oxetanes are quite susceptible to ring-opening in position 2 has allowed for their use as synthetic intermediates. Amongst many other examples, oxetanes can be readily ring-opened by various nucleophiles such as water[64], amines[65], alkynes[66] and allyl silanes[67] under acidic conditions. In recent years, Bull group has developed methods for the catalytic functionalisation of oxetane rings under acidic conditions via carbocation intermediates[68].



Scheme 1: *reactivity of the oxetane with different nucleophiles.*

After the discovery in the Bull group[69] that oxetan-3-ols can react with phenols and a Lewis acid in a tandem reaction to yield high-value dihydrobenzofuran structures, a variant of this transformation, was developed, testing the reactivity of oxetan-3-ols with other nucleophiles such as aliphatic alcohols in order to give oxetane ethers. The ability of oxetanes to react in this manner would widen the diversity of the many different classes of compounds which can be prepared. Bis-nucleophiles may be primarily sp2 or sp3 which would allow access to interesting heterocyclic structures that possess a combination of planar and three-dimensional geometry. Combing these two ways which nucleophiles can react with oxetanes would unlock a broad, divergent scope, whereby, tuning the nucleophiles will produce a vast array of different heterocyclic.

5.2 1,4-Dioxanes

Dioxanes are saturated hetorocyclic structures which are less rigid but can improve some properties of a bioactive compound (e.g., solubility, pharmacokinetics or bioavailability)[70]. For these reasons, the use of dioxanes as bioisosteres of carbocycles, morpholines, piperazines and piperidines is common[71]. The hydrogen-bonding strengths and hydrophilicity of a target molecule can be tuned by the incorporation of a dioxane ring. This motif is also found in a vast number of natural products and pharmaceuticals such as spectinomycin, 150 MK-2461, and gomphoside. The generation of 1,4-dioxanes relies mostly on CH bond cleavage or the intramolecular cyclisation of 1,2-diols, epoxides, oxetanes and alkenes. The majority of syntheses of chiral dioxanes is based on the use of enantioenriched starting materials.

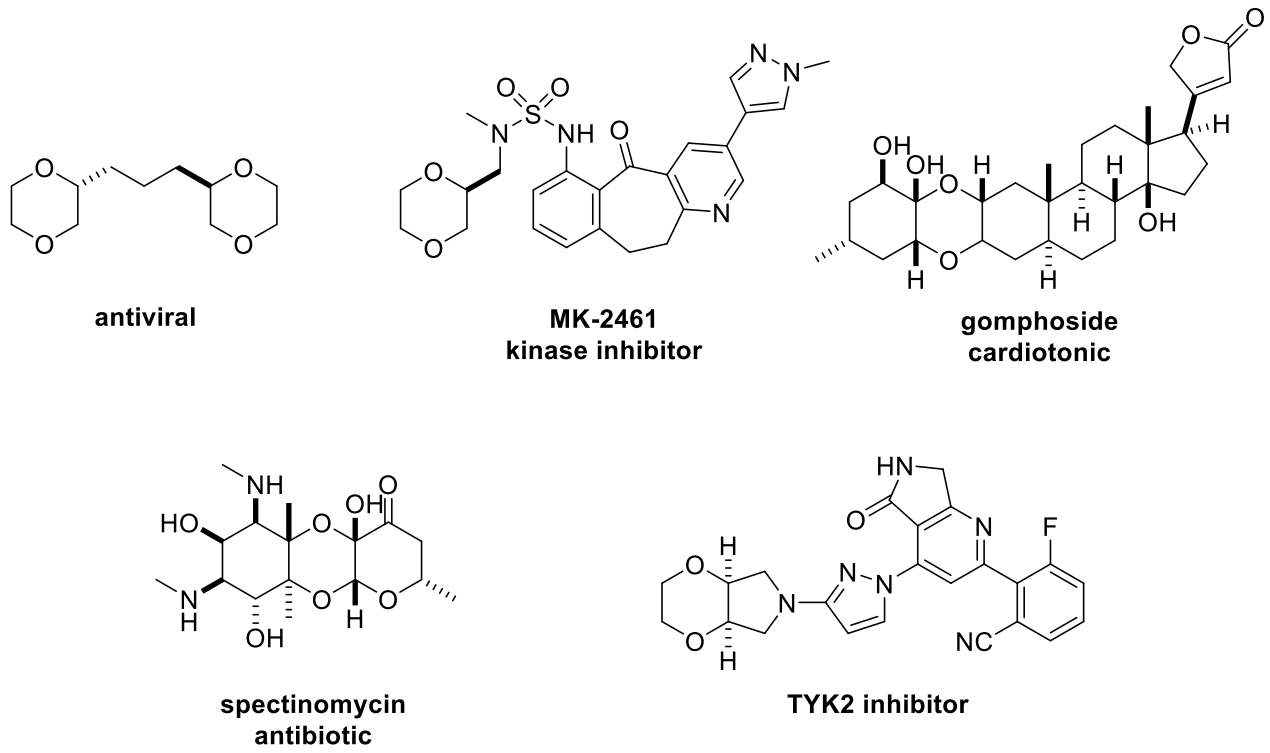


Fig 4*. Valuable dioxane-containing compounds.*

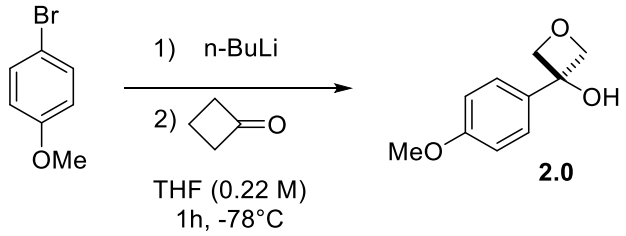
Project Aims

This project aimed to develop methodology to allow preparation of oxetane derivatives. Using the Lewis acid catalysed system previously developed within the group, different nucleophiles were tested to investigate whether they will attack the carbocationic intermediate. Consequently, we aimed to explore the versatility of the oxetane ring, by exploiting the electrophilic centres, by which the ring acts as a double electrophile that can react with bisnucleophiles (e.g., ethylene glycole). This diversity-oriented synthesis approach explored a range of oxetane electrophiles, and a range of bis-nucleophiles to generate diverse 1,4-dioxanes of value to medicinal chemistry. These fragments can act as molecular scaffolds which can be elaborated into lead-like compounds. For the scope, diols with different substitution patterns were used in order to investigate regio- and diastereoselectivity of the reaction.

6. Results and Discussion

6.1 Synthesis of Oxetanol Starting Material

Firstly, the synthesis of various 3-aryloxetan-3-ols were required to investigate further reactions. These were prepared readily, utilizing a reaction of organolithium reagent to commercially available oxetan-3-one, to afford the desired 3-aryloxetan-3ols in moderate to high yields.



Scheme 2: *synthesis of 3-Aryloxetan-3-ol*

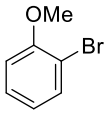
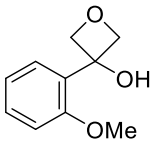
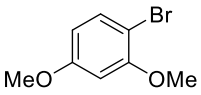
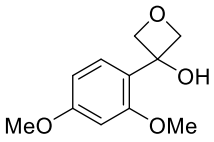
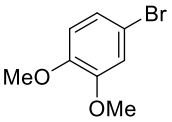
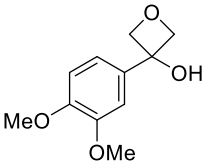
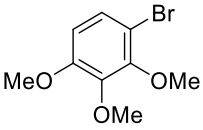
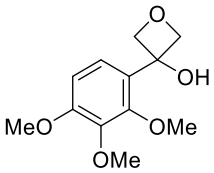
.Entry	Reagent	Product	Yield	mp/°C
1		 **2.1**	**36%**	**53**
2		 **2.2**	**54%**	**71**
3		 **2.3**	**42%**	**74-76**
4		 **2.4**	**30%**	**69**

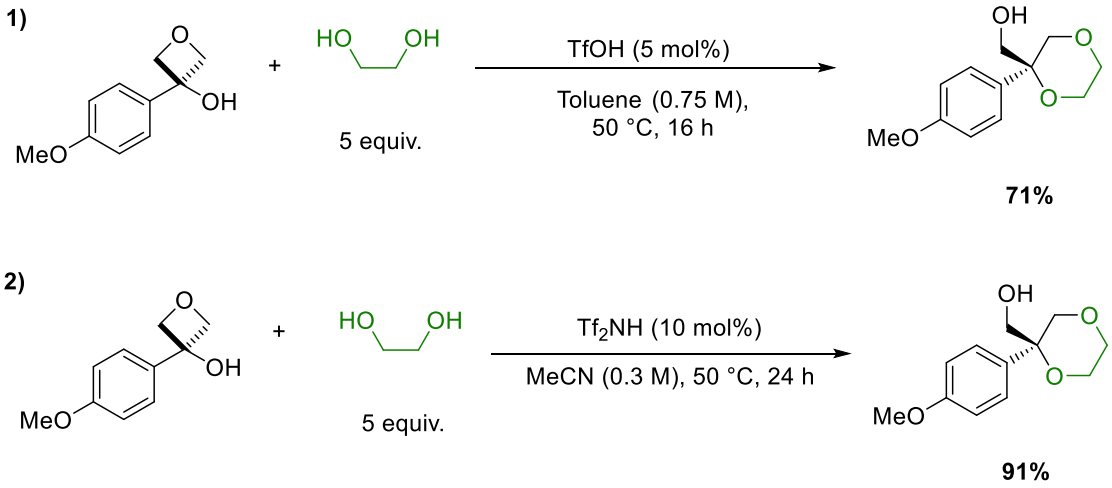
Table 1: p*reparation of 3-Aryloxetan-3-ol*

Short reaction times and respectable yields justified the use of this methodology.

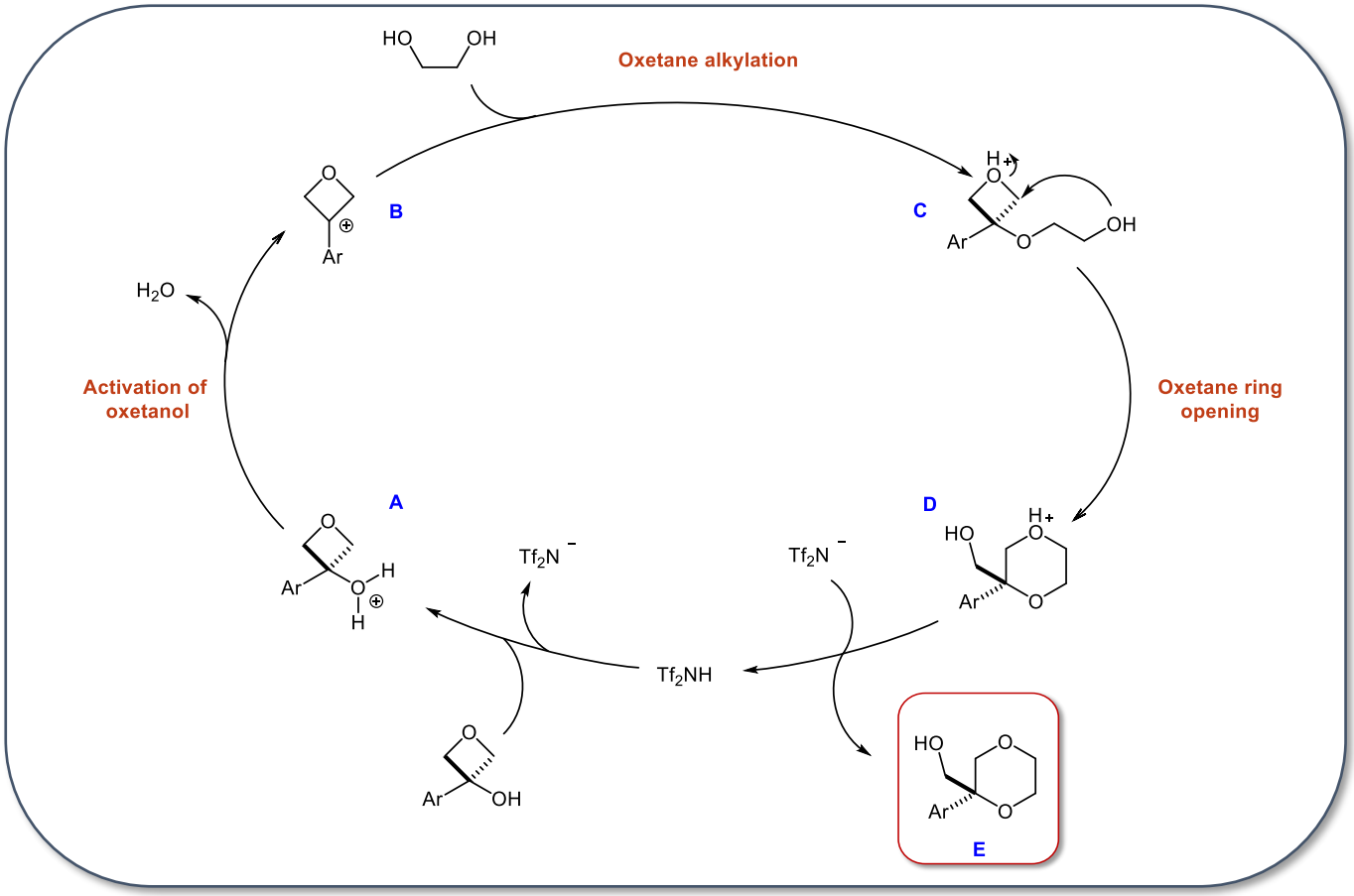
After successful preparation of the 3-aryloxetanol substrates, the next step was to investigate different nucleophiles.

6.2 Synthesis of 1,4-Dioxanes

After the original observation made by Rojas et al that oxetanols readily react with diols under Brønsted acidic conditions in acetonitrile to form 1,4-dioxanes, reaction conditions were optimised, that led to moderate to high yields of several dioxane examples. Tf_2NH was chosen as Brønsted acid catalyst due to its easier handling (a solid) compared to TfOH (a very corrosive fuming liquid).

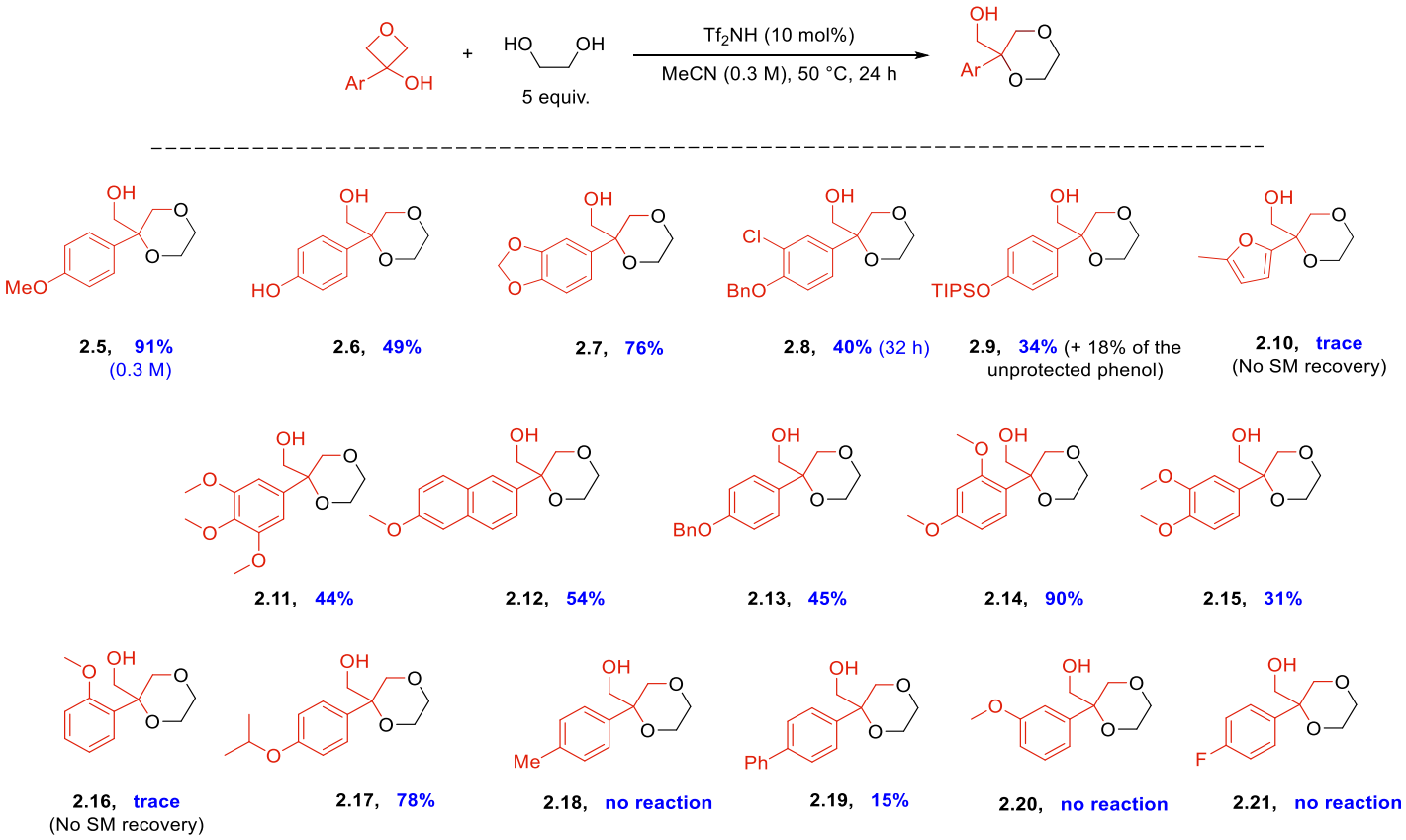


***Scheme 3**: 1) Optimised reaction conditions performed by Hossain for the synthesis of nonaromatic dioxanes. 2) Optimised oxetane ether conditions applied for the dioxane system.*



***Scheme 4** Proposed catalytic cycle for the synthesis of dioxanes.*

The proposed mechanism of the reaction involved a carbocation intermediate. First, the tertiary hydroxyl group of oxetanol **1** is protonated by the Brønsted acid catalyst to form the carbocation ***A***. Attack of the diol generates species ***B*** and protonation of the oxetane oxygen activates this intermediate towards intramolecular ring opening by the second hydroxyl group of the diol to yield 1,4-dioxanes.



Scheme 5*: scope of 1,4-dioxanes. All reactions were run on a 0.25 mmol scale.*

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Different aromatic structures on the oxetanol substrate were investigated. In particular, the aromatic group on the 3-aryloxetanol was varied to investigate the contribution of electronrich or electronpoor substituents to the reaction. High yields were obtained with electronrich aromatics (**2.5** and **2.17**) and a moderate yield with an electronpoor aromatic (**2.19**), probably due to a less stable carbocation intermediate. Unprotected phenol **6** led to lower yields compared to **2.5**, mostly because the phenol-

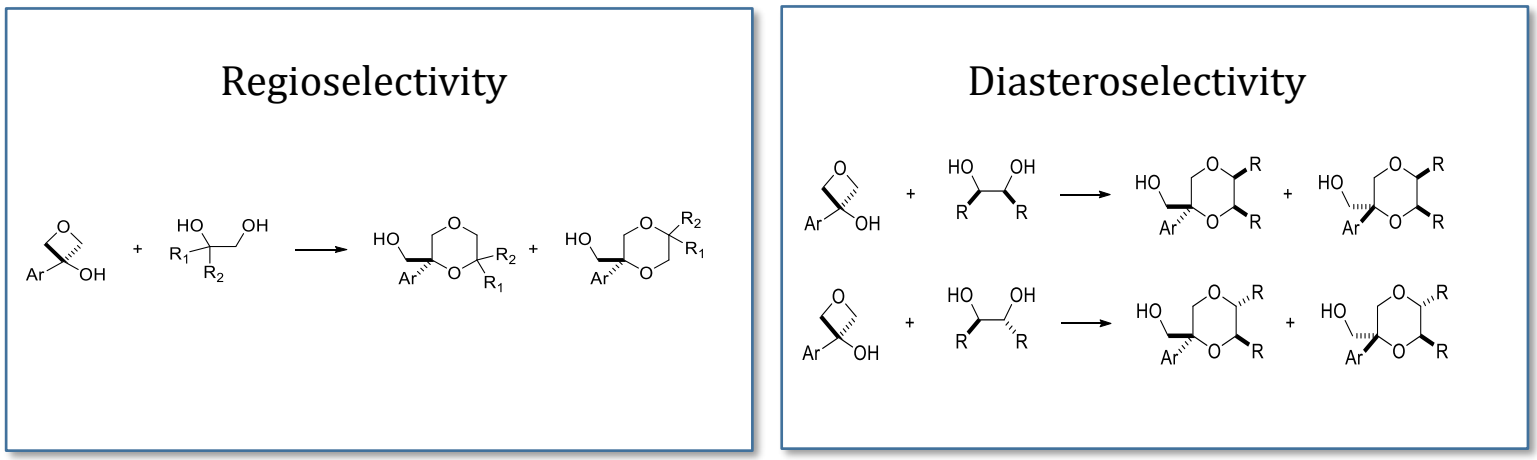
oxetanol possesses an additional reactive site (the phenolic hydroxyl) that may lead to a higher degradation and/or side products structures. Intriguingly, the yield with TIPS protected phenol (**2.9**) was lower than expected with an additional 18% of **2.6** (unprotected phenol) obtained. This is an indication that catalytic amounts of Tf_2NH under the reaction conditions were able to partially deprotect the OTIPS group. For compounds **2.5, 2.14, 2.15, 2.16** and **2.20** an evaluation of was made about the electron-withdrawing inductive effect of methoxy group in different positions: *p*-methoxy subsituent provided the best reactivity (**2.5**), while *m*-methoxy afforded no reaction at all (**2.20**). The *ortho* position, very low reactive for itself, seemed to enhance the reactivty of *p*-methoxy group (**2.14**) when are both present.

