Synthesis of Some Nitrogen Heterocycles of Medicinal Relevance

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In loving memory of my late grandmom (nani amma) who couldn't live long to see me prospering in all spheres of life.

Acknowledgement

This thesis is by for the most significant accomplishment in my life and it would be impossible without people who supported me and believed in me. First and foremost, I offer my utmost gratitude and deep appreciation to my supervisor, Dr. Bengt Erik Haug for his candid cooperation, valuable suggestions and ever encouraging attitude throughout the research work. I ardently extend deep emotions of appreciations and sincere thanks to my co-supervisor, Professor Leiv K. Sydnes for his erudite suggestions and insightful comments. I really feel extremely privileged to have worked under his dexterous and dynamic guidance.

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Abbreviations

^{13}C	Carbon-13 nucleus
^{1}H	Hydrogen-1 nucleus
Ac	acetyl
c	*cis*
DART	Direct analysis in real time
DCM	Dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	*N*,*N*-dimethylsulfoxide
DEPT	Distortionless enhancement by polarization transfer
ESI	Electron spray ionization
GC-MS	Gass chromatography-mass spectrometry
hr	Hour(s)
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
IR	Infrared spectroscopy
Keto-TEB	1,1-diethoxybut-3-yn-2-one
mp	Melting point
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
Ph	Phenyl

ppm	Parts per million
R_f	Retention factor
r.t.	Room temperature
t	*trans*
TBAI	Tetrabutyl ammonium iodide
TBDMS	*t*-Butyldimethylsilyl
TEB	3,3,4,4-Tetraethoxybut-1-yne
TEBA	Triethylbenzylammonium chloride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
Ts	Tosyl

Abstract

In the first part of the project, two highly functionalized terminal alkynes, 3,3,4,4-tetraethoxybut-1-yne (TEB) and 1,1-diethoxy-but-3-yn-2-one (keto-TEB) have been used for the synthesis of 1,4-disubstituted 1,2,3-triazoles. These 1,4-disubstituted 1,2,3-triazoles have also been converted into their corresponding *N*-unsubstituted 1,2,3-triazoles by removing the benzyl substituent on nitrogen. Exploring the debenzylation further, a number of 1,4- and 1,5-disubstituted 1,2,3-triazoles have been synthesized and converted exclusively into the corresponding C4-monosubstituted 1,2,3-triazoles after deprotection provided the substituent on the triazole C-atom contains at least one alkoxy group.

Secondly, a synthetic route for the synthesis of *cis* and *trans* 3,4-disubstituted piperidine as building blocks for the synthesis of a series of novel piperidines, has been developed. Furthermore, *trans* 3,4-disubstituted piperidine building block has been used for the synthesis of 1,4- and 1,5-disubstituted 1,2,3-triazoles as renin inhibitors.

Publication and Manuscript

The following papers containing results from this research project are organized in appendixes I-II.

Paper I

1,3-Dipolar cycloadditions of benzyl azide to two highly functionalized alkynes

Farooq, T.; Haug, B. E.; Sydnes, L. K.; Törnroos, K. W.

Monatsh. Chem. **2012**, 143:512.

Manuscript

Debenzylation of functionalized *N*-benzyl 4- and 5-substituted 1,2,3-triazoles

Farooq, T.; Sydnes, L. K.; Törnroos, K. W.; Haug, B. E.

Manuscript

Contents

Chapter 1

Introduction

1.1 Introduction

1,2,3-Triazoles are nitrogen heteroarenes that have received much attention over the past decades and display a range of applications in organic, organometallic, material science and combinatorial chemistry as well as agrochemicals.[1,2,3] Moreover, compounds containing 1,2,3-triazoles are being employed as dyes, corrosion inhibitors, photostabilizers and optical brightening agents.[4] Not present in natural products, their remarkable stability under different severe conditions has triggered their utility in a variety of scientific disciplines.[5]

The 1,2,3-triazole moiety exhibits structural similarity with the amide bond,[6] mimicking a *Z* or an *E* amide bond depending on the substitution pattern.[7] The 1,4-disubstituted triazole moiety shows similarity with a *Z*-amide bond, the lone pair of the N(3) mimics the carbonyl oxygen of the amide bond, the C(5)-H bond can show intermolecular interactions as a hydrogen bonding donor group,[8] like the N-H bond of amides, and the electophilic C(5) is electronically similar to carbonyl carbon in amide. The overall dipole moment of a triazole system is much stronger than an amide bond,[9] but this may actually increase the peptide bond mimicry by enhancing the hydrogen bond donor and acceptor properties of triazole.[10] Some structural differences between triazole and amide bond of course do exist, most notably, the extra atom in the triazole backbone leads to an overall increase in R^1-R^2 distance of 1.1 Å over the typical amide bond. While on the other hand the 1,5-substitution pattern mimics the *E*-amide bond. Here, the link between the substituents is identical in terms of atoms involved and the relative position of the hydrogen bonding donor and acceptor sites is similar as well.[11] However, the electrophilic carbonyl carbon is now replaced by a negatively polarized nitrogen atom, since there are some differences in atom polarization (Figure 1.1). The ability to mimic certain aspects of a peptide bond allow

1,2,3-triazoles to engage in productive interactions with a variety of other molecules including biological targets.[5]

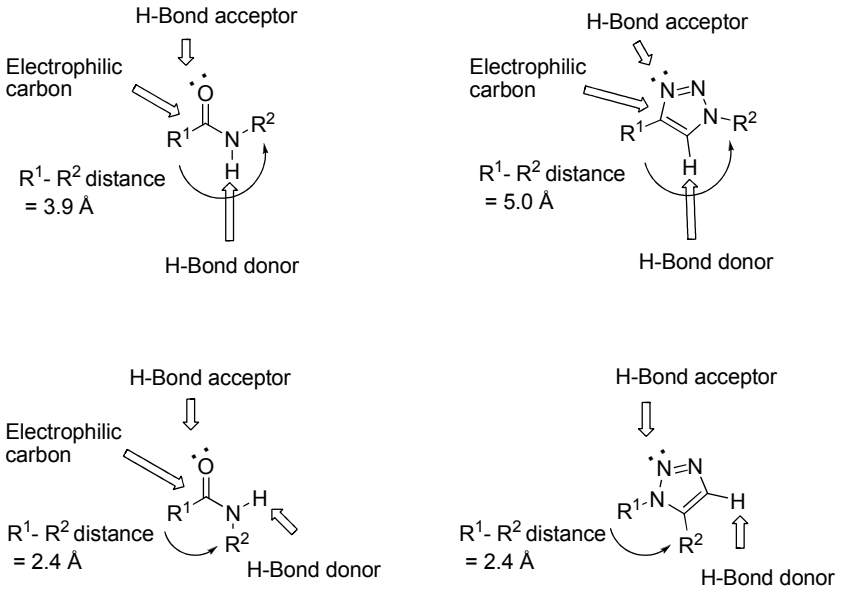


Figure 1.1 Topological and electronic similarities of 1,2,3-triazloes and amides[12]

Further, molecular modelling has also suggested that a 1,4-disubstituted 1,2,3-triazole can mimic the geometry of a β–turn. Indeed, a β-turn was achieved experimentally by using two three-carbon linkers in a simple model peptide system[13] (see **1**, Figure 1.2). In the field of peptidomimetics the use of triazoles is further strengthened by a report that showed that triazole ε^2-amino acids were effective surrogates of dipeptides in α-helical structures[8] (see **2**, Figure 1.2). Similarly, 1,4-disubstituted triazole oligomers have been suggested to mimic the structure of β-strands[14] (see **3**, Figure 1.2). The potential of triazole as an amide bond surrogate in peptidomimetic structures has also been evaluated experimentally.