6.3 Study on Regio- and Diasteroselectivities

Following optimisation of the reaction to form dioxanes, this work would focus on diols with different substitution patterns to investigate regio- and diastereoselectivities of the reaction.

As illustrated in Scheme 6, there are two types of selectivities which could be investigated around the dioxane structures: 1) regioselectivites with 1,1-disubstituted, 2) diastereoselectivities with 1,2-disubstituted. By changing the nature of the substituents both steric and electronic effects can be studied on the different types of selectivities. Furthermore, cyclic diols were used, and two examples of intriguing spirocycles were obtained.

Oxetanol **5** was chosen as the model substrate because the electron rich aromatic is more likely to stabilise the presumed carbocationic intermediate.



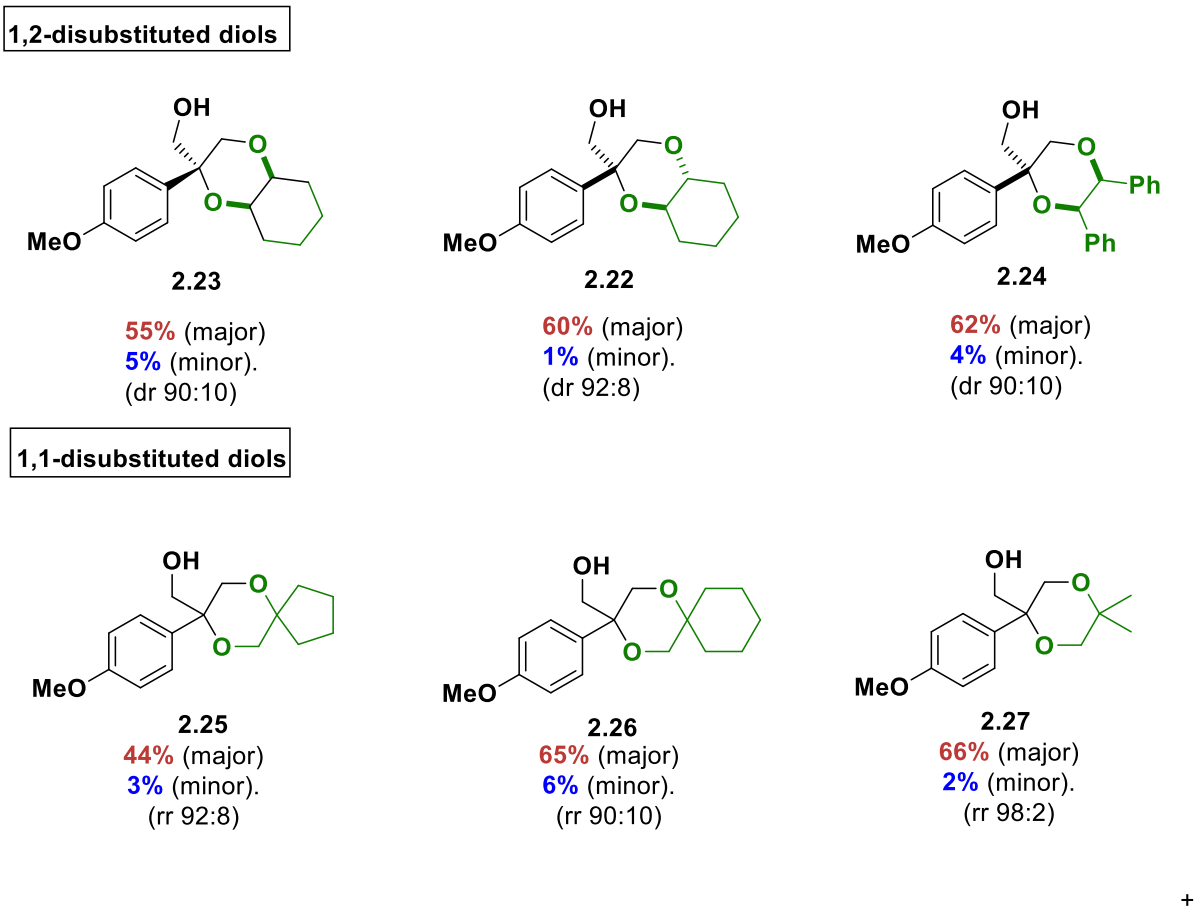
Scheme 6 *Regio- and diastereoselectivities to be investigated.*

After an initial condition screening, in which different concentrations and temperatures were examined, 0.3 M and 30° C were chosen as standard condition, since they represented the best compromise in terms of yield and diasteromeric ratio (Table 2). Lowering the concentration would increase interaction between the oxetanol and nucleophile, leading to higher yields and less degradation of carbocation intermediate, due to the nucleophile being in closer proximity to react.

T (°C)	time	M	dr	^{1}H-NMR yield
50° C	24 h	0.3 M	76:23	73%
40° C	24 h	0.3 M	86:13	85%
30° C	**24 h**	**0.3 M**	**92:8**	**70%**
20° C	48 h	0.3 M	90:10	52% (33% SM recovered)
0° C	48 h	0.3 M	100-0	23% (74% SM recovered)

Table 2: *Screening of conditions*

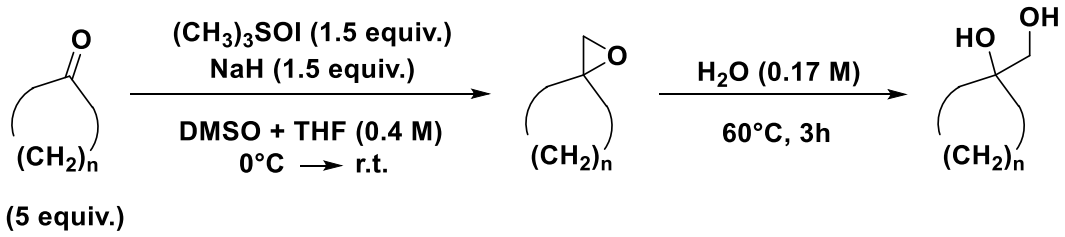
All the reactions were run in sealed microwave vials under argon on a 0.25 mmol scale. dr = diastereomeric ratio; both dr and yields were determined by 1H NMR from the crude reaction mixture after work up using 1,3,5-trimethoxybenzene as internal standartimised conditions in hand, the scope of the reaction was explored and different examples of 1,4-dioxane heterocycles were synthesised.



Scheme 7: *Scope of 1,4-dioxanes. All reactions were run on a 0.25 mmol scale. dr = diastereomeric ratio; determined by 1H NMR from the crude reaction mixture after work up. rr = regioisomeric ratio; determined by 1H NMR from the crude reaction mixture after work up*

1,2-Disubstituted diols gave dioxanes in moderate to high yields with excellent diastereoselectivities. All diastereomers were challenging to separate and required a long purification process, therefore leading to lower yields. Trans 1,2-diols also led to a higher selectivity compared to their cis analogues. The regioselectivity of the reaction was investigated on three examples, which led to good yields and an excellent regioisomeric ratio. The high *rr* of this substrate is not surprising, since it has been previously shown that the attack of primary alcohols is favoured over that of secondary alcohols and ergo, also over that of tertiary ones. Moreover, the subsequent cyclisation step is further enhanced by the Thorpe-Ingold effect of the gem-dimethyl group. Monosubstituted diols have not been investigated yet because they potentially yield four different isomers and thus, make the separation of the products and analysis of the outcome extremely complicated.

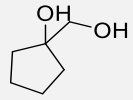
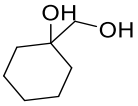
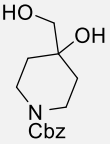
6.4 Synthesis of the Diols



Scheme 8: *Corey–Chaykovsky for diols*

The classical Corey–Chaykovsky reaction is a practical and useful transformation for the synthesis of epoxides (or cyclopropane derivatives) from the corresponding carbonyl compounds, which is thus widely used in the routine organic synthesis.

The synthesis of diols was performed readily in good yield, using a modified Corey-Chaykowsky reaction, involving THF as a co-solvent[72], to form epoxides from the corresponding ketones. Usually, this type of reactions is performed in DMSO but, because of its high boiling point (189 °C), DMSO led to loss of volatile products (particularly epoxides intermediate for **2.28** and **2.29**) in vacuo.

Compound	Product	Isolated yield
2.28		55%
2.29		27%
2.30		60%

7. Conclusions and future work

To conclude, the Brønsted acid system developed for the synthesis of oxetane ethers was applied successfully to give 1,4-dioxanes in one-pot from oxetan-3-ols and diols. Not only does this methodology demonstrate the divergent nature of the scope, it also shows the versatility of the oxetane as a precursor which can lead to markedly diverse structures.

Several examples were obtained in moderate to high yields, and interesting observations on how the use of electronrich or electronpoor aromatics can influence the formation of the carbocation intermediate were made. On regio- and diasteroselectivity studies, a condition screening has pointed out 30°C and 0.3 M as optimised conditions to obtain high selectivity rate. Compounds made from 1,2-disubstituted 1,2-diols led to good yields and a high diasteroselectivity, likewise compounds synthetized from 1,1-disubstituted 1,2-diol led to high regioselectivity rate.

There are two main points to work on in this project: first, continue expanding the the scope of diols used to access the dioxane motif, especially with regard to the different selectivities that could be achieved. Second, final derivatisation of the 1,4-dioxane products should be further attempted. Especially the hydroxyl group can be investigated as a useful vector for further reactions.

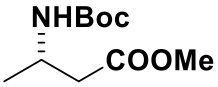
8. Experimental – Part 1

8.1 General methods

Melting points were determined on a Buchi B-540 capillary melting point apparatus and are uncorrected. 1 H NMR spectra were recorded on a Bruker AVANCE 200 or AVANCE 500 spectrometer, using CDCl3 as solvent unless otherwise noted. Chemical shifts (d scale) are reported in parts per million (ppm), coupling constants (J values) are given in hertz (Hz). Infrared spectra were obtained on a Nicolet Avatar 360 FT-IR spectrometer; absorbances are reported in m (cm^{-1}). Column chromatography purifications were performed under flash conditions using Merck 230–400 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on Merck silica gel 60 F254 plates. All chemicals were purchased from commercial suppliers and used directly without any further purification.

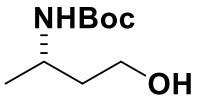
9. Experimental Details and Characterisation Data: Compounds for Chapter 3

Methyl (S)-3-((tert-butoxycarbonyl)amino)butanoate, 2a



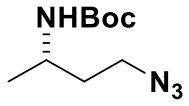
To a stirred solution of methyl (S)-3-aminobutanoate (0.25 g, 2.4 mmol) in dioxane (5 mL) was added at 0 °C a 0.5M aqueous $NaHCO_3$ solution (5 mL) followed by di-tert-butyl dicarbonate (0.80 g, 3.6 mmol). The reaction mixture was stirred for 12 h at room temperature before being concentrated. The resulting solution was acidified at 0 °C (pH = 3.0) by adjunction of 0.1 M HCl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **2a** (1.20 g, 90%) as a colourless oil. Rf = 0.48 (30% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (broad s, 1 H, NH), 4.04 (m, 1 H, CH), 3.60 (s, 3 H, CH_3), 2.57 (t, *J* = 5.9 Hz, 2 H, CH_2), 1.44 (d, *J* = 1.4 Hz, 9 H, *t*-Bu), 1.25 (d, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (CO_2Me), 155.6 ($NHCO_2$), 79.3 (C_q), 51.9 (OCH_3), 47.0 (CH), 43.7 (CH_2), 28.3 (*t*-Bu), 19.6 (CH_3). $[\alpha]D^{20}$ = - 18.1 (c 0.7, $CHCl_3$).

Tert-butyl (S)-(4-hydroxybutan-2-yl)carbamate, 3a



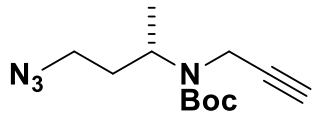
To a stirred solution of N-protected amino acid **2a** (1.8 g, 9.7 mmol) in THF (50 mL) at -10 °C N-methylmorpholine (1.07 mL, 9.7 mmol) was added, followed by isobutyl chloroformate (1.26 mL, 9.7 mmol). After 10 min, $NaBH_4$ (1.10 g, 29.1 mmol) was added in one portion. MeOH (100 mL) was then added dropwise to the mixture at 0 °C over a period of 20 min. The solution was stirred for 1 h and then neutralized with 1 M $KHSO_4$. The organic solvents were removed, and the product was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed consecutively with 1 M $KHSO_4$, aqueous $NaHCO_3$, brine and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (2% MeOH:DCM) afforded **3a** as a transparent oil (0.66 g, 36%). Rf = 0.1 (DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (broad s, 1 H, NH), 4.04 (m, 1 H, CH), 3.80 (t, *J* = 5.9 Hz, 2 H, CH_2OH), 2.57 (t, *J* = 5.8 Hz, 2 H, CH_2), 1.44 (d, *J* = 1.4 Hz, 9 H, *t*-Bu), 1.25 (d, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 ($NHCO_2$), 79.3 (C_q), 61.1 (CH_2OH), 47.0 (CH), 41.7 (CH_2), 28.3 (*t*-Bu), 19.6 (CH_3). $[\alpha]D^{20}$ = - 23.7 (c 0.7, $CHCl_3$).

Tert-butyl (S)-(4-azidobutan-2-yl) carbamate, 4a



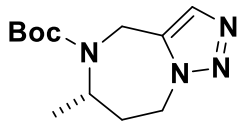
To a stirred solution of **3a** (0.66 g, 3.5 mmol) in anhydrous DCM (4 mL), triethylamine (0.73 mL, 5.25 mmol) and methanesulfonyl chloride (0.41 mL, 5.25 mmol) were added portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aqueous $NaHCO_3$, dried over Na2SO4 and concentrated in vacuo. The mesylate was dissolved in DMF (8 mL). Sodium azide (0.68 g, 10.5 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc:cyclohexane) afforded **4a** as a colourless oil (0.48 g, 63%). Rf = 0.2 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (broad s, 1 H, NH), 4.13 (m, 1 H, CH), 1.56-1.21 (m, 7 H, CH_3, 2 × CH_2), 1.44 (d, *J* = 1.4 Hz, 9 H, *t*-Bu. ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 ($NHCO_2$), 79.3 (C_q), 47.0 (CH), 41.7 (CH_2), 38.2 (CH_2), 28.3 (*t*-Bu), 19.6 (CH_3). [α]D^{20} = - 14.1 (c 0.7, $CHCl_3$).

Tert-butyl (S)-(4-azidobutan-2-yl)(prop-2-yn-1-yl)carbamate, 5a



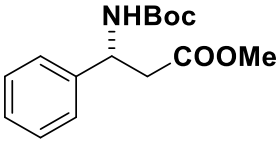
A solution of **4a** (0.11 g, 0.52 mmol) in anhydrous DMF (2.5 mL) was cooled to -30 °C. Propargyl bromide (92 µL, 1.04 mmol) was added and the mixture was allowed to stir for 10 min. NaH (60% dispersion in mineral oil, 52 mg, 2.1 mmol) was added in two portions and the mixture stirred for 3.5 h at -30 °C. The reaction was quenched with saturated NH_4Cl and the aqueous phase extracted with ethyl acetate (6 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:cyclohexane) afforded **5a** as a dark yellow oil (40 mg, 30%). Rf = 0.35 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (m, 1 H, CH), 3.69 (s, 2 H, CH_2), 3.01 (s, 1 H, CH), 1.56-1.21 (m, 7 H, CH_3, 2 × CH_2), 1.44 (d, *J* = 1.4 Hz, 9 H, *t*-Bu), 1.26 (d, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 ($NHCO_2$), 79.3 (C_q), 78.2 (**C**≡CH), 74.0 (C≡**CH**), 47.0 (CH), 41.7 (CH_2), 38.2 (CH_2), 28.3 (*t*-Bu), 19.6 (CH_3). [α]D^{20} = - 12.6 (c 0.7, $CHCl_3$).

Tert-butyl (S)-6-methyl-7,8-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate, 6a



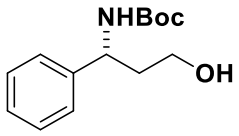
A 0.5 M solution of **5a** (80 mg, 0.32 mmol) in anhydrous chloroform (6.5 mL**)** was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **6a** as a colourless oil (52 mg, 65%). Rf = 0.1 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 16.2 Hz, 1 H, Ar-CH), 4.36 – 4.06 (m, 2 H, CH_2), 3.71 – 3.60 (m, 3 H, CH, CH_2), 2.38 – 2.15 (m, 2 H, CH_2), 1.42 (s, 9 H, *t*-Bu), 1.25 (d, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 ($NHCO_2$), 146.5 (Ar-C_q), 130.1 (Ar-CH), 79.8 (C_q), 63.4 (CH), 48.4 (CH_2), 44.2 (CH_2), 28.3 (*t*-Bu), 26.3 CH_2), 19.6 (CH_3). [α]D^{20} = - 41.1 (c 0.7, $CHCl_3$).

Methyl (R)-3-((tert-butoxycarbonyl)amino)-3-phenylpropanoate, 2b



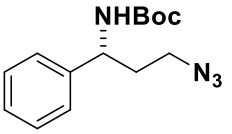
To a stirred solution of L-aspartic acid methyl ester hydrochloride (1.00 g, 5.6 mmol) in dioxane (20 mL) was added at 0 °C a 0.5M aqueous $NaHCO_3$ solution (16.4 mL) followed by di-tert-butyl dicarbonate (1.34 g, 6.14 mmol). The reaction mixture was stirred 12 h at room temperature before being concentrated. The resulting solution was acidified at 0 °C (pH = 3.0) by adjunction of 0.1M HCl and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **2b** (1.54 g, 90%) as a colourless oil. Rf = 0.15 (50% EtOAc:cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.27 (m, 5 H, Ar-CH), 5.08–5.48 (t, 1 H, CH), 3.70 (s, 3 H, OCH_3), 3.31 (q, *J* = 6.8 Hz, 2 H, CH_2), 1.41 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6 (CO_2Me), 155.6 ($NHCO_2$), 143.4 (Ar-C_q), 128.5 (2 × Ar-CH), 127.1 (2 × Ar-CH), 126.7 (Ar-CH), 79.8 (C_q), 59.4 (CH), 51.9 (OCH_3), 49.8 (CH_2), 36.4 (CH_2), 28.2 (*t*-Bu). [α]D^{20} = - 27.3 (c 0.5, $CHCl_3$).

Tert-butyl (R)-(3-hydroxy-1-phenylpropyl)carbamate, 3b



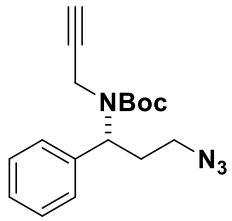
To a stirred solution of N-protected amino acid **2b** (1.54 g, 5.5 mmol) in THF (22 mL) at -10 °C N-methylmorpholine (0.64 mL, 5.8 mmol) was added, followed by isobutyl chloroformate (0.75 mL, 5.8 mmol). After 10 min, $NaBH_4$ (0.66 g, 17.4 mmol) was added in one portion. MeOH (56 mL) was then added dropwise to the mixture at 0 °C over a period of 20 min. The solution was stirred for 1 h and then neutralized with 1 M $KHSO_4$. The organic solvents were removed, and the product was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed consecutively with 1 M $KHSO_4$, aqueous $NaHCO_3$, brine and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **3b** as a white solid (1.2 g, 88%). Rf = 0.34 (40% EtOAc:cyclohexane). m.p. = 104-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.19 (m, 5 H, Ar-CH), 4.93 (broad s, 1 H, NH), 4.78 (m, 1 H, CH), 2.04 (q, *J* = 13.8, 10.9 Hz, 2 H, CH_2), 1.91 (td, *J* = 6.8, 4.3 Hz, 2 H, CH_2), 1.43 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 ($NHCO_2$), 143.4 (Ar-C_q), 128.5 (2 × Ar-CH), 127.1 (2 × Ar-CH), 126.7 (Ar-CH), 79.8 (C_q), 58.6 (CH_2), 54.9 (CH), 36.4 (CH_2), 28.2 (*t*-Bu). [α]D^{20} = - 27.0 (c 0.5, $CHCl_3$).

Tert-butyl (R)-(3-azido-1-phenylpropyl)carbamate, 4b



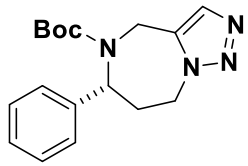
To a stirred solution of **3b** (0.64 g, 2.54 mmol) in anhydrous DCM (5 mL), triethylamine (0.35 mL, 3.8 mmol) and methanesulfonyl chloride (0.29 mL, 3.8 mmol) were added portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aqueous $NaHCO_3$, dried over Na2SO4 and concentrated in vacuo. The mesylate was dissolved in DMF (7 mL). Sodium azide (0.50 g, 7.7 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **4b** as a white solid (0.52 g, 74%). Rf = 0.72 (40% EtOAc:cyclohexane). m.p. = 118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.19 (m, 5 H, Ar-CH), 4.93 (broad s, 1 H, NH), 4.78 (m, 1 H, CH), 3.31 (td, *J* = 6.8, 4.3 Hz, 0H), 2.04 (q, *J* = 13.8, 10.9 Hz, 0H), 1.43 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 ($NHCO_2$), 140.8 (Ar-C_q), 131.9 (2 × Ar-CH), 127.9 (2 × Ar-CH), 121.4 (Ar-CH), 79.9 (C_q), 52.2 (CH), 48.3 (CH_2), 35.5 (CH_2), 28.3 (*t*-Bu). [α]D^{20} = - .3 (c 0.5, $CHCl_3$).