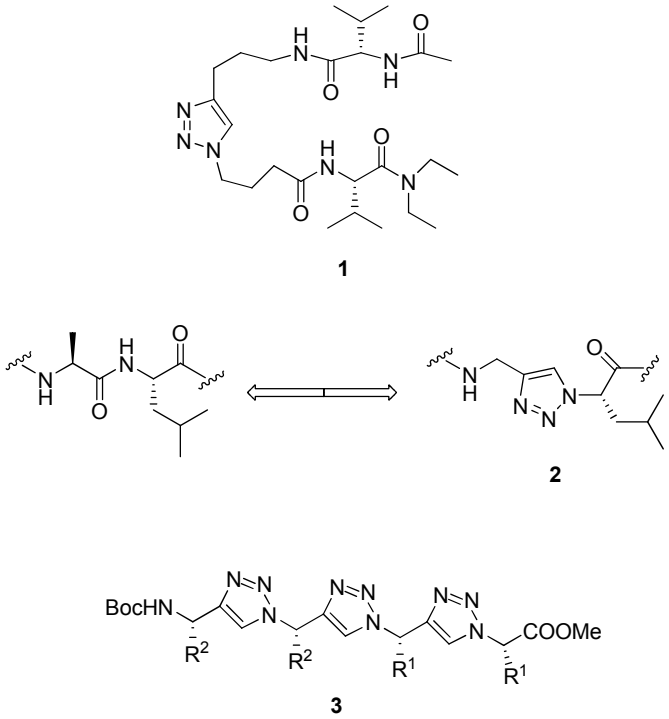


Figure 1.2 Examples of peptidomimetic structures

It has also been predicted that triazoles might act as bioisosteres of the acyl-phosphate and *trans*-olefinic moities, in addition to their potential in mimicking the amide of the peptide. During the efforts to prepare inhibitors of enzymes involved in the synthesis of siderophores (iron-chelators required for growth and virulence) in *Mycobacterium tuberculosis*, an acyl-phosphate (a good leaving group) was replaced with a stable triazole to generate intermediate mimics[15] (see **4**, Figure 1.3). In resveratrol (anticancer and antiaging), the substitution of a *trans*-olefinic group with a triazole moiety[16] proved to be more rewarding (see **5**, Figure 1.3). This idea was supported by molecular modelling that suggested this modification did not alter the spatial

arrangements of the phenolic hydroxyls that control the biological activity of this phytoalexin (synthesized by plants).

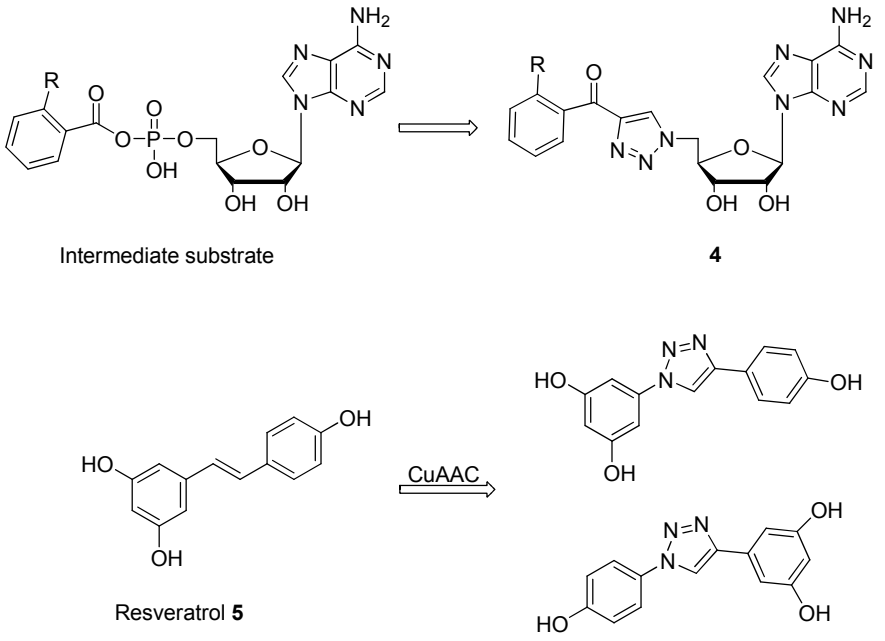


Figure 1.3 Triazole as a bioisostere of acylphosphate and *trans*-olefinic moieties

The effective 1,4-disubstituted triazole replacement is not limited to above mentioned examples, five membered rings containing two nitrogen atoms have been found as obvious candidates for bioisosteric substitution with triazoles. As an example of the success of this substitution is demonstrated by work on fipronil (an insecticide), a library of thirty 1-phenyl-1*H*-1,2,3-triazole derivatives was synthesised by replacing the pyrazole ring with a triazole[17] (see **6**, Figure 1.4). Interestingly, several 1,4-regioisomers were found to be more potent competitive inhibitors compared to fipronil. Similarly, in carbocyclic nucleosides, derivatives of neplanocin A were synthesised replacing the adenine with triazole. In particular, the 1,4-disubstituted

triazole derivative **8**, that had the most potent antiviral activity against vaccinia virus among the five-membered rings tested.[18]

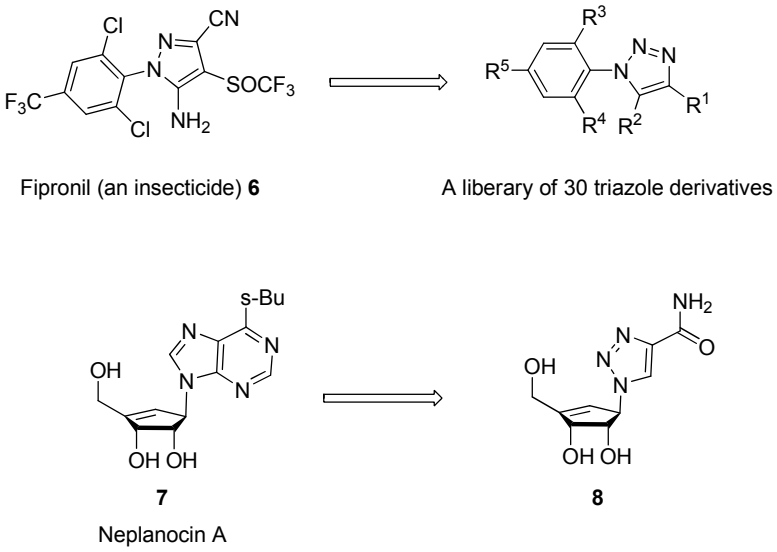


Figure 1.4 Triazole as a bioisostere of heterocycles

Besides the above mentioned potentials of triazoles, they have also been shown to possess a number of desirable features in the context of drug delivery and nanomedicine. For example, triazoles are stable to acid and basic hydrolysis, severe oxidizing and reducing agents, indicative of a high aromatic stabilization. At the same time, this moiety can also tolerate a large range of solvents and pH's and relatively resistant to metabolic degradation in living systems.[19,20]

The 1,4-disubstituted triazoles are not a novelty in the field of medicinal chemistry. Indeed, more than 7000 1,4-disubstituted triazole containing compounds had been reported[12] well before the recent advances in triazole syntheses (Chapter 2). These

1,2,3-triazole containing compounds exhibit anti-HIV,[21] anti-viral,[22] antibacterial,[23] anti-inflammatory properties and some compound show selective β_3 adrenergic[24] receptor inhibition and potent anti-histamine activity[25] and more. In antibiotics, triazoles have been used to improve pharmacokinetic properties of desired drugs.

An exciting example of triazole-containing compound is tazobactam, a β-lactamase inhibitor, and triazole ring appears to play a pivotal role for its potency.[26] Following are some of the selected examples[12,27,28] of triazole-containing compounds with their possible applications (Figure 1.5).