Tert-butyl (R)-(3-azido-1-phenylpropyl)(prop-2-yn-1-yl)carbamate, 5b



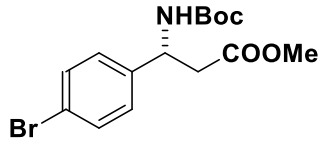
A solution of **4b** (0.20 g, 0.72 mmol) in anhydrous DMF (4 mL) was cooled to -30 °C. Propargyl bromide (128 µL, 1.44 mmol) was added and the mixture was allowed to stir for 10 min. NaH (60% dispersion in mineral oil, 64 mg, 1.8 mmol) was added in two portions and the mixture stirred for 3.5 h at -30 °C. The reaction was quenched with saturated NH_4Cl and the aqueous phase extracted with ethyl acetate (6 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (30% EtOAc:cyclohexane) afforded **5b** as a yellow oil (210 mg, 93%). Rf = 0.40 (10% EtOAc:cyclohexane).

Tert-butyl (R)-6-phenyl-7,8-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate, 6b



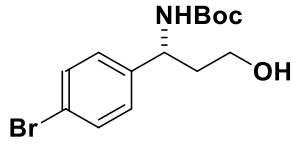
A 0.5 M solution of **5b** (210 mg, 0.67 mmol) in anhydrous chloroform (15 mL**)** was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **6b** as a colourless oil (52 mg, 65%). Rf = 0.25 (50% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.15 (m, 6 H), 5.94 – 4.85 (m, 2H), 4.83 (dd, *J* = 14.5, 7.6 Hz, 1H), 4.42 (ddd, *J* = 14.5, 10.1, 1.6 Hz, 1H), 3.97 (d, *J* = 16.7 Hz, 1H), 2.73 – 2.42 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 ($NHCO_2$), 146.5 (Ar-C_q), 135.0 (Ar-C_q), 131.5 (Ar-CH), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.147 (Ar-CH), 81.3 (C_q), 65.4 (CH), 48.4 (CH_2), 47.1 (CH_2), 31.7 (CH_2), 28.2. (*t*-Bu). [α]D^{20} = + 11.54 (c 0.5, $CHCl_3$).

Methyl (R)-3-(4-bromophenyl)-3-((tert-butoxycarbonyl)amino)propanoate, 2c



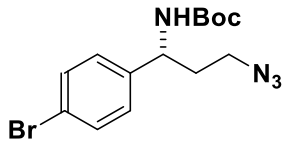
To a stirred solution of methyl (R)-3-amino-3-(4-bromophenyl)propanoate (1.00 g, 4.1 mmol) in dioxane (20 mL) was added at 0 °C a 0.5M aqueous $NaHCO_3$ solution (16.4 mL) followed by di-tert-butyl dicarbonate (0.98 g, 4.51 mmol). The reaction mixture was stirred 12 h at room temperature before being concentrated. The resulting solution was acidified at 0 °C (pH = 3.0) by adjunction of 0.1M HCl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **2c** (1.35 g, 92%) as a colourless oil. Rf 0.64 (30% EtOAc:cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (bs, 1 H, CO_2), 5.61 (d, J = 8.0 Hz, 1 H, NH), 4.58 (dt, J = 8.0, 4.0 Hz, 1 H, CH), 3.68 (s, 3 H, OCH_3), 2.99 (dd, J = 17.0, 4.0 Hz, 1 H, CH_2), 2.83 (dd, J = 17.0, 4.5 Hz, 1 H, CH_2), 1.42 (s, 9 H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4 (CO_2H), 171.6 (CO_2Me), 155.6 ($NHCO_2$), 80.4 (C_q), 52.5 (CH), 52.0 (OCH_3), 49.8 (CH_2), 36.4 (CH_2), 28.2 (*t*-Bu). $[\alpha]D^{20}$ = + 23.5 (c 0.26, $CHCl_3$).

Tert-butyl (R)-(1-(4-bromophenyl)-3-hydroxypropyl)carbamate, 3c



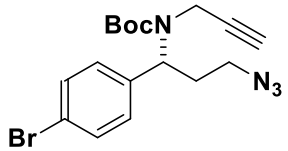
To a stirred solution of N-protected amino acid **2c** (1.0 g, 4.1 mmol) in THF (22 mL) at -10 °C N-methylmorpholine (0.45 mL, 4.1 mmol) was added, followed by isobutyl chloroformate (0.53 mL, 4.1 mmol). After 10 min, $NaBH_4$ (0.46 g, 12.3 mmol) was added in one portion. MeOH (56 mL) was then added dropwise to the mixture at 0 °C over a period of 20 min. The solution was stirred for 1 h and then neutralized with 1 M $KHSO_4$. The organic solvents were removed, and the product was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed consecutively with 1 M $KHSO_4$, aqueous $NaHCO_3$, brine and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc:cyclohexane) afforded **3c** as a white solid (1.3 g, 96%). Rf = 0.42 (40% EtOAc:cyclohexane); m.p. = 61-62 °C. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 7.15 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 4.93 (s, 1 H, NH), 4.74 (m, 1 H, CH), 3.31 (q, *J* = 6.8 Hz, 2 H, CH_2), 1.98 (m, 2 H, CH_2), 1.41 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 ($NHCO_2$), 143.4 (Ar-C_q), 128.5 (2 × Ar-CH), 127.1 (2 × Ar-CH), 126.7 (Ar-C-Br), 79.8 (C_q), 58.6 (CH_2), 54.9 (CH), 36.4 (CH_2), 28.2 (*t*-Bu). $[\alpha]D^{20}$ = +57.14 (c 4.8, $CHCl_3$).

Tert-butyl (R)-(3-azido-1-(4-bromophenyl)propyl)carbamate, 4c



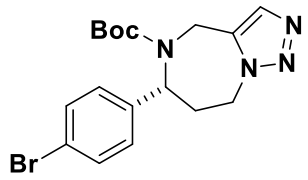
To a stirred solution of **3c** (1.3 g, 3.94 mmol) in anhydrous DCM (6 mL), triethylamine (0.82 mL, 5.9 mmol) and methanesulfonyl chloride (0.46 mL, 5.9 mmol) were added portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aqueous $NaHCO_3$, dried over Na2SO4 and concentrated in vacuo. The mesylate was dissolved in DMF (11 mL). Sodium azide (0.77 g, 11.8 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **4c** as a white solid (0.52 g, 74%). Rf = 0.55 (40% EtOAc:cyclohexane); m.p. = 134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2 H, 2 × Ar-CH), 7.15 (d, *J* = 8.1 Hz, 2 H, 2 × Ar-CH), 4.93 (s, 1 H, NH), 4.74 (m, 1 H, CH), 1.98 (m, 2 H, CH_2), 1.41 (s, 9 H, *t*-Bu), 1.21 (q, *J* = 6.8 Hz, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 ($NHCO_2$), 143.4 (Ar-C_q), 128.5 (2 × Ar-CH), 127.1 (2 × Ar-CH), 126.7 (Ar-C-Br), 79.8 (C_q), 55.4 (CH), 47.2 (CH_2), 36.4 (CH_2), 28.2 (*t*-Bu). $[\alpha]D^{20}$ = + 24.20 (c 4.5, $CHCl_3$).

Tert-butyl (R)-(3-azido-1-(4-bromophenyl)propyl)(prop-2-yn-1-yl)carbamate, 5c



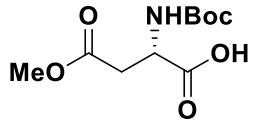
A solution of **4c** (0.35 g, 1 mmol) in anhydrous DMF (4.5 mL) was cooled to -30 °C. Propargyl bromide (178 µL, 2 mmol) was added and the mixture was allowed to stir for 10 min. NaH (60% dispersion in mineral oil, 90 mg, 3 mmol) was added in two portions and the mixture stirred for 3.5 h at -30 °C. The reaction was quenched with saturated NH_4Cl and the aqueous phase extracted with ethyl acetate (6 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:cyclohexane) afforded **5c** as a yellow oil (0.3 g, 76%). Rf = 0.50 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.5 Hz, 2 H, 2 × Ar-CH), 7.18 (d, *J* = 8.2 Hz, 2 H, 2 × Ar-CH), 5.33 (d, *J* = 25.2 Hz, 1 H, CH), 3.52 (t, *J* = 6.3 Hz, 1 H, CH), 3.46 – 3.30 (m, 2 H, CH_2), 2.36 (dd, *J* = 11.0, 5.5 Hz, 2 H, CH~~2~~), 1.51 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6 ($NHCO_2$), 143.4 (Ar-C_q), 128.5 (2 × Ar-CH), 127.1 (2 × Ar-CH), 126.7 (Ar-C-Br), 79.8 (C_q), 78.2 (**C**≡CH), 74.0 (C≡**CH**), 55.4 (CH), 46.2 (CH_2), 36.4 (CH_2), 35.2 (CH_2), 28.2 (*t*-Bu). $[\alpha]D^{20}$ = + 64.18 (c 0.7, $CHCl_3$).

Tert-butyl (R)-6-(4-bromophenyl)-7,8-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate, 6c



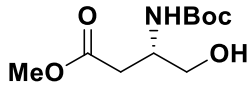
A 0.5 M solution of **5c** (196 mg, 0.5 mmol) in anhydrous chloroform was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% MeOH:EtOAc) afforded **6c** as a white solid (182 mg, 93%). Rf = 0.20 (50% EtOAc:cyclohexane). m.p. = 252 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (dd, *J* = 8.7, 2.5 Hz, 3 H, 1 × Ar-CH, 2 × Ar-CH), 7.18 (d, *J* = 8.2 Hz, 2 H, 2 × Ar-CH), 5.69 (broad s, 1 H, CH), 4.89 (dd, *J* = 14.5, 7.6 Hz, 2 H, CH_2),), 4.53 – 4.40 (m, 1 H, C**H**H), 3.99 (m, 1 H, CH**H**), 2.77 – 2.43 (m, 2 H, CH_2), 1.40 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 ($NHCO_2$), 146.5 (Ar-C_q), 135.0 (Ar-C_q), 131.5 (Ar-CH), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 120.4 (Ar-C_q), 81.6 (C_q), 65.4 (CH), 48.4 (CH_2), 47.1 (CH_2), 31.7 (CH_2), 28.2. (*t*-Bu). [α]D^{20} = + 16.99 (c 0.7, $CHCl_3$).

(S)-2-((tert-butoxycarbonyl)amino)-4-methoxy-4-oxobutanoic acid, 8



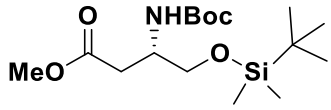
To a stirred solution of L-aspartic acid methyl ester hydrochloride (1.00 g, 5.4 mmol) in dioxane (20 mL) was added at 0 °C a 0.5M aqueous $NaHCO_3$ solution (22 mL) followed by di-tert-butyl dicarbonate (1.30 g, 6.0 mmol). The reaction mixture was stirred 12 h at room temperature before being concentrated. The resulting solution was acidified at 0 °C (pH = 3.0) by adjunction of 0.1M HCl and extracted with ethyl acetate (3x20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **8** (1.20 g, 90%) as a transparent gummy oil. Rf 0.64 (30% EtOAc:cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (bs, 1 H, CO_2H), 5.61 (d, J = 8.0 Hz, 1 H, NH), 4.58 (dt, J = 8.0, 4.0 Hz, 1 H, CH), 3.68 (s, 3 H, OCH_3), 2.99 (dd, J = 17.0, 4.0 Hz, 1 H, CH_2), 2.83 (dd, J = 17.0, 4.5 Hz, 1 H, CH_2), 1.42 (s, 9 H, *t*-Bu); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4 (CO_2H), 171.6 (CO_2Me), 155.6 ($NHCO_2$), 80.4 (C_q), 52.5 (CH), 52.0 (OCH_3), 49.8 (CH_2), 36.4 (CH_2), 28.2 (*t*-Bu). [α]D^{20} = + 23.5 (c 0.26, $CHCl_3$).

Methyl (S)-3-((tert-butoxycarbonyl)amino)-4-hydroxybutanoate, 9



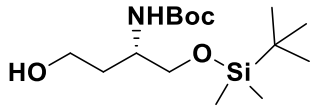
To a stirred solution of N-protected amino acid **8** (4 g, 16.2 mmol) in THF (80 mL) at -10 °C N-methylmorpholine (1.63 mL, 16.2 mmol) was added, followed by isobutyl chloroformate (2.11 mL, 16.2 mmol). After 10 min, $NaBH_4$ (1.84 g, 48.6 mmol) was added in one portion. MeOH (160 mL) was then added dropwise to the mixture at 0 °C over a period of 20 min. The solution was stirred for 1 h and then neutralized with 1 M $KHSO_4$. The organic solvents were removed, and the product was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed consecutively with 1 M $KHSO_4$, aqueous $NaHCO_3$, brine and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (5% MeOH:DCM) afforded **9** as a transparent oil (1.43 g, 38%). Rf = 0.22 (10% MeOH:DCM); ^{1}H NMR (400 MHz, $CDCl_3$) 5.27 (bs, 1 H, NH), 4.02-3.95 (m, 1 H, CH), 3.70-3.65 (m, 5 H, OCH_3, CH_2OH), 2.62 (d, 2 H, J=6.3 Hz, CH_2), 1.43 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2 (CO_2Me), 155.7 ($NHCO_2$), 79.6 (C_q), 63.8 (CH_2O), 52.5 (CH), 51.6 (OCH_3), 49.2 (CH_2), 35.7 (CH_2), 28.2 (*t*-Bu). $[\alpha]D^{20}$ = + 6.3 (c 0.5, $CHCl_3$).

Methyl (S)-3-((tert-butoxycarbonyl)amino)-4-((tert-butyldimethylsilyl)oxy)butanoate, 10



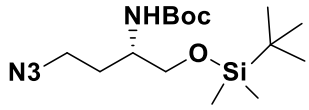
To a stirred solution of **9** (2.52 g, 10.8 mmol) in anhydrous dichloromethane (90 mL) at 0 °C and under nitrogen atmosphere was added imidazole (1.2 g, 18.4 mmol) followed 15 min later by tert-butyldimethylsilyl chloride (4.5 g, 16.2 mmol). The reaction mixture was slowly allowed to reach room temperature and stirred for 4 h. The combined organic phases were washed with water (30 mL), brine (20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **10** as a pale yellow oil (3.46 g, 92%). Rf = 0.77 (30% EtOAc:cyclohexane) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (d, *J* = 9.1 Hz, 1 H, NH), 4.00 (m, 1 H, CH), 3.67 – 3.56 (m, 5 H, OCH_3, CH_2OH), 2.55 (dd, *J* = 6.2, 4.1 Hz, 2 H, CH_2), 1.41 (s, 9 H, *t*-Bu), 0.85 (s, 9 H, *t*-Bu), 0.01 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8 (CO_2Me), 155.1 ($NHCO_2$), 79.3 (C_q), 64.9 (CH_2O), 52.5 (CH), 51.6 (OCH_3), 48.8 (CH_2), 35.9 (CH_2), 28.3 (*t*-Bu), 26.8 (*t*-Bu), 19.2 (C_q), -3.6 (CH_3), -5.5 (CH_3). $[\alpha]D^{20}$ = - 8.4 (c 2.0, $CHCl_3$).

Tert-butyl (S)-(1-((tert-butyldimethylsilyl)oxy)-4-hydroxybutan-2-yl)carbamate, 11



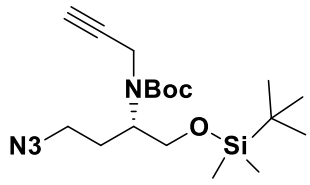
To a stirred solution of **10** (1.5 g, 4.32 mmol) in anhydrous tetrahydrofuran (90 mL), a 2.0 M lithium borohydride solution (3.24 ml, 6.5 mmol) in tetrahydrofuran was added at 0 °C. The resulting mixture was stirred for 6 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (30% EtOAc:cyclohexane) afforded **11** as a transparent oil (1.03 g, 74%). Rf = 0.44 (30% EtOAc:cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (d, *J* = 9.1 Hz, 1 H, NH), 4.05 (t, J = 5.5 Hz, 1 H, CH), 3.63 – 3.57 (m, 5 H, CH_2OSi, CH_2OH), 1.64 (m, 1 H, C**H**H), 1.45 (m, 1 H, CH**H**), 1.41 (s, 9 H, *t*-Bu), 0.85 (s, 9 H, *t*-Bu), 0.01 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 ($NHCO_2$), 79.8 (C_q), 65.6 (CH_2O), 58.6 (CH), 48.4 (CH_2), 35.4 (CH_2), 28.3 (*t*-Bu), 25.8 (*t*-Bu), 18.2 (C_q), -3.6 (CH_3), -5.5 (CH_3). [α]D^{20} = -30.22 (c 0.15, $CHCl_3$).

Tert-butyl (S)-(4-azido-1-((tert-butyldimethylsilyl)oxy)butan-2-yl)carbamate, 12



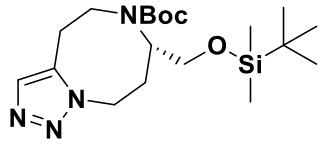
To a stirred solution of **11** (1.0 g, 3.2 mmol) in anhydrous DCM (5 mL), triethylamine (0.67 mL, 6.4 mmol) and methanesulfonyl chloride (0.37 mL, 6.4 mmol) were added portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aqueous $NaHCO_3$, dried over Na2SO4 and concentrated in vacuo. The mesylate was dissolved in DMF (20 mL). Sodium azide (0.63 g, 9.6 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc:cyclohexane) afforded **12** as a pale-yellow oil (0.70 g, 64%). Rf = 0.65 (40% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (broad s, 1 H, NH), 3.73 (m, 1 H, CH), 3.64 – 3.59 (dt, *J* = 10.0, 5.4 Hz, 2 H, CH_2OSi), 3.44 – 3.29 (m, 2 H, CH_2), 1.79 (td, *J* = 7.6, 5.5 Hz, 2 H, CH_2), 1.46 (s, 9 H, *t*-Bu), 0.90 (s, 9 H, *t*-Bu), 0.06 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 ($NHCO_2$), 79.8 (C_q), 65.6 (CH_2O), 58.6 (CH), 48.4 (CH_2), 35.4 (CH_2), 28.3 (*t*-Bu), 25.8 (*t*-Bu), 18.2 (C_q), -3.6 (CH_3), -5.5 (CH_3). [[α]D^{20} = -18.2 (c 0.5, $CHCl_3$).

Tert-butyl (S)-(4-azido-1-((tert-butyldimethylsilyl)oxy)butan-2-yl)(prop-2-yn-1-yl)carbamate, 13



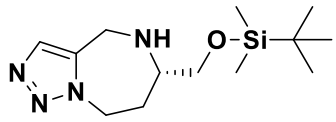
A solution of **13** (0.86 g, 2.5 mmol) in anhydrous DMF (22 mL) was cooled to -30 °C. Propargyl bromide (1.27 mL, 14 mmol) and 15-cown-5 (1.79 mL, 9 mmol) were added, and the mixture was allowed to stir for 10 min. NaH (60% dispersion in mineral oil, 0.36 g, 9 mmol) was added in two portions and the mixture stirred for 3.5 h at -30 °C. The reaction was quenched with saturated NH_4Cl and the aqueous phase extracted with ethyl acetate (6 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:cyclohexane) afforded **13** as a green oil. Rf = 0.36 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 – 3.88 (dt, *J* = 10.0, 5.4 Hz, 2 H, CH_2OSi), 3.73 (m, 1 H, CH), 3.70 (dd, *J* = 13.1, 4.2 Hz, 2 H, CH_2N), 3.44 – 3.29 (m, 2 H, CH_2), 3.09 (s, 1 H, CH), 1.79 (td, *J* = 7.6, 5.5 Hz, 2 H, CH_2), 1.46 (s, 9 H, *t*-Bu), 0.90 (s, 9 H, *t*-Bu), 0.06 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 ($NHCO_2$), 79.8 (C_q), 78.2 (**C**≡CH), 74.0 (C≡**CH**), 65.6 (CH_2O), 58.6 (CH), 48.4 (CH_2), 41.3 (CH_2N), 35.4 (CH_2), 28.3 (*t*-Bu), 25.8 (*t*-Bu), 18.2 (C_q), -3.6 (CH_3), -5.5 (CH_3). [[α]D^{20} = -74.3 (c 1.5, $CHCl_3$).

Tert-butyl (S)-7-(((tert-butyldimethylsilyl)oxy)methyl)-4,5,8,9-tetrahydro-[1,2,3]triazolo[1,5-a][1,5]diazocine-6(7H)-carboxylate, 14



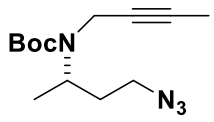
A 0.5 M solution of **13** (0.6 g, 1.56 mmol) in anhydrous chloroform (3.5 mL**)** was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **14** as a colourless oil (0.47 g, 81%). Rf = 0.4 (5% MeOH:DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 16.2 Hz, 1 H, Ar-CH), 4.91 – 4.61 (m, 2 H, CH_2OSi), 4.36 – 4.06 (m, 3 H, CH, CH_2), 3.85 – 3.60 (m, 2 H, CH_2), 2.38 – 2.15 (m, 2 H, CH_2), 1.32 (s, 9 H, *t*-Bu), 0.81 (d, *J* = 2.2 Hz, 9 H, *t*-Bu), -0.01 (d, *J* = 2.0 Hz, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 ($NHCO_2$), 146.5 (Ar-C_q), 130.1 (Ar-CH), 79.8 (C_q), 65.6 (CH_2O), 63.4 (CH), 48.4 (CH_2), 44.2 (CH_2), 28.3 (*t*-Bu), 26.3 CH_2), 25.8 (*t*-Bu), 18.2 (C_q), -3.6 (CH_3), -5.5 (CH_3). [α]D^{20} = -47.1 (c 0.8, $CHCl_3$).

(S)-6-(((tert-butyldimethylsilyl)oxy)methyl)-5,6,7,8-tetrahydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine, 15



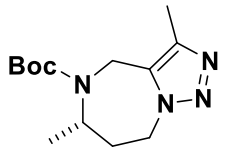
To a stirred solution of **14** (0.12 g, 0.3 mmol) in anhydrous THF (4 mL) tetrabutylammonium fluoride (0.14 g, 0.45 mmol) was added. After 1 h at room temperature, the reaction mixture was diluted with dichloromethane (5 mL), washed with water (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (30% EtOAc:cyclohexane) afforded **15** as a colourless oil (0.28 g, 94%). Rf = 0.15 (5% MeOH:DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 16.2 Hz, 1 H, Ar-CH), 4.50 (broad s, 1 H, NH), 4.45 – 4.31 (m, 2 H, CH_2OSi), 4.36 – 4.06 (m, 3 H, CH, CH_2), 3.85 – 3.60 (m, 2 H, CH_2), 2.38 – 2.15 (m, 2 H, CH_2), 1.32 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.5 (Ar-C_q), 130.1 (Ar-CH), 65.6 (CH_2O), 63.4 (CH), 48.4 (CH_2), 44.2 (CH_2), 26.3 (CH_2), 25.8 (*t*-Bu), 18.2 (C_q), -3.6 (CH_3), -5.5 (CH_3). $[\alpha]D^{20}$ = -12.3 (c 0.5, $CHCl_3$).

Tert-butyl (S)-(4-azidobutan-2-yl)(but-2-yn-1-yl)carbamate, 16



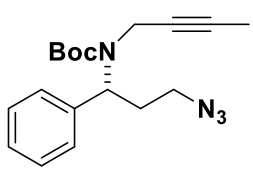
A solution of **4a** (530 g, 2 mmol) in anhydrous DMF (7 mL) was cooled to -30 °C. 1-bromobut-2-yne (350 µL, 4 mmol) was added and the mixture was allowed to stir for 10 min. NaH (60% dispersion in mineral oil, 105 mg, 4.4 mmol) was added in two portions and the mixture stirred for 3.5 h at -30 °C. The reaction was quenched with saturated NH_4Cl and the aqueous phase extracted with ethyl acetate (6 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:cyclohexane) afforded **16** as a brown oil (40 mg, 30%). Rf = 0.28 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (m, 1 H, CH), 3.60 (s, 2 H, CH_2), 1.81 (s, 3 H, C3), 1.56-1.21 (m, 7 H, CH_3, 2 × CH_2), 1.44 (d, *J* = 1.4 Hz, 9 H, *t*-Bu), 1.25 (d, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 ($NHCO_2$), 79.8 (**C**≡C), 79.6 (C≡**C**), 79.3 (C_q), 58.1 (CH), 47.0 (CH_2), 41.7 (CH_2), 38.2 (CH_2), 28.3 (*t*-Bu), 19.6 (CH_3), 3.1 (CH_3). $[\alpha]D^{20}$ = - 14.6 (c 0.7, $CHCl_3$).

Tert-butyl (S)-3,6-dimethyl-7,8-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate, 17



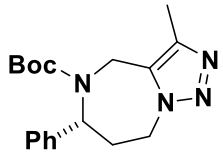
A 0.5 M solution of **16** (164 mg, 0.50 mmol) in anhydrous chloroform was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **17** as a colourless (131 mg, 80%). Rf = 0.25 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 – 4.06 (m, 2 H, CH_2), 3.71 – 3.60 (m, 3 H, CH, CH_2), 2.38 – 2.15 (m, 2 H, CH_2), 2.41 (s, 3 H, CH_3) 1.42 (s, 9 H, *t*-Bu), 1.25 (d, *J* = 6.8 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0 ($NHCO_2$), 146.5 (Ar-C_q), 130.1 (Ar-C_q), 79.8 (C_q), 63.4 (CH), 48.4 (CH_2), 44.2 (CH_2), 28.3 (*t*-Bu), 26.3 CH_2), 19.6 (CH_3), 11.0 (CH_3). $[\alpha]D^{20}$ = - 32.1 (c 0.7, $CHCl_3$)

Tert-butyl (R)-(3-azido-1-phenylpropyl)(but-2-yn-1-yl)carbamate, 18



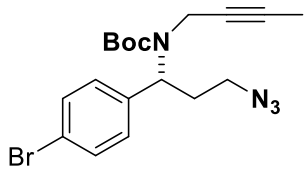
A solution of **4b** (656 mg, 2 mmol) in anhydrous DMF (7 mL) was cooled to -30 °C. 1-bromobut-2-yne (350 µL, 4 mmol) was added and the mixture was allowed to stir for 10 min. NaH (60% dispersion in mineral oil, 105 mg, 4.4 mmol) was added in two portions and the mixture stirred for 3.5 h at -30 °C. The reaction was quenched with saturated NH_4Cl and the aqueous phase extracted with ethyl acetate (6 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:cyclohexane) afforded **18** as a green oil (393 mg, 60%). Rf = 0.42 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.27 (m, 5 H, 5 ×Ar-CH), 4.78 (m, 1 H, CH), 3.60 (s, 2 H, CH_2), 1.90 – 1.79 (m, 5 H, CH_2, CH_3), 1.44 (d, *J* = 1.4 Hz, 9 H, *t*-Bu), 1.25 (m, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 ($NHCO_2$), 138.5 (Ar-C_q), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.147 (Ar-CH), 79.8 (**C**≡C), 79.6 (C≡**C**), 79.3 (C_q), 59.0 (CH), 47.0 (CH_2), 35.1 (CH_2), 35.0 (CH_2), 28.3 (*t*-Bu), 3.4 (CH_3). $[\alpha]D^{20}$ = - 2.3 (c 0.5, $CHCl_3$).

Tert-butyl (R)-3-methyl-6-phenyl-7,8-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate, 19



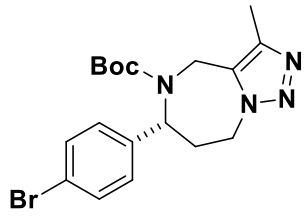
A 0.5 M solution of **18** (210 mg, 0.50 mmol) in anhydrous chloroform (15 mL**)** was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **19** as a colourless oil (52 mg, 65%). Rf = 0.25 (50% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.15 (m, 6 H, 6 ×Ar-CH), 4.83 (dd, *J* = 13.5, 7.6 Hz, 1H), 4.42 (d, *J* = 14.3 Hz, 1 H, C**H**H), 3.97 (d, *J* = 14.5 Hz 1 H, CH**H**), 3.71 – 3.59 (m, 2 H, CH_2), 2.73 – 2.42 (m, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 1.36 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 ($NHCO_2$), 146.5 (Ar-C_q), 140.0 (Ar-C_q), 138.5 (Ar-C_q), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.147 (Ar-CH), 79.8 (C_q), 66.4 (CH), 49.1 (CH_2), 44.1 (CH_2), 32.7 (CH_2), 28.2. (*t*-Bu), 11.0 (CH_3). [α]D^{20} = + 15.4 (c 0.5, $CHCl_3$)

Tert-butyl (R)-(3-azido-1-(4-bromophenyl)propyl)(but-2-yn-1-yl)carbamate, 20



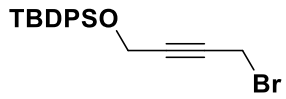
A solution of **4c** (814 mg, 2 mmol) in anhydrous DMF (10 mL) was cooled to -30 °C. 1-bromobut-2-yne (350 µL, 4 mmol) was added and the mixture was allowed to stir for 10 min. NaH (60% dispersion in mineral oil, 105 mg, 4.4 mmol) was added in two portions and the mixture stirred for 3.5 h at -30 °C. The reaction was quenched with saturated NH_4Cl and the aqueous phase extracted with ethyl acetate (6 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:cyclohexane) afforded **20** as a green oil (520 mg, 64%). Rf = 0.48 (10% EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (d, *J* = 8.7, 2 H, 2 × Ar-CH), 7.17 (d, *J* = 8.2 Hz, 2 H, 2 × Ar-CH), 4.90 (m, 1 H, CH), 3.60 (s, 2 H, CH_2), 1.90 – 1.79 (m, 5 H, CH_2, CH_3), 1.44 (d, *J* = 1.4 Hz, 9 H, *t*-Bu), 1.25 (m, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (CO_2NH), 138.5 (Ar-C_q), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 120.2 (Ar-Cq), 79.8 (**C**≡C), 79.6 (C≡**C**), 79.3 (C_q), 59.0 (CH), 47.0 (CH_2), 35.1 (CH_2), 35.0 (CH_2), 28.3 (*t*-Bu), 3.4 (CH_3). [α]D^{20} = - 11.3 (c 0.5, $CHCl_3$)

Tert-butyl (R)-6-(4-bromophenyl)-3-methyl-7,8-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate, 21



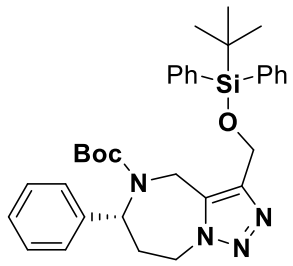
A 0.5 M solution of **20** (204 mg, 0.5 mmol) in anhydrous chloroform was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **21** as a white solid (182 mg, 93%). Rf = 0.32 (50% EtOAc:cyclohexane). m.p. = 67-70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.85 (d, *J* = 8.7, 2 H, 2 × Ar-CH), 7.17 (d, *J* = 8.2 Hz, 2 H, 2 × Ar-CH), 4.83 (dd, *J* = 13.5, 7.6 Hz, 1H), 4.42 (d, *J* = 14.3 Hz, 1 H, C**H**H), 3.97 (d, *J* = 14.5 Hz 1 H, CH**H**), 3.71 – 3.59 (m, 2 H, CH_2), 2.73 – 2.42 (m, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 1.36 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 ($NHCO_2$), 146.5 (Ar-C_q), 140.0 (Ar-C_q), 138.5 (Ar-C_q), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.147 (Ar-CH), 120.4 (Ar-C_q), 79.8 (C_q), 65.7 (CH), 49.1 (CH_2), 44.1 (CH_2), 32.7 (CH_2), 28.2. (*t*-Bu), 11.3 (CH_3). $[\alpha]D^{20}$ = + 12.4 (c 0.5, $CHCl_3$).

((4-bromobut-2-yn-1-yl)oxy)(tert-butyl)diphenylsilane, 22



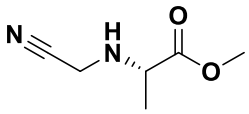
To a THF (30 ml) suspension of NaH (60% in oil dispersion 905 mg, 22.6mmol) was added a THF (5.0 ml) solution of 1,4-dihydroxy-2-butyne (1.56 g, 18.1 mmol) from the dropping funnel over 10 min at 0 °C. After 30 min, a THF (5.0 ml) solution of TBSCl (3.0 g, 19.9 mmol) was added to the mixture, and the mixture was stirred for 3 h at the same temperature. The reaction was quenched with water (10 mL) and organic layers were extracted with ethyl acetate (3 x 50 ml). The organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded the monoprotected alcohol as a colourless oil (4.8 g, 82%). Alcohol (2.22 g, 12.6 mmol) was added to a THF (28.0 ml) solution of PPh3 (4.26 g, 16.4 mmol) and the mixture was cooled to 0 °C. CBr_4 (4.17 g, 12.6 mmol) was added in five portions over 20 min at 0 °C, and the mixture was stirred at 0 °C for 1 h. Hexane (28.2 ml) was then added to dilute the solution, which resulted in the precipitation of Ph_3PO. The solid was removed by filtration. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **22** as a yellow oil (3.61 g, 74%). The observed characterisation data (Rf, ^{1}H, ^{13}C) was consistent with that previously reported in the literature[73].

Tert-butyl (R)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-6-phenyl-7,8-dihydro-4H-[1,2,3]triazolo[1,5-a][1,4]diazepine-5(6H)-carboxylate, 23



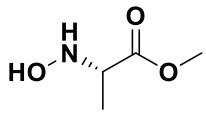
A 0.5 M solution of N-(3-azido-1-phenylpropyl)-4-((tert-butyldiphenylsilyl)oxy)but-2-yn-1-amine (154 mg, 0.26 mmol) in anhydrous chloroform was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **22** as a yellow oil (114 mg, 96%). Rf = 0.25 (50% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.79 – 7.65 (m, 5 H, 5 × Ar-CH), 7.54 – 7.23 (m, 10 H, 10 × Ar-CH), 5.05 (s, 2 H, OCH2), 4.83 (dd, *J* = 13.5, 7.6 Hz, 1H), 4.42 (d, *J* = 14.3 Hz, 1 H, C**H**H), 3.97 (d, *J* = 14.5 Hz 1 H, CH**H**), 3.53 – 3.28 (m, 2 H, CH_2), 2.27 – 2.13 (m, 2 H, CH_2), 1.36 (s, 9 H, *t*-Bu), 0.99 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 ($NHCO_2$), 146.5 (Ar-C_q), 141.9 (Ar-C_q), 138.045 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 79.8 (C_q), 66.4 (CH), 63.4 (OCH_2), 49.1 (CH_2), 44.1 (CH_2), 32.7 (CH_2), 28.8 (C_q), 28.2. (*t*-Bu), 23.6 (*t*-Bu). $[\alpha]D^{20}$ = - 27.91 (c 0.5, $CHCl_3$)

Methyl (cyanomethyl)-L-alaninate, 25



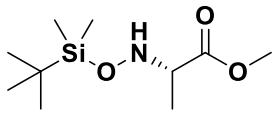
To a stirred solution of (S)-1-methoxy-1-oxopropan-2-aminium chloride (558 mg, 4 mmol) in anhydrous MeCN (15 mL) bromoacetonitrile (0.31 mL, 4.4 mmol) and DIPEA (1.38 mL, 8 mmol) were added. The reaction stirred at room temperature for 16 h. After completion, the mixture was washed with aqueous $NaHCO_3$ and extracted with DCM (3 × 30 mL). The combined organic layers dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (5% MeOH/DCM) afforded **25** as a yellow oil (360 mg, 63%). Rf = 0.80 (5% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) 3.67-3.61 (m, 5 H, CH_2, OCH_3), 3.48 (dt, *J* = 8.2, 4.4 Hz, 2 H, CH), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3).). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO), 117.7 (CN), 66.6 (CH), 51.9 (OCH_3), 34.4 (CH_2), 17.2 (CH_3).

Methyl hydroxy-L-alaninate, 26



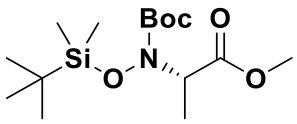
M-Chloroperbenzoic acid (873 mg, 5.06 mmlol) was added in portions over 30 min to a solution of **25** (360 mg, 2.53 mmol) in DCM at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1 h. After completion, it was quenched with aqueous $NaHCO_3$, extracted with DCM (3 × 30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in MeOH (5 mL) and hydroxylamine hydrochloride () was added. The resulting mixture was heated to 50 °C for 6 h, then the solvent was removed, and the residue taken up in EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. Rf = 0.9 (5% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) 10.38 (broad s, 1 H, OH), 6.59 (broad s, 1 H, NH), 3.66 (s, 3 H, OCH_3), 3.74 (dd, *J* = 5.6, 4.0 Hz, 1 H, CH), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO), 66.6 (CH), 51.9 (OCH_3), 17.2 (CH_3).

Methyl ((tert-butyldimethylsilyl)oxy)-L-alaninate, 27



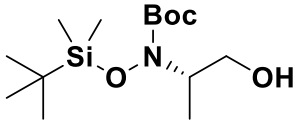
To a stirred solution of **26** (240 mg, 2 mmol) in anhydrous dichloromethane (10 mL) at 0 °C and under nitrogen atmosphere was added imidazole (1.2 g, 18.4 mmol) followed 15 min later by tert-butyldimethylsilyl chloride (345 mg, 3.22 mmol). The reaction mixture was slowly allowed to reach room temperature and stirred for 4 h. The combined organic phases were washed with water (5 mL), brine (10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:cyclohexane) afforded **27** as a colourless oil (245 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3 H, OCH_3), 3.74 (dd, *J* = 5.6, 4.0 Hz, 1 H, CH), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3), 0.99 (s, 9 H, *t*-Bu), 0.21 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO), 66.6 (CH), 51.9 (OCH_3), 28.1 (C_q), 23.6 (*t*-Bu), 17.2 (CH_3), -4.9 (2 × CH_3).

Methyl N-(tert-butoxycarbonyl)-N-((tert-butyldimethylsilyl)oxy)-L-alaninate, 28



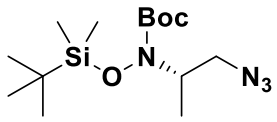
To a stirred solution of **27** (245 mg, 1.05 mmol) in dioxane (10 mL) was added at 0 °C triethylamine (160 µL) followed by di-tert-butyl dicarbonate (250 mg, 1.15 mmol). The reaction mixture was stirred 12 h at room temperature before being concentrated. The resulting solution was acidified at 0 °C (pH = 3.0) by adjunction of 0.1M HCl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **28** (350 mg g, 96%) as a colourless oil. Rf = 0.60 (20% EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3 H, OCH_3), 3.74 (dd, *J* = 5.6, 4.0 Hz, 1 H, CH), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3), 1.42 (s, 9 H, *t*-Bu), 0.99 (s, 9 H, *t*-Bu), 0.21 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO), 155.1 (CONH), 81.1 (C_q), 66.6 (CH), 51.9 (OCH_3), 28.1 (C_q), 28.0 (*t*-Bu), 23.6 (*t*-Bu), 17.2 (CH_3), -4.9 (2 × CH_3).

Tert-butyl (S)-((tert-butyldimethylsilyl)oxy)(1-hydroxypropan-2-yl)carbamate, 29



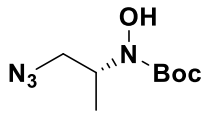
To a stirred solution of **28** (350 mg, 1 mmol) in anhydrous tetrahydrofuran (5 mL), a 2.0 M lithium borohydride solution (1 ml, 2 mmol) in tetrahydrofuran was added at 0 °C. The resulting mixture was stirred for 6 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **29** as a transparent oil (286 mg, 90%). Rf = 0.22 (50% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 5.5 Hz, 1 H, OH), 3.95 – 3.42 (m, 3 H, CH, CH_2), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3), 1.41 (s, 9 H, *t*-Bu), 0.82 (s, 9 H, *t*-Bu), 0.20 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (CONH), 81.1 (C_q), 66.6 (CH), 61.9 (CH_2), 28.1 (C_q), 28.0 (*t*-Bu), 23.6 (*t*-Bu), 17.2 (CH_3), -4.9 (2 × CH_3).

Tert-butyl (S)-(1-azidopropan-2-yl)((tert-butyldimethylsilyl)oxy)carbamate, 30



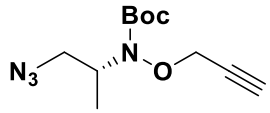
To a stirred solution of **29** (366 mg, 1.05 mmol) in anhydrous DCM (5 mL), triethylamine (220 µL, 1.6 mmol) and methanesulfonyl chloride (122 µL,1.6 mmol) were added portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aqueous $NaHCO_3$, dried over Na2SO4 and concentrated in vacuo. The mesylate was dissolved in DMF (10 mL). Sodium azide (205 mg, 3.14 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc/cyclohexane) afforded **30** as a colourless oil (177 mg, 53%). Rf = 0.5 (50% EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 – 4.02 (m, 1 H, CH), 1.71 (dd, *J* = 11.5, 3.1 Hz, 1 H, C**H**H), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3), 1.43 (dd, *J* = 11.5, 4.9 Hz, 1 H, CH**H**,) 1.41 (s, 9 H, *t*-Bu), 0.82 (s, 9 H, *t*-Bu), 0.20 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (CONH), 81.1 (C_q), 66.6 (CH), 51.9 (CH_2), 28.1 (C_q), 28.0 (*t*-Bu), 23.6 (*t*-Bu), 11.8 (CH_3), -4.9 (2 × CH_3).