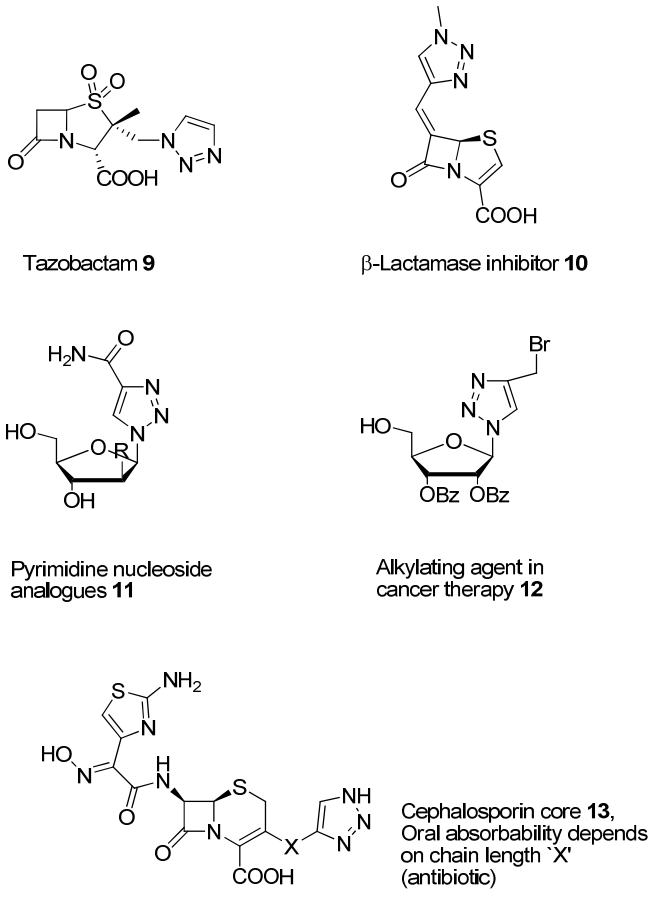
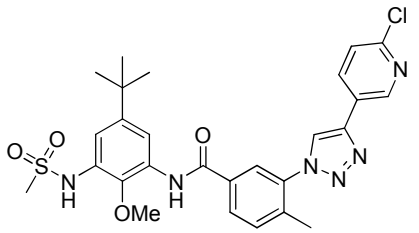
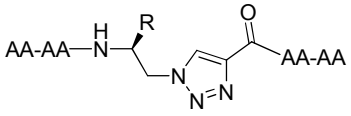


Figure 1.5 Triazole-containing compounds known before appearance of Cu-catalyzed azide-alkyne cycloadditions[29]

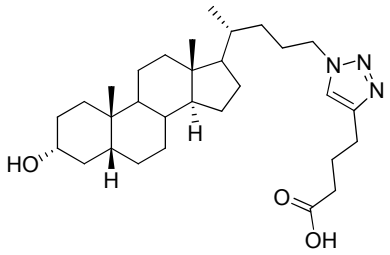
Recent advances in the syntheses of 1,2,3-triazoles has made them readily accessible moieties (Chapter 2) and opened new opportunities in generating a number of compounds with biological potential.[30,31]



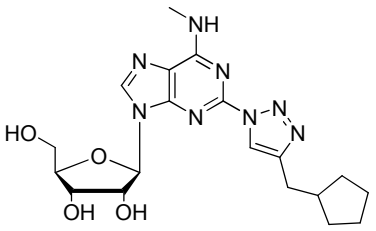
Cytokine inhibitors **14**



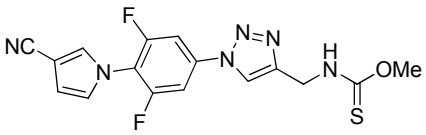
Cystein protease inhibitors **15**



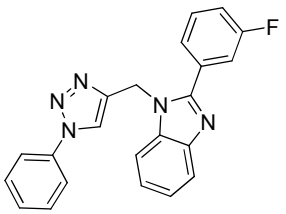
Sialyltransferase inhibitor **16**



A3 Antagonist **17**



Antibacterial **18**



H37Rv inhibitor **19**
(Antitubercular activity)

Figure 1.6 Triazole-containing compounds currently in use [32,33,34]

1.2 Aim of the project

The aim of this work has been twofold.