Tert-butyl (R)-(1-azidopropan-2-yl)(hydroxy)carbamate, 31



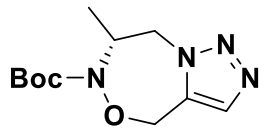
To a stirred solution of **30** (177 mg, 0.82 mmol) in anhydrous THF (4 mL) tetrabutylammonium fluoride (310 mg, 1.22 mmol) was added. After 1 h at room temperature, the reaction mixture was diluited with dichloromethane (5 mL), washed with water (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (30% EtOAc:cyclohexane) afforded **31** as a yellow oil (160 mg, 90%). Rf = 0.10 (5% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (broad s, 1 H, OH), 4.11 – 4.02 (m, 1 H, CH), 1.71 (dd, *J* = 11.5, 3.1 Hz, 1 H, C**H**H), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3), 1.43 (dd, *J* = 11.5, 4.9 Hz, 1 H, CH**H**,) 1.41 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (CONH), 81.1 (C_q), 66.6 (CH), 51.9 (CH_2), 28.1 (C_q), 28.0 (*t*-Bu), 11.8 (CH_3).

Tert-butyl (R)-(1-azidopropan-2-yl)(prop-2-yn-1-yloxy)carbamate, 32



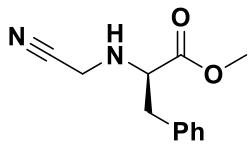
A solution of **31** (160 mg g, 0.74 mmol) in anhydrous DMF (4 mL) was cooled to -30 °C. Propargyl bromide (131 µL, 1.5 mmol) was added and the mixture was allowed to stir for 10 min. NaH (60% dispersion in mineral oil, 45 mg, 1.85 mmol) was added in two portions and the mixture stirred for 3.5 h at -30 °C. The reaction was quenched with saturated NH_4Cl and the aqueous phase extracted with ethyl acetate (6 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (30% EtOAc:cyclohexane) afforded **32** as a yellow oil (114 mg, 61%). Rf = 0.58 (40% EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (broad s, 2 H, OCH_2), 3.52 (t, *J* = 6.3 Hz, 1 H, CH), 3.46 (m, 1 H, CH), 1.71 (dd, *J* = 11.5, 3.1 Hz, 1 H, C**H**H), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3), 1.43 (dd, *J* = 11.5, 4.9 Hz, 1 H, CH**H**,) 1.41 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (CONH), 81.1 (C_q), 77.4 (**C**≡CH), 68.3 (C≡**CH**), 66.6 (CH), 59.3 (CH_2), 52.0 (CH_2), 28.4 (*t*-Bu), 11.8 (CH_3).

Tert-butyl (R)-7-methyl-7,8-dihydro-4H,6H-[1,2,3]triazolo[1,5-e][1,2,5]oxadiazepine-6-carboxylate, 33



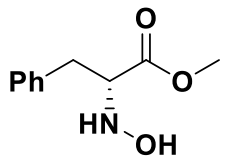
A 0.5 M solution of **32** (114 mg, 0.45 mmol) in anhydrous chloroform was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **33** as a pale rose oil (73 mg, 64%). Rf = 0.18 (50% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1 H, Ar-CH), 4.80 (s, 2 H, CH_2), 4.05 – 3.81 (m, 3 H, CH, CH_2), 1.59 (dd, *J* = 7.1, 4.0 Hz, 3 H, CH_3), 1.40 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 ($NHCO_2$), 142.5 (Ar-CH), 130.0 (Ar-C_q), 81.2 (C_q), 66.1 (CH_2O), 54.9 (CH), 54.1 (CH_2), 28.2. (*t*-Bu), 11.8 (CH_3).

Methyl (cyanomethyl)-D-phenylalaninate, 34



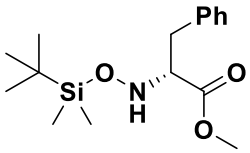
To a stirred solution of (R)-1-methoxy-1-oxo-3-phenylpropan-2-aminium chloride (1.5 g, 6.95 mmol) in anhydrous MeCN (30 mL) bromoacetonitrile (0.96 mL, 13.9 mmol) and DIPEA (3.6 mL, 20.8 mmol) were added. The reaction stirred at room temperature for 16 h. After completion, the mixture was washed with aqueous $NaHCO_3$ and extracted with DCM (3 × 50 mL). The combined organic layers dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (2% MeOH/DCM) afforded **34** as a pale yellow oil (1 g, 65%). Rf = 0.80 (5% MeOH/DCM). ^{1}H NMR (400 MHz, $CDCl_3$) 7.20-7.14 (m, 5 H, 5 × Ar-CH), 3.84 (dt, *J* = 8.2, 4.4 Hz, 2 H, CH), 3.67-3.61 (m, 5 H, CH_2, OCH_3), 3.40-3.15 (m, 2 H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (CO_2), 135.6 (Ar-C_q), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.1 (Ar-CH), 114.7 (CN), 66.6 (CH), 51.9 (OCH_3), 34.4 (CH_2), 17.2 (CH_2).

Methyl hydroxy-D-phenylalaninate, 35



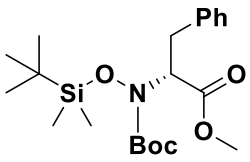
M-Chloroperbenzoic acid (1.11 g, 6.41 mmol) was added in portions over 30 min to a solution of **34** (0.7 g, 3.2 mmol) in DCM (12 mL) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1 h. After completion, it was quenched with aqueous $NaHCO_3$, extracted with DCM (3 × 30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in MeOH (5 mL) and hydroxylamine hydrochloride (1.12 g, 16 mmol) was added. The resulting mixture was heated to 50 °C for 6 h, then the solvent was removed, and the residue taken up in EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **35** as a white solid (0.47 g, 76%). Rf = 0.50 (50% EtOAc:cyclohexane). m.p. = 65-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 10.50 (broad s, 1 H, OH), 9.13 (broad s, 1 H, NH), 7.20-7.14 (m, 5 H, 5 × Ar-CH), 3.84 (dd, *J* = 5.6, 4.0 Hz, 1 H, CH), 3.64 (dd, *J* = 11.5, 3.1 Hz, 1 H, C**H**H), 3.60 (s, 3 H, OCH_3), 3.50 (dd, *J* = 11.5, 4.9 Hz, 1 H, CH**H**). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO), 135.6 (Ar-C_q), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.1 (Ar-CH), 69.6 (CH), 51.9 (OCH_3), 34.4 (CH_2).

Methyl ((tert-butyldimethylsilyl)oxy)-D-phenylalaninate, 36



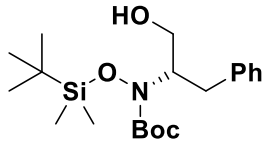
To a stirred solution of **35** (0.47 g, 2.4 mmol) in anhydrous dichloromethane (20 mL) at 0 °C and under nitrogen atmosphere was added imidazole (0.26 g, 3.84 mmol) followed 15 min later by tert-butyldimethylsilyl chloride (1.17 g, 7.81 mmol). The reaction mixture was slowly allowed to reach room temperature and stirred for 4 h. The combined organic phases were washed with water (10 mL), brine (20 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **36** as a colourless oil (0.75 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.14 (m, 5 H, 5 × Ar-CH), 3.84 (dd, *J* = 5.6, 4.0 Hz, 1 H, CH), 3.64 (dd, *J* = 11.5, 3.1 Hz, 1 H, C**H**H), 3.60 (s, 3 H, OCH_3), 3.50 (dd, *J* = 11.5, 4.9 Hz, 1 H, CH**H**), 1.01 (s, 9 H, *t*-Bu), 0.21 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO), 135.6 (Ar-C_q), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.1 (Ar-CH), 69.6 (CH), 67.1 (CH), 51.9 (OCH_3), 28.1 (C_q), 26.2 (*t*-Bu), -4.9 (2 × CH_3).

Methyl N-(tert-butoxycarbonyl)-N-((tert-butyldimethylsilyl)oxy)-D-phenylalaninate, 37



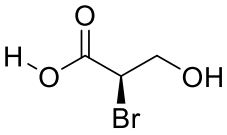
To a stirred solution of **36** (0.74 g, 2.4 mmol) in dioxane (20 mL) was added at 0 °C triethylamine (370 µL, 2.65 mmol) followed by di-*tert*-butyl dicarbonate (0.58 g, 2.65 mmol). The reaction mixture was stirred 12 h at room temperature before being concentrated. The resulting solution was acidified at 0 °C (pH = 3.0) by adjunction of 0.1 M HCl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **37** (0.90 g, 96%) as a pale-yellow oil. Rf = 0.650 (10% EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.14 (m, 5 H, 5 × Ar-CH), 3.84 (dd, *J* = 5.6, 4.0 Hz, 1 H, CH), 3.66 (s, 3 H, OCH_3), 3.64 (dd, *J* = 11.5, 3.1 Hz, 1 H, C**H**H), 3.50 (dd, *J* = 11.5, 4.9 Hz, 1 H, CH**H**), 1.42 (s, 9 H, *t*-Bu), 1.01 (s, 9 H, *t*-Bu), 0.21 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5 (CO), 155.1 (CONH), 135.6 (Ar-C_q), 128.9 (2 × Ar-CH), 127.7 (2 × Ar-CH), 126.1 (Ar-CH), 81.1 (C_q), 73.1 (CH), 51.6 (OCH_3), 30.5 (CH_2), 28.4 (*t*-Bu), 28.0 (C_q), 23.6 (*t*-Bu), -3.4 (2 × CH_3).

Tert-butyl (S)-((tert-butyldimethylsilyl)oxy)(1-hydroxy-3-phenylpropan-2-yl)carbamate, 38



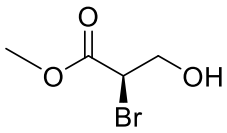
To a stirred solution of **37** (380 mg, 1 mmol) in anhydrous tetrahydrofuran (5 mL), a 2.0 M lithium borohydride solution (1 ml, 2 mmol) in tetrahydrofuran was added at 0 °C. The resulting mixture was stirred for 6 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **38** as a transparent oil (286 mg, 90%). Rf = 0.35 (50% EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 5.5 Hz, 1 H, OH), 7.26-7.14 (m, 5 H, 5 × Ar-CH), 3.08 (dd, *J* = 5.6, 4.0 Hz, 1 H, CH), 3.50 (dd, *J* = 11.5, 3.3 Hz, 1 H, C**H**H), 3.25 (dd, *J* = 11.3, 4.9 Hz, 1 H, CH**H**), 2.92 (dd, *J* = 7.1, 4.0 Hz, 1 H, C**H**H), 2.50 (dd, *J* = 7.3, 4.0 Hz, 1 H, CH**H**), 1.44 (s, 9 H, *t*-Bu), 0.99 (s, 9 H, *t*-Bu), 0.20 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (CONH), 81.1 (C_q), 66.6 (CH), 61.9 (CH_2), 28.1 (C_q), 28.0 (*t*-Bu), 23.6 (*t*-Bu), 17.2 (CH_3), -4.9 (2 × CH_3).

(R)-2-bromo-3-hydroxypropanoic acid, 45



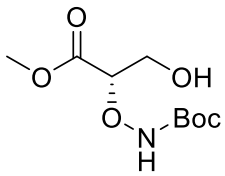
To a solution of L-serine (3 g, 28.53 mmol) in water (25 mL), H_2SO_4 (60 mL, 75 mmol) and KBr (11.88 g, 99.8 mmol) were added. The solution was stirred at -15°C for 10 minutes, then $NaNO_2$ (9.87 g, 142.8 mmol) was added in ten portions (1.15 g, 16.64 mmol). Following complete addition, the solution was slowly warmed up to r.t. and stirred for an additional 8 hours. The solution was saturated with NaCl and extracted with Et_2O (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **45** (4.04 g, 84%) as a yellow oil. Rf = 0.11 (50% EtOAc:pentane); ^{1}H NMR (400 MHz, MeOD) δ 12.2 (s, 1 H, COOH), 4.24 (dd, J = 8.0, 5.7 Hz, 1 H, CH), 3.95 (dd, J = 11.6, 8.0 Hz, 1 H, C**H**H), 3.81 (dd, J = 11.6, 5.8 Hz, 1 H, CH**H**). ^{13}C NMR (101 MHz, MeOD) δ 171.87 (COOH), 64.57 (CH_2), 46.30 (CH). $[\alpha]_D^{20}$ -8.87 (c 2.78, MeOH)

Methyl (R)-2-bromo-3-hydroxypropanoate, 46



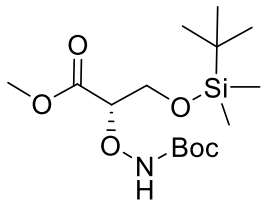
Acetyl chloride (2.67 mL, 37.4 mmol) was slowly added to a solution of **45** (4.04 g, 24 mmol) in MeOH (30 mL). The solution was stirred under reflux for 4 hours. After completion, the reaction was cooled to r.t. and concentrated to a yellow residue. The residue was dissolved in EtOAc, washed with $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **46** as a white solid (3381 mg, 78%). Rf = 0.40 (5% MeOH/DCM); mp = 71° C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.33 (dd, *J* = 7.5, 5.4 Hz, 1 H, CH), 4.09 – 3.87 (m, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 2.96 (s, 1 H, OH). ^{13}C NMR (101 MHz $CDCl_3$) δ 169.4 (COOMe), 63.7 (CH_2), 52.6 (CH), 44.3 (CH_3). $[\alpha]_D^{20}$ -26.49 (c: 0.73, $CDCl_3$).

Methyl (S)-2-(((tert-butoxycarbonyl)amino)oxy)-3-hydroxypropanoate, 47



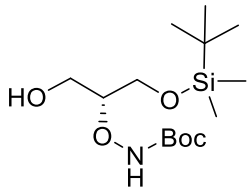
To a solution of $(Boc)_2NOH$ (3.07 g, 23 mmol), in anhydrous MeCN (55 mL) **46** (3.5 g, 19.2 mmol) was added at 0 °C, followed by DBU (3.44 mL, 23 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. After completion, the reaction was extracted with DCM (3 x 100 mL) and washed with saturated aqueous $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **47** as a white solid (4.16 g, 92%). Rf = 0.40 (60% EtOAc:cyclohexane); mp = 101° C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1 H, NH), 4.49 (dd, *J* = 7.7, 3.4 Hz, 1 H, CH), 4.12 (s, 1 H, OH), 3.91 (qd, *J* = 12.7, 5.5 Hz, 2 H, CH_2), 3.76 (s, 3 H, CH_3), 1.46 (s, 9 H, *t*Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (COOMe), 157.9 (COONH), 84.4 (CH), 83.1 (Cq), 60.1 (CH_2), 52.3 (CH_3), 28.1 (3 × CH_3). $[\alpha]_D^{20}$ + 22.43 (c: 0.7, $CDCl_3$)

Methyl (S)-2-(((tert-butoxycarbonyl)amino)oxy)-3-((tert-butyldimethylsilyl)oxy)propanoate, 48



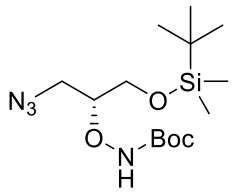
To a solution of **47** (1.2 g, 5 mmol), DMAP (62 mg, 0.5 mmol) and imidazole (555 mg, 8.1 mmol) in anhydrous DCM (40 mL), TBSCl (1.23 g, 8.1 mmol) was added. The mixture was stirred for 3h at room temperature. The reaction was quenched with water and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to afford **48** as a colourless oil (1.65 g, 92%). Rf = 0.70 (60% EtOAc:Cy); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1 H, NH), 4.47 (t, *J* = 3.5 Hz, 1 H, CH), 4.02 (d, *J* = 3.5 Hz, 2 H, CH_2), 3.78 (s, 3 H, CH_3), 1.46 (s, 9 H, *t*Bu), 0.86 (s, 9 H, *t*Bu), 0.05 (s, 6 H, 2 × CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.069 (COOMe), 156.228 (COONH), 84.868 (CH), 81.959 (Cq), 62.548 (CH_2), 52.0 (CH_3), 28.157 (*t*Bu), 25.702 (*t*Bu), 18.221 (Cq), -5.496 (CH_3), -5.601 (CH_3). $[\alpha]_D^{20}$ + 42.60 (c: 0.7, $CDCl_3$).

Tert-butyl (R)-((1-((tert-butyldimethylsilyl)oxy)-3-hydroxypropan-2-yl)oxy)carbamate, 49



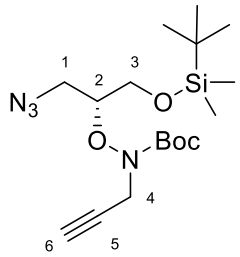
To a stirred solution of **48** (1.6 g, 4.7 mmol) in anhydrous tetrahydrofuran (50 mL), a 2.0 M lithium borohydride solution (4.7 ml, 9.4 mmol) in tetrahydrofuran was added at 0 °C. The resulting mixture was stirred for 6 h at 20 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (5% MeOH/DCM) afforded **49** as a white solid (1.36 g, 90%). Rf = 0.43 (30% EtOAc:Cy); m.p. = 79° C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1 H, NH), 3.96 (broad s, 1 H, OH), 3.85 (dp, *J* = 8.6, 2.9 Hz, 1 H, CH), 3.74 - 3.60 (m, 4 H, 2 × CH_2), 1.48 (s, 9 H, *t*Bu), 0.90 (s, 9 H, *t*Bu), 0.07 (s, 6 H, 2 × CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.318 (COONH), 87.677 (CH), 82.600 (C_q), 61.8 (CH_2), 60.281 (CH_2), 28.118 (*t*Bu), 25.823 (*t*Bu), 18.221 (C_q), -5.434 (CH_3), -5.457 (CH_3). $[\alpha]_D^{20}$ -11.98 (c: 0.4, $CHCl_3$).

Tert-butyl (R)-((1-azido-3-((tert-butyldimethylsilyl)oxy)propan-2-yl)oxy)carbamate, 50



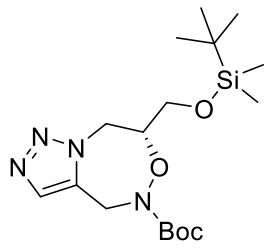
To a stirred solution of **49** (1.36 g, 4.25 mmol) in anhydrous DCM (20 mL), triethylamine (0.88 mL, 6.4 mmol) and methanesulfonyl chloride (0.5 mL, 6.4 mmol) were added portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aqueous $NaHCO_3$, dried over Na2SO4 and concentrated in vacuo. The mesylate was dissolved in DMF (20 mL). Sodium azide (0.83 g, 12.7 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **50** as a colourless oil (1.03 g, 70%). Rf = 0.35 (20% EtOAc: cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1 H, NH), 3.98 – 3.91 (m, 1 H, CH), 3.83 (dd, *J* = 10.7, 4.7 Hz, 1 H, C**H**HO), 3.73 (dd, *J* = 10.7, 6.3 Hz, 1 H, CH**H**O), 3.55 (dd, *J* = 13.1, 4.2 Hz, 1 H, C**H**HN), 3.47 (dd, *J* = 13.1, 5.9 Hz, 1 H, CH**H**N), 1.49 (s, 9 H, tBu), 0.89 (s, 9 H, tBu), 0.07 (s, 6 H, 2 x CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3 (COONH), 87.6 (CH), 82.6 (C_q), 61.8 (CH_2O), 48.1 (CH_2N), 28.1 (*t*Bu), 25.8 (*t*Bu), 18.221 (C_q), -5.4 (CH_3), -5.4 (CH_3). $[\alpha]_D^{20}$ -24.74 (c: 0.7, CHCl3).

Tert-butyl (R)-((1-azido-3-((tert-butyldimethylsilyl)oxy)propan-2-yl)oxy)(prop-2-yn-1-yl)carbamate, 51



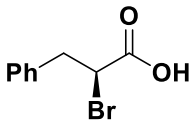
Propargyl bromide (0.26 mL, 3 mmol) was added to a solution of **50** (0.51 g, 1.5 mmol) in anhydrous DMF (5 mL) at 0 °C. After 10 min, NaH (150 mg, 3.75 mmol, 60% dispersion in mineral oil) was added in two portions and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc/cyclohexane) afforded **51** as a colourless oil (450 mg, 78%). Rf: 0.50 (20% EtOAc: cyclohexane). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.19 (dd, *J* = 3.4, 2.4 Hz, 2 H, CH_2O), 4.03 (ddt, *J* = 7.0, 5.7, 4.4 Hz, 1 H, CH), 3.84 (dd, *J* = 10.6, 4.6 Hz, 1 H, NC**H**H), 3.71 (dd, *J* = 10.6, 6.9 Hz, 1 H, NCH**H**), 3.58 (dd, *J* = 13.1, 4.3 Hz, 1 H, CH), 3.50 (dd, *J* = 13.1, 5.7 Hz, 1 H, CH), 2.25 (t, *J* = 2.4 Hz, 1 H, CH), 1.51 (s, 9 H, tBu), 0.89 (s, 9 H, tBu), 0.07 (d, *J* = 1.6 Hz, 6 H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.025 (CO_2NH), 83.904 (Cq), 82.842 (C2), 78.214, (C5), 72.032 (C6), 60.855 (C3), 50.328 (C1), 41.426 (C4), 28.1 (tBu), 25.8 (tBu), 18.2 (Cq), -5.5 (CH_3), -5.4 (CH_3).

Tert-butyl (R)-7-(((tert-butyldimethylsilyl)oxy)methyl)-7,8-dihydro-[1,2,3]triazolo[5,1-d][1,2,5]oxadiazepine-5(4H)-carboxylate, 52



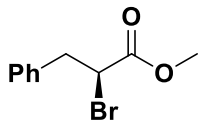
A 0.5 M solution of **51** (450 mg, 1.17 mmol) in anhydrous chloroform was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **52** as a colourless gummy oil (350 mg, 78%). Rf = 0.4 (5% MeOH:DCM). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.56 (s, 1 H, Ar-CH), 5.22 – 5.05 (m, 2 H, 2 x H_4), 4.65 – 4.54 (m, 2 H, 2 x H_1), 4.28 – 4.16 (m, 1 H, H_2), 3.91 (dd, *J* = 10.6, 4.3 Hz, 1 H, H_3), 3.67 (dd, *J* = 10.7, 7.3 Hz, 1 H, H_3), 1.46 (s, 9 H, tBu), 0.89 (s, 9 H, tBu), 0.07 (d, *J* = 3.9 Hz, 6 H, 2 x CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.915 (COONH), 133.704 (C5), 132.377 (C6), 82.825 (Cq), 82.243 (C2), 61.859 (C3), 52.412 (C1), 44.1 (C4), 28.1 (tBu), 25.8 (tBu), 18.2 (Cq), -5.5 (CH_3), -5.4 (CH_3).

(S)-2-bromo-3-phenylpropanoic acid, 54



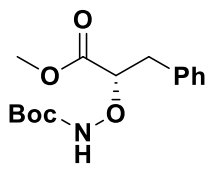
To a solution of L-phenylalanine (3.4 g, 20.6 mmol) in water (43 mL), 1.25 M H_2SO_4 (50 mL, 62.5 mmol) and KBr (8.6 g, 72.0 mmol) were added. The solution was stirred at -15°C for 10 minutes, then $NaNO_2$ (1.77 g, 25.7 mmol) was added in ten portions. Following complete addition, the solution was slowly warmed up to room temperature. and stirred for an additional 8 hours. The solution was saturated with NaCl and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **54** (4.7 g, 99%) as a yellow oil. Rf = 0.35 (5% MeOH:DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.11 (m, 5 H, Ar-CH), 4.42 (dd, *J* = 8.4, 7.1 Hz, 1 H, CH), 3.48 (dd, *J* = 14.1, 8.4 Hz, 1 H, C**H**H), 3.26 (dd, *J* = 14.1, 7.1 Hz, 1 H, CH**H**). ^{13}C NMR (101 MHz, MeOD) δ 171.87 (COOH), 139.4 (C_q), 128.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.9 (Ar-CH), 53.5 (CH), 46.30 (CH_2).

Methyl (S)-2-bromo-3-phenylpropanoate, 55



Acetyl chloride (2.67 mL, 37.4 mmol) was slowly added to a solution of **54** (5.8 g, 24 mmol) in MeOH (40 mL). The solution was stirred under reflux for 4 hours. After completion, the reaction was cooled to room temperature and concentrated to a yellow residue. The residue was dissolved in EtOAc, washed with $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **55** as a pale-yellow oil (4.29 g, 74%). Rf = 0.59 (20% EtOAc:cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) 7.39 – 7.11 (m, 5 H, Ar-CH), 5.01 (dd, *J* = 7.5, 5.4 Hz, 1 H, CH), 3.80 (s, 3 H; OCH_3), 3.48 (dd, *J* = 14.1, 8.4 Hz, 1 H, C**H**H), 3.26 (dd, *J* = 14.1, 7.1 Hz, 1 H, CH**H**). ^{13}C NMR (101 MHz $CDCl_3$) δ 169.4 (CO_2Me), 139.4 (C_q), 128.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.9 (Ar-CH), 52.9 (CH_3), 52.6 (CH), 44.3 (CH_2).

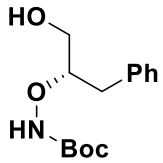
Methyl (S)-2-(((tert-butoxycarbonyl)amino)oxy)-3-phenylpropanoate, 56



To a solution of $(Boc)_2NOH$ (3.9 g, 16.2 mmol), in anhydrous MeCN (50 mL) **55** (2.58 g, 19.4 mmol) was added at 0 °C, followed by DBU (3.69 mL, 24.3 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. After completion, the reaction was extracted with DCM (3 × 100 mL) and washed with saturated aqueous $NaHCO_3$ and brine. The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to afford **56** as a colourless oil (2.4 g, 41%). Rf = 0.40 (10% EtOAc:cyclohexane); ^{1} NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.21 (m, 5 H, 5 × Ar-CH), 4.81 (dd,

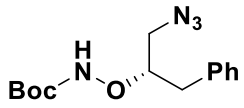
J = 7.7, 3.4 Hz, 1 H, CH), 3.8’ (s, 3 H, CH_3), 3.50 (dd, *J* = 14.1, 8.4 Hz, 1 H, C**H**H), 3.16 (dd, *J* = 14.1, 7.1 Hz, 1 H, CH**H**). 1.46 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3 (COOMe), 157.9 (CO_2NH), 139.4 (C_q), 128.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.9 (Ar-CH), 84.4 (CH), 83.1 (Cq), 52.3 (CH_3), 35.1 (CH_2), 28.1 (*t-Bu*).

Tert-butyl (S)-((1-hydroxy-3-phenylpropan-2-yl)oxy)carbamate, 57



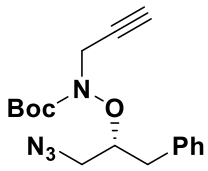
To a stirred solution of **56** (1.26 g, 4.73 mmol) in anhydrous tetrahydrofuran (50 mL), a 2.0 M lithium borohydride solution (4.7 ml, 9.4 mmol) in tetrahydrofuran was added at 0 °C. The resulting mixture was stirred for 6 h at 20 °C. The reaction was quenched with saturated aqueous NH_4Cl and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (5% MeOH/DCM) afforded **57** as a colourless oil (2.5 g, 54%). Rf = 0.27 (30% EtOAc:cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.21 (m, 5 H, 5 × Ar-CH), 4.01 (broad s, 1 H, OH), 3.85 (m, 1 H, C H), 3.74 - 3.60 (m, 4 H, 2 × CH_2), 3.50 (dd, *J* = 14.1, 8.4 Hz, 1 H, C**H**H), 3.16 (dd, *J* = 14.1, 7.1 Hz, 1 H, CH**H**).1.48 (s, 9 H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.318 (CO_2NH), 139.4 (C_q), 128.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.9 (Ar-CH), 84.4 (CH), 83.1 (Cq), 61.8 (CH_2), 38.2 (CH_2), 28.118 (*t*-Bu).

Tert-butyl (S)-((1-azido-3-phenylpropan-2-yl)oxy)carbamate, 58



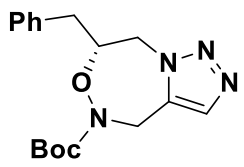
To a stirred solution of **57** (1.24 g, 4.25 mmol) in anhydrous DCM (20 mL), triethylamine (0.88 mL, 6.4 mmol) and methanesulfonyl chloride (0.5 mL, 6.4 mmol) were added portionwise at 0 °C. The mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The organic phase was washed consecutively with brine, 1 M $KHSO_4$, brine, 5% aqueous $NaHCO_3$, dried over Na2SO4 and concentrated in vacuo. The mesylate was dissolved in DMF (20 mL). Sodium azide (0.83 g, 12.7 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **58** as a yellow oil (0.84 g, 68%). Rf = 0.9 (10% EtOAc: cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.27 (m, 5 H, 5 × Ar-CH), 4.0 – 3.92 (m, 1 H, CH), 3.90 (dd, *J* = 10.7, 4.7 Hz, 1 H, C**H**H), 3.43 (dd, *J* = 10.7, 6.3 Hz, 1 H, CH**H**), 2.70 (dd, *J* = 13.1, 4.2 Hz, 1 H, C**H**HN), 2.44 (dd, *J* = 13.1, 5.9 Hz, 1 H, CH**H**N). 1.49 (s, 9 H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (CO_2NH), 140.4 (C_q), 128.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.9 (Ar-CH), 84.4 (CH), 83.1 (Cq), 52.1 (CH_2), 38.2 (CH_2), 28.118 (*t*-Bu).

tert-butyl (R)-((1-azido-3-phenylpropan-2-yl)oxy)(prop-2-yn-1-yl)carbamate, 59



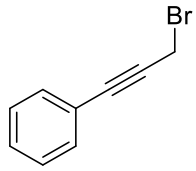
Propargyl bromide (0.26 mL, 3 mmol) was added to a solution of **58** (495 mg, 1.5 mmol) in anhydrous DMF (5 mL) at 0 °C. After 10 min, NaH (150 mg, 3.75 mmol, 60% dispersion in mineral oil) was added in two portions and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (10% EtOAc:cyclohexane) afforded **59** as a green oil (327 mg, 66%). Rf: 0.66 (20% EtOAc: cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.27 (m, 5 H, 5 × Ar-CH), 4.03 (ddt, *J* = 7.0, 5.7, 4.4 Hz, 1 H, CH), 3.70 (dd, *J* = 13.1, 4.2 Hz, 1 H, C**H**H), 3.44 (dd, *J* = 13.1, 5.9 Hz, 1 H, CH**H**), 3.48 (dd, *J* = 13.1, 5.7 Hz, 1 H, CH), 3.90 (dd, *J* = 10.7, 4.7 Hz, 1 H, C**H**H), 3.43 (dd, *J* = 10.7, 6.3 Hz, 1 H, CH**H**), 2.70 (dd, *J* = 13.1, 4.2 Hz, 1 H, C**H**HN), 2.44 (dd, *J* = 13.1, 5.9 Hz, 1 H, CH**H**N). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (CO_2NH), 140.4 (C_q), 128.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.9 (Ar-CH), 84.4 (CH), 83.1 (Cq), 52.1 (CH_2), 38.2 (CH_2), 28.118 (*t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1 (CO_2NH), 140.4 (C_q), 128.7 (2 × Ar-CH), 127.2 (2 × Ar-CH), 125.9 (Ar-CH), 82.0 (Cq), 79.1 (CH), 77.4 (**C**≡CH), 68.3 (C≡**CH**), 56.1 (CH_2), 44.8.2 (CH_2), 36.6 (CH_2), 28.4(*t*-Bu).

Tert-butyl (R)-7-benzyl-7,8-dihydro-[1,2,3]triazolo[5,1-d][1,2,5]oxadiazepine-5(4H)-carboxylate, 60



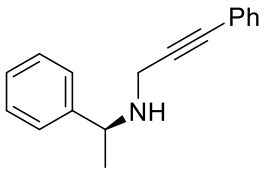
A 0.5 M solution of **59** (327 mg, 1.0 mmol) in anhydrous chloroform was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc:cyclohexane) afforded **60** as a pale rose solid (234 mg, 71%). Rf = 0.20 (50% EtOAc:cyclohexane). m. p. = 96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 6 H, 6 × Ar-CH), 4.23 (s, 2 H, CH_2), 4.05 – 3.81 (m, 3 H, CH, CH_2), 2.60 (d, *J* =17.0 Hz, 1 H, C**H**H), 2.41 (d, *J* =17.0 Hz, 1 H, CH**H**), 1.46 (s, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2 ($NHCO_2$), 146.5 (Ar-C_q), 138.0 (Ar-C_q), 130.0 (Ar-CH), 128.4 (2 × Ar-CH), 127.1 (2 × Ar-CH), 126.2 (Ar-CH), 81.2 (C_q), 76.1 (CH), 54.9 (CH_2), 50.1 (CH_2), 38.1 (CH2), 28.2. (*t*-Bu).

(3-bromoprop-1-yn-1-yl)benzene, 62



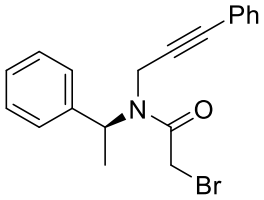
3-phenylprop-2-yn-1-ol (792 mg, 6 mmol) was added to a DCM (25.0 mL) solution of PPh3 (1.57 g, 6 mmol) and the mixture was cooled to 0 °C. CBr_4 (2.18 g, 6.6 mmol) was added in five portions over 20 min at 0 °C, and the mixture was stirred at 0 °C for 1 h. Hexane (20 ml) was then added to dilute the solution, which resulted in the precipitation of Ph_3PO. The solid was removed by filtration. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **62** as a yellow oil (968 mg g, 84%). Rf = 0.51 (30% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) 7.53-7.42 (m, 5 H, 5 ×Ar-CH), 4.02 (s, 2 H, CH_2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.7 (5 × Ar-CH), 123.4 (Ar-C_q), 77.2 (**C**≡C), 68.3 (C≡**C),** 12.8 (CH_2).

(S)-3-phenyl-N-(1-phenylethyl)prop-2-yn-1-amine, 63



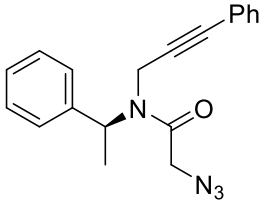
(3-bromoprop-1-yn-1-yl)benzene (644 mg, 3.3 mmol) was added to a MeCN (25.0 mL) solution of (S)-1-phenylethan-1-amine (363 mg, 3 mmol) and triethylamine (0.41 mL, 3 mmol), The reaction stirred for 16 h. After completion, the solvent was removed and the residue taken up in EtOAC, washed with brine (20 mL) and extracted with ethyl acetate (3× 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **63** as a pale yellow oil oil (437 mg g, 62%). Rf = 0.60 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.15 (m, 10 H, 10 ×Ar-CH), 4.11 (q, *J* = 6.6 Hz, 1 H, CH), 3.59 (d, *J* = 17.1 Hz, 1 H, C**H**H), 3.41 (d, *J* = 17.1 Hz, 1 H, CH**H**), 1.43 (d, *J* = 6.6 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 87.6 (**C**≡C), 83.4 (**C**≡C), 56.5 (CH), 36.8 (CH_2), 23.9 (CH_3).

(S)-2-bromo-N-(1-phenylethyl)-N-(3-phenylprop-2-yn-1-yl)acetamide, 64



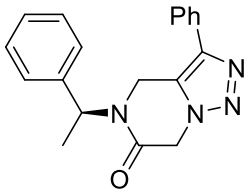
2-chloroacetyl bromide (106 µL, 1.27 mmol) was added dropwise at 0 °C to a solution of **63** (200 mg, 0.85 mmol) and triethylamine (297 µL, 2.12 mmol) in DCM (7.0 mL). The reaction stirred for 12 h. After completion, the solvent was removed. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **64** as a pale yellow oil oil (158 mg g, 51%). Rf = 0.42 (20% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 10 H, 10 ×Ar-CH), 6.10 (q, *J* = 7.2 Hz, 1 H, CH), 4.32 – 4.08 (m, 2 H, CH_2Br), 3.99 – 3.76 (m, 2 H, CH_2), 1.67 (d, *J* = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (CO_2NH), 144.4 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 87.6 (**C**≡C), 83.4 (**C**≡C), 56.5 (CH), 36.8 (CH_2), 25.6 (CH_2), 23.9 (CH_3).

(S)-2-azido-N-(1-phenylethyl)-N-(3-phenylprop-2-yn-1-yl)acetamide, 65



To a stirred solution of **64** (158 mg, 0.44 mmol) in DMF (10 mL) sodium azide (166 mg, 2.55 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **65** as a colourless oil (95 mg, 68%). Rf = 0.52 (30% EtOAc: cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.24 (m, 10 H, 10 ×Ar-CH), 6.10 (q, *J* = 7.2 Hz, 1 H, CH), 3.99 – 3.76 (m, 2 H, CH_2), 2.26 (m, 2 H, CH_2Br), 1.67 (d, *J* = 7.2 Hz, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (CO_2NH), 144.4 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 87.6 (**C**≡C), 83.4 (**C**≡C), 56.5 (CH), 52.0 (CH_2), 36.8 (CH_2), 23.9 (CH_3).

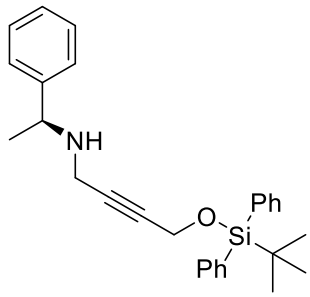
(S)-3-phenyl-5-(1-phenylethyl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-6(7H)-one, 66



A 0.5 M solution of **65** (95 mg, 0.3 mmol) in anhydrous chloroform was stirred at 60 °C for 72 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (2% EtOAc:cyclohexane) afforded **66** as a white solid (234 mg, 71%). Rf = 0.80 (5% EtOAc:cyclohexane). m. p. = 219 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.21 (m, 10 H, 10 ×Ar-

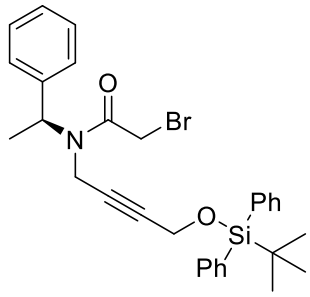
CH), 6.10 (q, *J* = 7.2 Hz, 1 H, CH), 4.62 (s, 2 H, CH_2), 4.49 (s, 2 H, CH_2), 1.73 (d, *J* = 7.2 Hz, 3 H, CH_3).δ 169.8 (CO_2N), 144.4 (Ar-C_q), 143.0 (Ar-C_q), 140.1 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 69.5 (CH), 57.0 (CH_2), 36.8 (CH_2), 22.4 (CH_3).

(S)-4-((tert-butyldiphenylsilyl)oxy)-N-(1-phenylethyl)but-2-yn-1-amine, 67



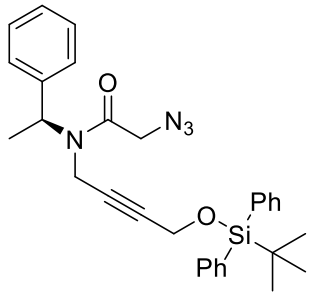
Propargyl bromide **22** (774 mg, 2 mmol) was dropwise added at 0 °C to a solution of (S)-1-phenylethan-1-amine (242 mg, 2 mmol) and triethylamine (278 µL, 2 mmol) in MeCN (20 mL). The reaction stirred for 12 h. After completion, the solvent was removed and the residue directly purified by flash column chromatography (10% EtOAc:cyclohexane) afforded **67** as a yellow oil oil (248 mg g, 30%). Rf = 0.25 (10% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.14 (m, 15 H, 15 × Ar-CH), 5.11 – 4.94 (m, 1 H, CH), 3.27 (qd, *J* = 7.3, 4.2 Hz, 4 H, 2 × CH_2), 1.50 (d, *J* = 6.9 Hz, 3 H, CH_3), 1.14 (t, *J* = 7.1 Hz, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ144.4 (Ar-C_q), 130.1 (2 × Ar-C_q), 128.6 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 126.9 (Ar-CH), 85.2 (**C**≡C), 80.4 (**C**≡C), 56.5 (CH), 51.7 (CH_2), 35.9 (CH_2), 31.0 (C_q), 27.1 (*t*-Bu), 23.9 (CH_3).

(S)-2-bromo-N-(4-((tert-butyldiphenylsilyl)oxy)but-2-yn-1-yl)-N-(1-phenylethyl)acetamide, 68



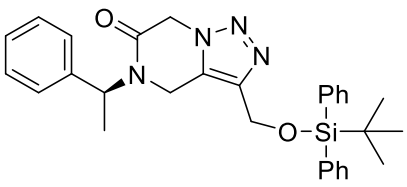
2-chloroacetyl bromide (125 µL, 0.87 mmol) was added dropwise at 0 °C to a solution of **67** (248 mg, 0.58 mmol) and triethylamine (202 µL, 1.45 mmol) in DCM (7.0 mL). The reaction stirred for 12 h. After completion, the solvent was removed. Purification by flash column chromatography (20% EtOAc:cyclohexane) afforded **68** as a yellow oil oil (219 mg g, 69%). Rf = 0.71 (30% EtOAc:cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.27 (m, 15 H, 15 × Ar-CH), 6.12 (q, *J* = 7.2 Hz, 1 H, CH), 4.48 (s, 2 H, CH_2O), 4.08 (s, 2 H, CH_2Br), 4.08 (s, 2 H, CH_2Br), 3.83 (d, *J* = 19.0 Hz, 1 H, NC**H**H), 3.66 (d, *J* = 19.3 Hz, 1 H, NCH**H**), 1.67 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.14 (t, *J* = 7.1 Hz, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (CO_2NH), 144.4 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 87.6 (**C**≡C), 83.4 (**C**≡C), 58.1 (CH), 51.2 (CH_2), 32.7 (CH_2), 31.0 (C_q), 27.1 (*t*-Bu), 23.9 (CH_3).

(S)-2-azido-N-(4-((tert-butyldiphenylsilyl)oxy)but-2-yn-1-yl)-N-(1-phenylethyl)acetamide, 69



To a stirred solution of **68** (312 mg, 0.56 mmol) in DMF (5 mL) sodium azide (166 mg, 2.55 mmol) was added, and the mixture was heated at 60 °C for 6 h. After completion, the solvent was removed and the residue was extracted with ethyl acetate (3 × 50 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (30% EtOAc:cyclohexane) afforded **69** as a colourless oil (150 mg, 52%). Rf = 0.50 (30% EtOAc: cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.17 (m, 15 H, 15 ×Ar-CH), 6.10 (q, *J* = 7.3 Hz, 1 H, CH), 4.48 (s, 2 H, CH_2O), 4.53 (d, *J* = 16.8 Hz, 1 H, NC**H**H), 4.16 (d, *J* = 16.9 Hz, 1 H, NCH**H**), 2.02 (s, 2 H, CH_2), 1.68 (d, *J* = 7.2 Hz, 3 H, CH_3),1.10 (t, *J* = 7.1 Hz, 9 H, *t*-Bu). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (CO_2NH), 144.4 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 87.6 (**C**≡C), 83.4 (**C**≡C), 56.5 (CH), 52.0 (CH_2), 36.8 (CH_2), 23.9 (CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8 (CO_2NH), 144.4 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 87.6 (**C**≡C), 83.4 (**C**≡C), 58.1 (CH), 51.2 (CH_2), 32.7 (CH_2), 31.0 (C_q), 27.1 (*t*-Bu), 23.9 (CH_3).