1) We aimed at the synthesis of 1,2,3-triazoles from the highly functionalised terminal alkynes encompassing polar substituents. We envisioned that triazoles with polar substituents could be useful as peptidomimetics, and that these substituents could further be modified. As we have access to two densely functionalized terminal alkynes[35] (Figure 1.7) we wanted to investigate their reactivity towards the synthesis of 1,2,3-triazoles. This is discussed in detail in Chapter 2.

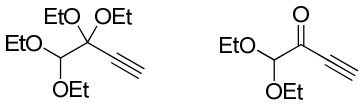


Figure 1.7 Highly functionalized terminal alkynes

2) The piperidine moiety is an important structural motif in natural alkaloids[36] and is a widely used building block, especially in the field of medicinal chemistry.[37] Preparation of piperidine derivatives is a research field in continuous evolution and a number of synthetic methodologies for the synthesis of piperidines and their incorporation into more complex structures have been developed. Ultimately, a number of functionalized piperidine derivatives appear quite frequently in biologically active compounds.[38] We aimed at the synthesis of a *trans*-3,4-disubstituted piperidine derivative (Figure 1.8) and the utilization of this building block for the synthesis of non-peptide

aspartic protease inhibitors containing 1,2,3-triazole substituent in position 4. (Figure 1.9) This is discussed in Chapter 3.

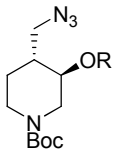


Figure 1.8 Target building block

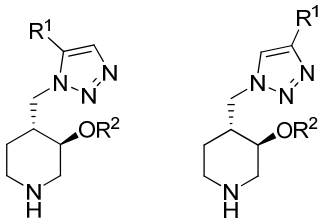


Figure 1.9 Target aspartic protease inhibitors

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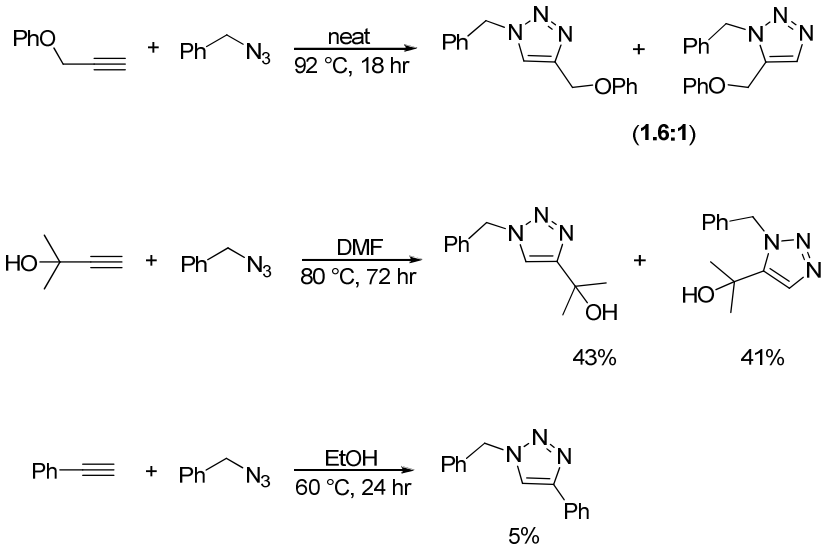
Chapter2

Synthesis of 1,2,3-triazoles

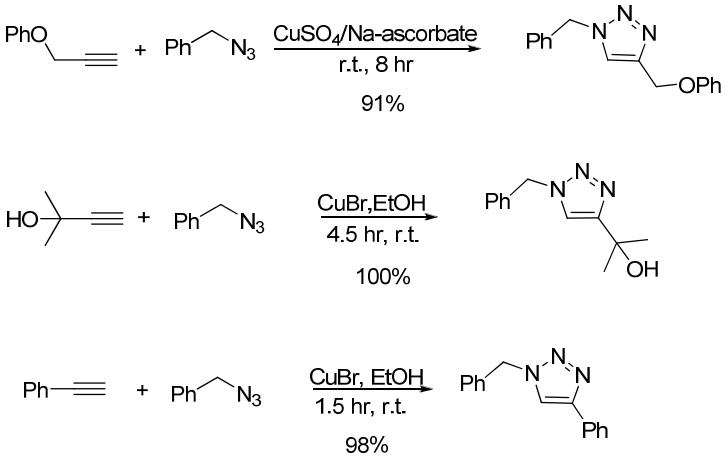
2.1. Introduction

The importance of 1,2,3-triaoles in various scientific fields has resulted in the development of several successful synthetic methodologies for their constructions.[1] The most widely used synthetic route involved the thermal 1,3-dipolar [3+2]-cycloaddition of azides and alkynes investigated by Huisgen and co-workers in the 1950's to 1970's.[2,3] The potential of such a thermal cycloadditions is very high as alkyne and azide component can be incorporated into a range of substituents.[2] In fact, due to the kinetic stability of alkynes and azides and usually a weak directing effect of substituents, for more than 40 years this reaction suffered from a lack of a selectivity producing a mixture of 1,4- and the 1,5-regioisomers (Scheme 2.1).[2] Furthermore, such reaction requires heating and longer reaction time to go to completion.



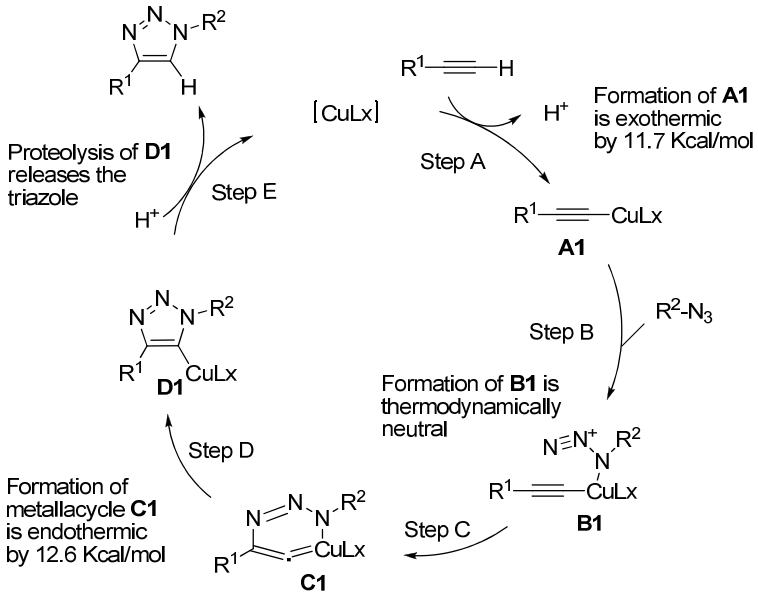
Scheme 2.1 Thermal 1,3-dipolar cycloaddition [4,5]

A recent discovery, reported independently by Sharpless[6] and Meldal[7] groups described that copper(I) salts were able to accelerate [3+2]-cycloaddition reaction between a terminal alkyne and organic azides by up to 10^7 times,[8,9] eliminating the need for elevated temperature. More importantly, Cu(I) catalysis dramatically improves the regioselectivity to afford the 1,4-regioisomer exclusively with minimal work-up and purification.[6] This high-yielding reaction tolerates a variety of functional groups, converting a very good reaction into the "cream of the crop."[10] However, this type of copper catalysis does not promote the cycloadditions of internal alkynes.