(S)-3-(((tert-butyldiphenylsilyl)oxy)methyl)-5-(1-phenylethyl)-4,5-dihydro-[1,2,3]triazolo[1,5-a]pyrazin-6(7H)-one, 70



A 0.5 M solution of **69** (250 mg, 0.50 mmol) in anhydrous chloroform was stirred at 60 °C for 24 h. After completion, the reaction was quenched with water. The solvent was removed, and the aqueous phase extracted with ethyl acetate (3× 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc:cyclohexane) afforded **70** as a white solid (40 mg, 16%). Rf = 0.44 (50% EtOAc:cyclohexane). m. p. = 134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (tt, *J* = 6.1, 1.5 Hz, 4 H, 4 ×Ar-CH), 7.49 – 7.17 (m, 11 H, 11 ×Ar-CH), 6.24 (q, *J* = 7.1 Hz, 1 H, CH), 5.10 (t, *J* = 1.5 Hz, 2 H, CH_2), 4.86 (dd, 2 H, CH_2), 4.53 (d, *J* = 16.8 Hz, 1 H, CH**H**), 4.16 (d, *J* = 16.9 Hz, 1 H, C**H**H), 1.55 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.00 (s, 9 H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (CO_2N), 161.5 (Ar-C_q), 141.960 (Ar-C_q), 138.045 (Ar-C_q), 131.6 (Ar-C_q), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.2 (Ar-CH), 126.9 (Ar-CH), 123.2 (Ar-CH), 69.5 (CH), 57.0 (CH_2), 36.8 (CH_2), 26.9 (*t*-Bu), 22.4 (CH_3)

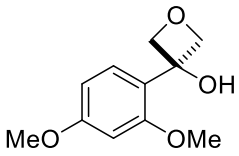
Experimental - Part II

General methods

General Commercial reagents were used as supplied. Anhydrous solvents were obtained by filtration through drying columns ($CH2Cl_2$, THF, MeCN) or used as supplied (DMSO). All reactions were run under an inert atmosphere (argon) with flame-dried glassware using standard techniques. All reactions were carried out under continuous stirring (PTFE stirring bar) in sealed Biotage microwave reaction vials (2—5 mL) with an aluminium cap equipped with a moulded PTFE septum (unless otherwise specified). Analytical thin-layer chromatography was performed on pre-coated, glass-backed silica gel plates. Visualisation of the developed chromatogram was performed by UV absorbance (254 nm), or by exposure to a p-anisaldehyde, ninhydrin or PMA (phosphomolybdic acid) stain followed by heating. Flash column chromatography used silica gel (40-63 μm, 230-400 mesh) purchased from Sigma Aldrich. IR spectra (νmax, FT-IR ATR) were obtained using a Perkin Elmer Spectrum 100 FT-IR Spectrometer and recorded in reciprocal centimetres (cm^{-1}). Nuclear magnetic resonance spectra were recorded on a 400 or 500 MHz Bruker AV spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the residual protic solvent resonance as the internal standard ($CDCl_3$: δ = 7.27 ppm, CD_3OD: δ = 3.31 ppm). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant in Hz, integration and assignment]. ^{13}C NMR spectra were recorded with complete proton decoupling. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard ($^{13}CDCl_3$: δ = 77.0 ppm, $^{13}CD_3OD$: δ = 49.0 ppm). J values are reported in Hz. Assignments of the 1H and 13C-NMR spectra were done by analysing δ and J values and by COSY, NOESY and HMBC experiments where appropriate. Mass spectra were obtained through the Imperial College or EPSRC mass spectrometry service by electrospray ionisation (ES) or atmospheric pressure chemical ionisation (APCI). Melting points were obtained using a Stuart melting point apparatus.

Experimental Details and Characterisation Data: Compounds for Chapter 6

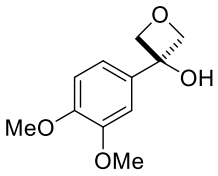
3-(2,4-Dimethoxyphenyl)oxetan-3-ol 2.2



n-BuLi (1.46 M in THF, 8.2 mL, 12.0 mmol, 1.2 equiv.) was added dropwise over 5 min to a solution of 1-bromo-2,4-dimethoxybenzene (1.68 mL, 13.0 mmol, 1.3 equiv.) in anhydrous THF (43 mL) in a 250 mL round bottom flask at —78 °C. After stirring for 20 min, oxetan3-one (0.64 mL, 10.0 mmol, 1.0 equiv.) was added dropwise to the reaction mixture. After further 25 min of stirring at —78 °C, the reaction mixture was warmed to r.t. and allow to stir for 1h. The reaction was quenched with water (60 mL) and the aqueous layer was extracted with diethylether (3 × 45 mL). The organic parts were combined, washed with brine, dried over Na2SO4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetanol **2.3** as a yellow solid (2.0 g, 74%). Rf = 0.33 (50% EtOAc/pentane); mp = 71 °C; IR (film)/cm^{-1} 3324 (br OH), 2952, 2877, 2836, 1822, 1587, 1517, 1453, 1394, 1323, 1252, 1162, 1133, 1066, 1021, 969, 916, 849, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.08 (m, 2 H, Ar-CH), 6.91 (d, 1 H, *J* = 8.2 Hz, Ar-CH), 4.92 (d, 4 H, *J* = 2.2 Hz, CHHOCHH), 3.93 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.048(Ar-C_qOMe), 148.552(Ar-C_qOMe), 116.802(Ar-C_q), 110.981 (Ar-CH), 107.998 (Ar-CH), 85.778 (2 × CH_2), 75.410 (C_q), 55.938 (2 × OCH_3).

The observed characterisation data was consistent with that previously reported in the literature

3-(3,4-Dimethoxyphenyl)oxetan-3-ol 2.3

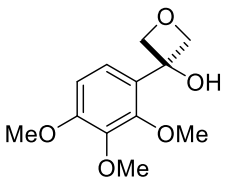


n-BuLi (1.426 M in THF, 8.45 mL, 12.0 mmol, 1.2 equiv.) was added dropwise over 5 min to a solution of 1-bromo-3,4-dimethoxybenzene (1.66 mL, 13.0 mmol, 1.3 equiv.) in anhydrous THF (45 mL) in a 250 mL round bottom flask at —78 °C. After stirring for 20 min, oxetan3-one (0.64 mL, 10.0 mmol, 1.0 equiv.) was added dropwise to the reaction mixture. After further 25 min of stirring at —78 °C, the reaction mixture was warmed to r.t. and allow to stir for 1 h. The reaction was quenched with water (60 mL) and the aqueous layer was extracted with diethyl ether (3 × 45 mL). The organic parts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded oxetanol **2.3** as a white solid (0.89 g, 42%). Rf = 0.33 (50% EtOAc/pentane); mp = 74—76 °C; IR (film)/cm^{-1} 3324 (br OH), 2952, 2877, 2832, 1587, 1513, 1453, 1394, 1323, 1252, 1162, 1133, 1021, 969, 916, 861, 797, 760.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.09 (m, 2 H, Ar-CH), 6.90 (dd, 1 H, *J* = 8.2, 1.2 Hz, Ar-CH), 4.92 (dd, 4 H, CHHOCHH), 3.92 (s, 3 H, OCH_3), 3.91 (s, 1 H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.182 (Ar-C_qOMe), 148.698 (Ar-C_qOMe), 134.955 (Ar-C_q), 116.779 (Ar-CH), 110.986 (Ar-CH), 107.927 (Ar-CH), 85.634 (2 × CH_2), 75.761 (C_q), 55.977 (OCH_3).

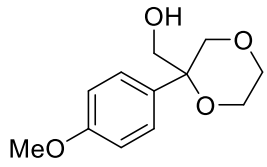
The observed characterisation data was consistent with that previously reported in the literature

3-(2,3,4-Trimethoxyphenyl)oxetan-3-ol 2.4



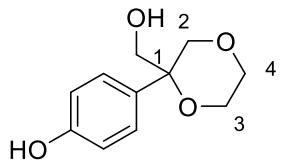
n-BuLi (1.426 M in THF, 2.52 mL, 3.6 mmol, 1.2 equiv.) was added dropwise over 5 min to a solution of 1-bromo-2,3,4-trimethoxybenzene (0.95 g, 3.9 mmol, 1.3 equiv.) in anhydrous THF (14 mL) in a 100 mL round bottom flask at —78 °C. After stirring for 20 min, oxetan3-one (0.19 mL, 10.0 mmol, 1.0 equiv.) was added dropwise to the reaction mixture. After further 25 min of stirring at —78 ◦C, the reaction mixture was warmed to r.t. and allow to stir for 1h. The reaction was quenched with water (60 mL) and the aqueous layer was extracted with diethyl ether (3 × 45 mL). The organic parts were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (40% EtOAc/pentane) afforded oxetanol **2.4** as a white solid (0.22 g, 30%). Rf = 0.37 (50% EtOAc/pentane); mp = 69 °C; IR (film)/cm^{-1} 3339, 2974, 2937, 2881, 2863, 1606, 1502, 1461, 1412, 1267, 1238, 1192, 1144, 1114, 1080, 1006, 946, 812, 693. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, 1 H, *J* = 8.6 Hz, Ar-CH), 6.65 (d, 1 H, *J* = 8.6 Hz, Ar-CH), 5.02 (d, 2 H, *J* = 6.9 Hz, CHHOCHH), 4.85 (d, 2 H, *J* = 7.8 Hz, CHHOCHH), 3.96 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.45 (s, 1 H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.085 (Ar-C_qOMe), 151.307 (Ar-C_qOMe), 142.148 (Ar-C_qOMe), 127.469 (C_q), 120.454 (Ar-CH), 106.618 (Ar-CH), 83.583 (2 × CH_2), 75.705 (C_q), 61.168 (OCH_3), 60.774 (OCH_3), 56.053 (OCH_3). FTMS (APCI) m/z calcd for $C12H17O5^{+}$: 241.1071; found: 241.1073.

(2-(4-Methoxyphenyl)-1,4-dioxan-2-yl)methanol 2.5



Oxetanol (45.0 mg, 0.25 mmol) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol) and ethylene glycol (0.07 mL, 1.25 mmol) in anhydrous MeCN (0.6 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (20 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (20% Et2O/CH2Cl2) afforded dioxane **2.5** as a colourless gum that solidified in the freezer to a white solid (45.0 mg, 80%). Rf = 0.16 (20% Et2O/CH2Cl2); m. p. = 55 ◦C; IR (film)/cm^{-1} 3451 (br. OH), 2961, 2865, 2248, 1611, 1512, 1308, 1249, 1181, 1110, 1026, 1008, 986, 907, 865, 830, 727, 691; ^{1}H NMR (400 MHz, CDCl3) δ 7.42-7.38 (m, 2 H, 2 × Ar-CH), 6.97-6.93 (m, 2 H, 2 × Ar-CH), 4.27 (d, 1 H, J = 12.3 Hz, $H2_{eq}$), 3.99 (1 d, H, *J* = 12.3 Hz, $H2_{ax}$), 3.82 (s, 3 H, OCH_3), 3.76-3.59 (m, 6 H, 2 × H1, 2 × H3, 2 × H4), 1.88 (1 H, br, OH); ^{13}C NMR (101 MHz CDCl3) δ 159.1 (Ar-CqOMe), 130.1 (Ar-CqCq), 128.2 (2 × Ar-CH), 114.1 (2 × Ar-CH), 76.8 (Cq), 69.2 (C2), 67.6 (C1 or C3), 66.8 (C1 or C3), 61.3 (C4), 55.3 (OCH_3). The observed characterisation data (Rf , IR, 1H, 13C) was consistent with that previously reported within the group.

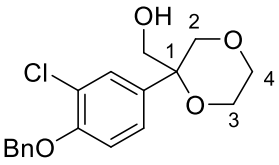
4-(2-(Hydroxymethyl)-1,4-dioxan-2-yl)phenol 2.6



Oxetanol (41.4 mg, 0.25 mmol) was added to a solution of trifluoromethane sulfonimide (7.1 mg, 0.025 mmol) and ethylene glycol (0.07 mL, 1.25 mmol) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (20 mL). The aqueous mixture was acidified with aq. HCl (1 M, 20 mL) and extracted with dichloromethane (6 × 20 mL). The aqueous part still contained product so it was extracted with EtOAc (6 × 50 mL). The combined organic extracts were dried over Na2SO4, filtered and concentrated in vacuo. Purification by flash column chromatography (65% EtOAc/pentane) afforded dioxane **2.6** as a white solid (25.9 mg, 49%). Rf = 0.18 (5% MeOH/CH_2Cl_2); m. p. = 119-126 ◦C; IR (film)/cm^{-1} 3367 (br. OH), 2963, 2933, 2870, 2508, 1613, 1597, 1515, 1450, 1371, 1312, 1248, 1179, 1104, 1068, 1026, 1010, 984, 937, 889, 863, 833, 687; 1H NMR (400 MHz, CD_3OD) δ 7.31-7.28 (m, 2 H, 2 × Ar-CH), 6.82-6.78 (m, 2 H, 2 × Ar-CH), 4.25 (d, 1 H *J* = 12.1 Hz, $H2_{eq}$), 3.91 (d, 1 H, *J* = 12.1 Hz, $H2_{ax}$), 3.72-3.52 (m, 6 H, 2 × H1, 2 × H3, 2 × H4); ^{13}C NMR (101 MHz CD_3OD) δ 157.8 (Ar-CqOMe), 131.8 (Ar-CqCq), 129.5 (2 × Ar-

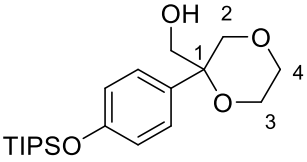
CH), 116.1 (2 × Ar-CH), 78.1 (C_q), 70.5 (C2), 68.2, 67.9 (C1 and C3), 62.2 (C4), 55.3 (OCH_3). The observed characterisation data (IR, 1H, 13C) was consistent with that previously reported within the group.

(2-(4-(Benzyloxy)-3-chlorophenyl)-1,4-dioxan-2-yl)methanol 2.8



Oxetanol (72.6 mg, 0.25 mmol) was added to a solution of trifluoromethane sulfonimide (7.1 mg, 0.025 mmol) and ethylene glycol (0.07 mL, 1.25 mmol) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (20 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.8** as a colourless gum (33.3 mg, 40%). Rf = 0.26 (50% EtOAc/pentane); IR (film)/cm^{-1} 3440 (br. OH), 3033, 2920, 2865, 1602, 1499, 1454, 1383, 1295, 1261, 1207, 1111, 1080, 1060, 1023, 943, 895, 865, 810, 735, 696, 676, 654; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 1 H, *J* = 2.3 Hz, H7), 7.49-7.32 (m, 5 H, 5 × Ar-CH), 7.28 (dd, 1 H, *J*= 8.6, 2.3 Hz, H5), 6.99 (d, 1 H, *J* = 8.6 Hz, H6), 5.18 (s, 2 H, CH_2Ph), 4.21 (d, 1 H, *J* = 12.3 Hz, $H2_{eq}$), 3.98 (d, 1 H, *J* = 12.3 Hz, $H2_{ax}$), 3.76-3.59 (m, 6 H, 2 × H1, 2 × H3, 2 × H4). ^{13}C NMR (101 MHz $CDCl_3$) δ 153.7 (Ar-CqO), 136.4 (Ar-CqCq), 132.7 (Ar-CqCH2), 129.0 (Ar-CH), 128.6 (2 × Ar-CH), 128.0 (C7), 127.0 (2 × Ar-CH), 126.3 (C5), 123.6 (Ar-CqCl), 113.9 (C6), 76.5 (Cq), 70.8 (CH2O), 69.0 (C2), 67.4, 66.7 (C1 and C3), 61.3 (C4); FTMS (APCI) m/z calcd for C18H18O3Cl $[M\text{-}OH]^+$: 317.0939; found: 317.0938.

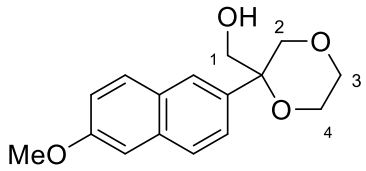
(2-(4-((Triisopropylsilyl)oxy)phenyl)-1,4-dioxan-2-yl)methanol 2.9



Oxetanol (80.6 mg, 0.25 mmol) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol.) and ethylene glycol (0.07 mL, 1.25 mmol) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (20 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded TIPS protected dioxane **2.9** as a 59colourless oil (31.1 mg, 34%) followed by deprotected dioxane as a white solid (9.5 mg, 18%). Rf = 0.54 (50% EtOAc/ pentane); IR (film)/cm^{-1} 3460 (br.

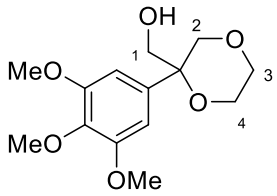
OH), 2945, 2867, 1607, 1509, 1563, 1389, 1266, 1175, 1114, 1071, 1011, 997, 916, 883, 836, 751, 684; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2 H, 2 × Ar-CH), 6.93-6.89 (m, 2 H, 2 × Ar-CH), 4.26 (d, 1 H, *J* = 12.3 Hz, $H2_{eq}$), 3.99 (d, 1 H, *J* = 12.3 Hz, $H2_{ax}$), 3.77-3.59 (m, 6 H, 2 × H1, 2 × H3, 2 × H4), 1.85 (dd, 1 H, *J* = 8.1, 5.2 Hz, OH), 1.31-1.22 (m, 3 H, 3 × CH), 1.11 (d, 18 H, *J* = 7.3 Hz, 6 × CH3); ^{13}C NMR (101 MHz $CDCl_3$) δ 155.6 (Ar-CqOTIPS), 131.1 (Ar-CqCq), 128.1 (2 × Ar-CH), 119.9 (2 × Ar-CH), 76.9 (Cq), 69.1 (C2), 67.5, 66.8 (C1 and C3), 61.3 (C4), 17.9 (6 × CH_3), 12.6 (3 × CH); FTMS (+ p NSI) m/z calcd for C20H38NO4Si [M+NH4] +: 384.2565; found: 384.2568.The observed characterisation data (Rf , IR, 1H, 13C) was consistent with that previously reported within the group.

2-(3,4,5-Trimethoxyphenyl)-1,4-dioxan-2-yl) methanol 2.11



Oxetanol (54.5 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and ethylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (70% EtOAc/pentane) afforded dioxane **2.11** as a transparent oil (31.0 mg, 44%). Rf = 0.11 (50% EtOAc/pentane); IR (film)/cm^{-1} 3466 (br OH), 2963, 2870, 2951, 2251, 1587, 1509, 1461, 1416, 1334, 1241, 1166, 1006, 909, 872, 820. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 2 H, 2 × Ar-CH), 4.23 (d, 1 H, *J* = 12.3 Hz, $H2_{eq}$), 3.99 (d, 1 H, *J* = 12.3 Hz, $H2_{ax}$), 3.89 (s, 6 H, 2 × *m*-OCH_3), 3.86 (s, 3 H, *p*-OCH_3), 3.84 — 3.64 (m, 6 H, 2 × H1, 2 × H3, 2 × H4). ^{13}C NMR (101 MHz $CDCl_3$) δ 153.5 (2 × Ar-C_qOMe), 137.5 (Ar-C_q), 134.9 (Ar-C_qOMe), 103.0 (2 × Ar-CH), 114.1 (2 × Ar-CH), 76.8 (C_q), 69.2 (C2), 67.6 (C1 or C3), 66.8 (C1 or C3), 61.3 (C4), 55.3 (OCH_3), 60.8 (*p*-OCH_3), 56.2 (2 × *m*-OCH_3). FTMS (APCI) *m/z* calcd for $C14H21O6^+$ $[M+H]^+$: 285.1333; found: 285.1329

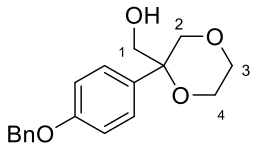
(2-(6-Methoxynaphthalen-2-yl)-1,4-dioxan-2-yl)methanol 2.12



Oxetanol (57.0 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and ethylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.12** as a transparent oil m that solidified in the freezer to a white solid (37.0 mg, 54%). Rf = 0.45 (50% EtOAc/pentane); mp = 97° C; IR (film)/cm^{-1} 3436 (br OH), 3056, 2955, 2858, 2243, 1632, 1606, 1483, 1461, 1390, 1312, 1267, 1218, 1103, 1028, 987, 943, 916, 853, 812, 730, 674. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, 1 H, *J* = 1.9 Hz, Ar-CH), 7.78 (dd, 2 H, *J* = 10.8, 8.8 Hz, 2 × Ar-CH), 7.55 (dd, 1 H, *J* = 8.6, 1.9 Hz, Ar-CH), 7.21 – 7.12 (m, 2 H, 2 × Ar-CH), 4.43 (d, 1 H, *J* = 12.3 Hz, $H2_{eq}$), 4.08 (d, 1 H, *J* = 12.3 Hz, $H2_{ax}$), 3.93 (s, 3 H, OCH_3), 3.83 – 3.61 (m, 6 H, 2 × H1, 2 × H3, 2 × H4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.013 (Ar-C_qOMe), 134.135 (Ar-C_q), 134.032 (Ar-C_q), 129.733 (Ar-CH), 128.745 (Ar-

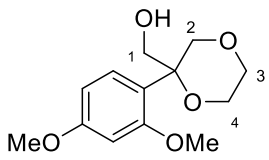
CH), 127.386 (Ar-CH), 126.497 (Ar-CH), 124.832 (Ar-CH), 119.098 (Ar-CH), 105.459 (Ar-CH), 77.295 (C_q), 69.261 (C2), 67.548 (C1 or C3), 66.837 (C1 or C3), 61.530 (C4), 55.352 (OCH_3). FTMS (APCI) *m/z* calcd for $C16H19O4^+$ $[M+H]^+$: 275.1278; found: 275.1273.

(2-(4-(Benzyloxy)phenyl)-1,4-dioxan-2-yl)methanol 2.13



Oxetanol (54.5 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and ethylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (70% EtOAc/pentane) afforded dioxane **2.13** as a transparent oil (31.0 mg, 44%). Rf = 0.46 (50% EtOAc/pentane); IR (film)/cm^{-1} 3444 (br OH), 3034, 2959, 2922, 2866, 2251, 1610, 1509, 1453, 1382, 1345, 1308, 1245, 1181, 1110, 1021, 909, 827, 730. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.32 (m, 7 H, 7 × Ar-CH), 7.03 (dd, 2 H, *J* = 8.9 Hz, 2 × Ar-CH), 5.08 (s, 2 H, CH_2-Ph), 4.28 (d, 1 H, *J* = 12.3 Hz, $H2_{eq}$), 4.00 (d, 1 H, *J* = 12.3 Hz, $H2_{ax}$), 3.79 – 3.57 (m, 6 H, 2 × H1, 2 × H3, 2 × H4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.396 (Ar-C_qOBn), 136.903 (C_q), 131.260 (C_q), 128.625 (Ar-CH), 128.229 (Ar-CH), 128.024 (Ar-CH), 127.481 (Ar-CH), 114.993 (Ar-CH), 76.851 (C_q), 70.037 (C-Ph), 69.231 (C2), 67.653 (C1 or C3), 66.834 (C1 or C3), 61.315 (C4). FTMS (APCI) m/z calcd for $C18H19O^+$ (M-OH) $^+$: 283.1329; found: 283.1320.

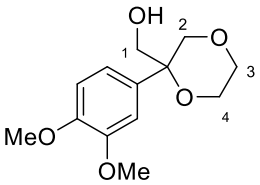
(2-(2,4-Dimethoxyphenyl)-1,4-dioxan-2-yl)methanol 2.14



Oxetanol (52.5 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and ethylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.14** as a transparent oil (57.2 mg, 90%). Rf = 0.40 (50% EtOAc/pentane); IR (film)/cm^{-1} 3324 (br OH), 2952, 2870, 1587, 1513, 1453, 1412, 1326, 1252, 1166, 1129, 1080, 1021, 946, 905, 864, 812, 764, 685. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.97 (m,

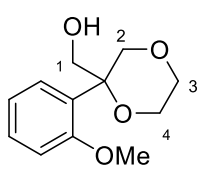
2 H, 2 × Ar-CH), 6.90 (d, 1 H, *J* = 8.3 Hz, Ar-CH), 4.26 (d, 1 H, *J* = 12.3 Hz, $H2_{eq}$), 3.99 (d, 1 H, *J* = 12.3 Hz, $H2_{ax}$), 3.91 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.81 – 3.59 (m, 6 H, 2 × H1, 2 × H3, 2 × H4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.270 (Ar-C_qOMe), 148.585 (Ar-C_qOMe), 131.540 (Ar-C_q), 119.387 (Ar-CH), 111.076 (Ar-CH), 109.906 (Ar-CH), 76.969 (C_q), 69.259 (C2), 67.587(C1 or C3), 66.764 (C1 or C3), 61.380 (C4), 55.973 (OCH_3), 55.905 (OCH_3). FTMS (APCI) *m/z* calcd for $C11H13O3^+$ $(M\text{-}OH)^+$ = 193.0859; found = 193.0854

(2-(3,4-dimethoxyphenyl)-1,4-dioxan-2-yl)methanol 2.15



Oxetanol (53.0 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and ethylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.15** as a transparent oil (20.0 mg, 31%). Rf = 0.45 (50% EtOAc/pentane); IR (film)/cm^{-1} 3462 (br OH), 2952, 2862, 1591, 1513, 1461, 1412, 1326, 1259, 1110, 1025, 950, 894, 868, 808, 767, 689; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.98 (m, 2 H, 2 × Ar-CH), 6.90 (d, 1 H, *J* = 8.3 Hz, Ar-CH), 4.27 (1 H, d, *J* = 12.3 Hz, $H2_{eq}$), 3.99 (1 H, d, *J* = 12.3 Hz, $H2_{ax}$), 3.91 (s, 3 H, OCH_3), 3.89 (s, 3H, OCH_3), 3.80 – 3.62 (m, 6 H, 2 × H1, 2 × H3, 2 × H4), 1.90 (dd, 1 H, *J* = 8.0, 5.4 Hz, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.282 (Ar-C_qOMe), 148.599 (Ar-C_qOMe), 131.531 (Ar-C_q), 119.386 (Ar-CH), 111.084 (Ar-CH), 109.906 (Ar-CH), 76.957 (C_q), 69.265 (C2), 67.597 (C1 or C3), 66.772 (C1 or C3), 61.387 (C4), 55.981 (OCH_3), 55.910 (OCH_3). FTMS (APCI) m/z calcd for $C13H17O4^+$ $(M\text{-}OH)^+$: 237.1121; found: 237.1122.

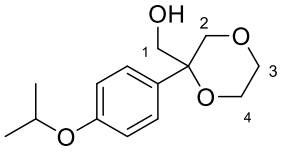
2-(2-Methoxyphenyl)-1,4-dioxan-2-yl)methanol 2.16



Oxetanol (45.1 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and ethylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.2** as a transparent oil (2 mg, 1%). Rf = 0.58 (50% EtOAc/pentane); ^{1}H NMR (400 MHz,

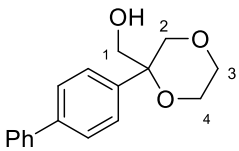
$CDCl_3$) δ 7.60 (dd, 1 H, *J* = 7.8, 1.8 Hz, Ar-CH), 7.32 – 7.27 (m, 1 H, Ar-CH), 7.03 (td, 1 H, *J* = 7.6, 1.1 Hz, Ar-CH), 6.92 (dd, 1 H, *J* = 8.2, 1.1 Hz, Ar-CH), 4.27 (d, 2 H, *J* = 2.8 Hz), 4.12 (m, 1 H, CH), 3.94 (m, 3 H, 3 × CH), 3.82 (s, 3 H, OCH_3), 3.81 – 3.74 (m, 1 H, CH), 3.70 – 3.61 (m, 1 H, CH). FTMS (APCI) *m/z* calcd for $C12H15O3^+$ $(M\text{-}OH)^+$ = 207.1016; found: = 207.1021

(2-(4-Isopropoxyphenyl)-1,4-dioxan-2-yl)methanol 2.17



Oxetanol (52.0 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and ethylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.17** as a pale rose oil (49.4 mg, 78%). Rf = 0.50 (30% EtOAc/pentane); IR (film)/cm^{-1} 3436 (br OH), 2974, 2922, 2866, 1893, 1740, 1610, 1580, 1509, 1461, 1371, 1297, 1241, 1185, 1110, 954, 890, 831, 752, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, 2 H, *J* = 8.9 Hz, 2 × Ar-CH), 6.91 (d, 2 H, *J* = 8.8 Hz, 2 × Ar-CH), 4.56 (hept, 1 H, *J* = 6.1 Hz, OCH), 4.26 (d, 1 H, *J* = 12.2 Hz, $H2_{eq}$), 3.98 (d, 1 H, *J* = 12.3 Hz, $H2_{ax}$), 3.78 – 3.56 (m, 6 H, 2 × H1, 2 × H3, 2 × H4), 1.90 (broad s, 1 H, OH), 1.35 (s, 3 H, OCH_3), 1.34 (s, 3 H, OCH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.502 (Ar-C_qOiPr), 130.697 (C_q), 128.178 (2 ×Ar-CH), 115.829 (2 ×Ar-CH), 76.874 (C_q), 69.843 (C_q), 69.254 (C2), 67.614 (C1 or C3), 66.812 (C1 or C3), 61.288 (C4), 22.078 (2 ×CH_3). FTMS (APCI) m/z calcd for $C14H19O3^+$ $(M\text{-}OH)^+$ = 235.1329; found: 235.1333

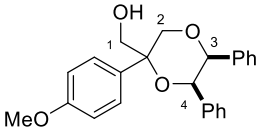
(2-([1,1'-Biphenyl]-4-yl)-1,4-dioxan-2-yl)methanol 2.19



Oxetanol (57.1 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and ethylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.19** as a transparent oil (10.0 mg, 15%). Rf = 0.39 (50% EtOAc/pentane); IR (film)/cm^{-1} 3403(br OH), 3034, 2948, 2918, 2862, 1487, 1446, 1401, 1315, 1285, 1203, 1107, 1069, 1028, 939, 887, 864, 834, 760,

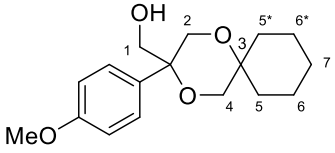
723, 685. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.53 (m, 5 H, 5 × Ar-CH), 7.49 – 7.43 (m, 2 H, 2 × Ar-CH), 7.39 – 7.34 (m, 1 H, Ar-CH), 4.35 (d, 2 H, *J* = 12.3 Hz, $H2_{eq}$), 4.06 (d, 2 H, *J* = 12.3 Hz, $H2_{ax}$), 3.86 – 3.61 (m, 6 H, 2 × H1, 2 × H3, 2 × H4), 1.93 (dd, 1 H, *J* = 7.9, 5.4 Hz, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.717 (Ar-C_q), 140.594 (Ar-C_q), 138.152 (Ar-C_q), 128.785 (Ar-CH), 127.455 (Ar-CH), 127.406 (Ar-CH), 127.313 (Ar-CH), 127.103 (Ar-CH), 77.202 (C_q), 69.280 (C2), 67.589 (C1 or C3), 66.826 (C1 or C3), 61.489 (C4). FTMS (APCI) m/z calcd for $C17H17O2^{+}$ $(M\text{-}OH)^{+}$ = 253.1223; found = 253.1225.

((5S,6R)-2-(4-Methoxyphenyl)-5,6-diphenyl-1,4-dioxan-2-yl)methanol 2.24



Oxetanol **2.0** (52.5 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and 1,2-diphenylethane-1,2-diol (267 mg, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.24** as a transparent oil (20.0 mg, 31%). Rf = 0.45 (50% EtOAc/pentane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 2 H, 2 × Ar-CH), 7.30 – 6.99 (m, 10 H, 10 × Ar-CH), 6.87 – 6.83 (m, 2 H, 2 × Ar-CH), 4.82 (d, *J* = 12.4 Hz, 2 H, $H2_{eq}$), 4.53 (d, *J* = 9.3 Hz, 1 H, H3 or H4), 4.48 (d, *J* = 9.3 Hz, 1 H, H3 or H4), 4.42 (d, *J* = 12.4 Hz, 2 H, $H2_{ax}$), 3.90 (s, 3 H, OCH_3), 3.83 (dd, *J* = 11.8, 4.9 Hz, 1 H, H1), 3.58 (dd, *J* = 11.8, 9.0 Hz, 1 H, H1). ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.909, 128.193, 128.055, 127.858, 127.766, 127.484, 125.891, 114.165, 114.038, 92.908, 85.564, 84.051, 78.206, 69.199, 68.377, 55.348, 55.311. FTMS (APCI) m/z calcd for C24H23O3+ (M-OH)+ = 359.1642; found: 359.1634.

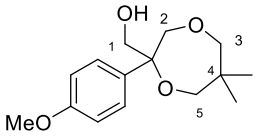
(3-(4-Methoxyphenyl)-1,4-dioxaspiro[5.5]undecan-3-yl)methanol 2.26



Oxetanol **2.0** (52.0 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and 1-(hydroxymethyl)cyclohexan-1-ol (162.6 mg, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50%

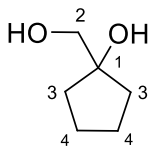
EtOAc/pentane) afforded dioxane **2.26** as a white solid (36.0 mg, 50%). Rf = 0.45 (50% EtOAc/pentane); IR (film)/cm^{-1} 3447 (br OH), 2929, 2858, 1736, 1610, 1513, 1446, 1371, 1304, 1244, 1177, 1073, 1028, 961, 924, 879, 827, 685. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.9 Hz, 2 H, 2 × Ar-CH), 6.93 (d, *J* = 8.8 Hz, 2 H, 2 × Ar-CH), 4.15 (d, *J* = 12.6 Hz, 1 H, $H2_{eq}$), 4.07 (d, *J* = 12.7 Hz, 1 H, $H2_{ax}$), 3.83 (s, 3 H, OCH_3), 3.66 (m, 2 H, 2 × H1), 3.49 (d, *J* = 11.5 Hz, 1 H, 1 × H4), 3.38 (d, *J* = 11.5 Hz, 1 H, 1 × H4), 2.09 (bs,1 H, OH), 1.98 – 1.90 (m, 1 H, OH), 1.63 – 1.15 (m, 10 H, 4 × H5, 4 × H6, 2 × H7). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.021(Ar-C_qOMe), 131.256 (Ar-C_q), 128.108 (2 × Ar-CH), 128.034 (2 × Ar-CH), 113.908 (C_q), 76.271 (C3), 70.434 (C2), 68.456 (C4), 67.371(C1), 61.580, 55.230 (OCH_3), 33.002 (C5), 30.375 (C5*), 26.057 (C7), 21.407 (C6), 21.283 (C6*). FTMS (APCI) m/z calcd for $C17H25O4^+$ = 293.1759; found: 293.1753.

(2-(4-Methoxyphenyl)-6,6-dimethyl-1,4-dioxepan-2-yl)methanol 2.27



Oxetanol **2.0** (52.8 mg, 0.25 mmol, 1.0 equiv.) was added to a solution of trifluoromethane sulfonimide (7.0 mg, 0.025 mmol, 0.1 equiv.) and propylene glycol (0.07 mL, 1.25 mmol, 5.0 equiv.) in anhydrous MeCN (0.83 mL). The reaction mixture was stirred at 50 °C for 24 h and then quenched by the addition of a saturated aqueous sodium bicarbonate solution (10 mL). The aqueous mixture was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography (50% EtOAc/pentane) afforded dioxane **2.27** as a transparent oil (8.0 mg, 14%). Rf = 0.6 (40% EtOAc/pentane); IR (film)/cm^{-1} 2952, 2840, 1610, 1513, 1468, 1394, 1297, 1248, 1181, 1125, 1021, 987, 834, 745. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.9 Hz, 2 H, 2 × Ar-CH), 6.88 (d, *J* = 8.9 Hz, 2 H, 2 × Ar-CH), 5.54 (s, 1 H, OH), 5.47 (d, *J* = 1.3 Hz, 1 H, $H2_{eq}$), 5.20 (d, *J* = 0.7 Hz, 1 H, $H2_{ax}$), 3.82 (s, 3 H, OCH_3), 3.75 (d, *J* = 11.3 Hz, 2 H, 2 × H3), 3.60 (d, *J* = 10.9 Hz, 2 H, 2 × H5), 1.27 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.284 (Ar-C_qOMe), 144.815(Ar-C_q), 130.656, 128.152 (2 × Ar-CH), 114.953, 113.614(2 × Ar-CH), 102.574 (C5), 77.783 (C_q), 77.219 (C2), 64.147 (C1 or C3), 60.404 (C1 or C3), 55.250 (OCH_3), 30.294 (C4), 23.302 (2 × CH_3), 21.919 (2 × CH_3). FTMS (APCI) m/z calcd for $C15H21O3^+$ $(M\text{-}OH)^+$: 249.1485; found: 249.1477.

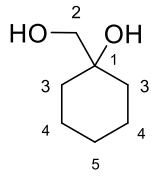
Hydroxymethyl)cyclopentan-1-ol 2.28



NaH (600 mg, 15.0 mmol, 60% dispersion in mineral oil) in DMSO (10 mL) was heated to 70 °C. After 20 min, the reaction mixture was diluted with THF (10 mL) and then cooled to 0°C. A solution of trimethyl-sulfonium iodide (3.06 g, 15.0 mmol) in DMSO (10 mL) was added over a period of 5 min, followed by a solution of cyclopentanone in THF. The reaction was stirred at room temperature for 1 h, then quenched with water and extracted with Et_2O (200 mL). The organic layer was washed with water (10 mL), brine and dried over $Na_2SO_4$and concentrated in vacuo to give the epoxide as a pale yellow oil. The crude epoxide was taken up in water (60 mL) and stirred for 3 h at 60° C, then extracted with ethyl acetate. The combined organic layers were concentrated in vacuo to afford diol **2.28** as a transparent oil (364 mg, 31%). IR (film)/cm^{-1} 3350 (br OH), 2952, 2870, 1654, 1435, 1319, 1215, 1043, 998, 954, 905. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (s, 2 H, OCH_2), 2.89 (s, 1 H, OH), 2.64 (s, 1 H, OH), 1.96 – 1.45 (m, 8 H, 4 ×CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 82.770 (C1), 69.575 (C2), 36.890 (2 × C3), 24.175 (2 × C4).

The observed characterisation data was consistent with that previously reported in the literature

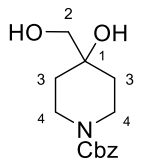
1-(Hydroxymethyl)cyclohexan-1-ol 2.29



NaH (600 mg, 15.0 mmol, 60% dispersion in mineral oil) in DMSO (10 mL) was heated to 70 °C. After 20 min, the reaction mixture was diluted with THF (10 mL) and then cooled to 0°C. A solution of trimethyl-sulfonium iodide (3.06 g, 15.0 mmol) in DMSO (10 mL) was added over a period of 5 min, followed by a solution of cyclohexanone (1.03 mL, 10.0 mmol) in THF (5 mL). The reaction was stirred at room temperature for 1 h, then quenched with water and extracted with Et_2O (200 mL). The organic layer was washed with water (10 mL), brine and dried over Na_2SO_4 and concentrated in vacuo to give the epoxide as a pale yellow oil. The crude epoxide was taken up in water (60 mL) and stirred for 3 h at 60° C, then extracted with ethyl acetate. The combined organic layers were concentrated in vacuo to afford diol **2.29** as a white solid (780 mg, 60%). IR (film)/cm^{-1} 3261 (br OH), 2929, 2847, 1446, 1371, 1282, 1237, 1166, 1077, 1043, 995, 961, 894, 834, 735, 685. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 2 H, OCH_2), 2.01 (bs, 2 H), 1.79 – 1.05 (m, 10 H, 5 × CH_2). ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.730 (C1), 70.222 (C2), 34.161 (2 × C3), 25.902 (C5), 21.880 (2 × C4).

The observed characterisation data was consistent with that previously reported in the literature

Benzyl 4-hydroxy-4-(hydroxymethyl)piperidine-1-carboxylate 2.30



NaH (600 mg, 15.0 mmol, 60% dispersion in mineral oil) in DMSO (10 mL) was heated to 70 °C. After 20 min, the reaction mixture was diluted with THF (10 mL) and then cooled to 0°C. A solution of trimethyl-sulfonium iodide (3.06 g, 15.0 mmol) in DMSO (10 mL) was added over a period of 5 min, followed by a solution of benzyl 4-oxopiperidine-1-carboxylate (2.28 mL, 10.0 mmol) in THF (5 mL). The reaction was stirred at room temperature for 1 h, then quenched with water and extracted with Et_2O (200 mL). The organic layer was washed with water (10 mL), brine and dried over Na_2SO_4 and concentrated in vacuo to give the epoxide as a pale yellow oil. The crude epoxide was taken up in water (60 mL) and stirred for 3 h at 60° C, then extracted with ethyl acetate. The combined organic layers were concentrated in vacuo to afford diol **2.30** as a white solid (745 mg, 28%). 3384, 3034, 2952, 2922, 2862, 2344, 2109, 1874, 1692, 1528, 1498, 1468, 1423, 1364, 1271, 1226, 1114, 1066, 991, 913, 846, 812, 697. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5 H, 5 × Ar-CH), 5.16 (s, 2 H, NCH_2-Ar), 3.94 – 3.75 (m, 2 H, 2 × H3), 3.49 (ddd, *J* = 13.4, 9.7, 3.7 Hz, 2 H, 2 × H3), 2.71 (s, 2 H, CH_2), 1.84 (s, 2 H, 2 × H4), 1.46 (d, *J* = 13.5 Hz, 2 H, 2 × H4). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.251 (C=O), 136.702 (Ar-C_q), 128.525 (Ar-CH), 128.063 (Ar-CH), 127.922 (Ar-CH), 67.255(C1), 56.950 (C_2), 53.761 (OCH_2-Ar), 42.663 (2 × C4), 32.921 (2 × C3). FTMS (APCI) m/z calcd for $C14H18NO3^+$ $(M\text{-}OH)^+$: 248.1288; found: 248.1287.

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