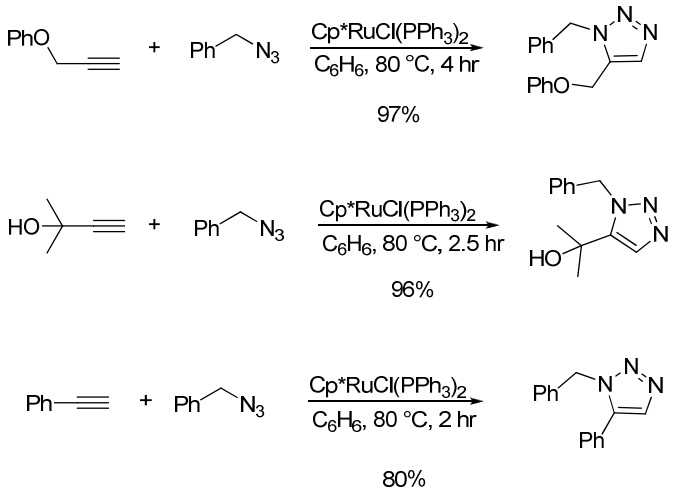
Scheme 2.2 Cu(I)-catalysed [3+2]-cycloaddition[11]

Since the initial discovery of Cu(I)-catalyzed azide-alkyne coupling, numerous examples have been reported, reaction conditions have varied widely, especially with respect to generation of the active copper(I) species. Sources of copper(I) include Cu(I) salts,[7] *in-situ* reduction of Cu(II) salts[6] and comproportionation of Cu(II) and Cu(0).[12] The improvement of copper-based catalysis is still ongoing at various levels.

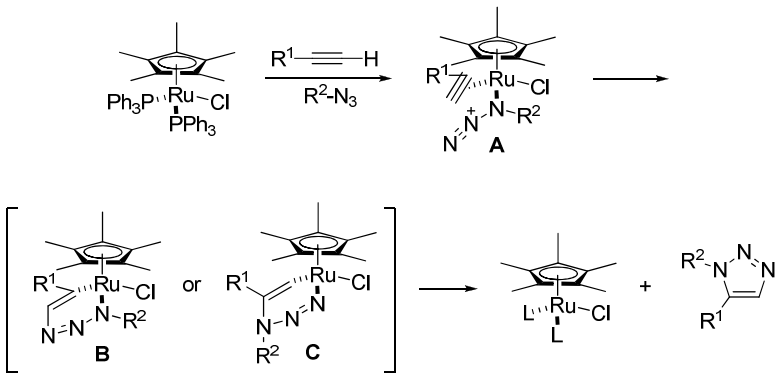


Scheme 2.3 Proposed mechanism for Cu(I)-catalysed cycloaddition[13]

The very success of Cu-catalysed azide-alkyne cycloaddition highlighted the need for selective access to the complementary regioisomers, 1,5-disubstituted 1,2,3-triazoles. Although, they can be synthesized as prevalent isomers by the action of bromomagnesium acetylide with azides (see Section 2.1.4),[14] this methodology lacks the scope and thereby leads to the loss of versatility. In 2005, Fokin and Sharpless[15] reported that the Ru(II)-catalysed approach directs 1,3-dipolar cycloaddition between alkynes and azides to afford complimentary regioisomers, the 1,5-disubstituted 1,2,3-triazoles exclusively (Scheme 2.4). In contrast to the 1,3-dipolar cycloaddtions promoted by copper, the ruthenium complex ($Cp^*RuCl(PPh_3)_2$) was also reported to catalysed the cycloaddition reaction of internal alkynes and azides.[15]



Scheme 2.4 Ru(II)-catalysed [3+2]-cycloaddition [15,16]



Scheme 2.5 Proposed mechanism for Ru(II)-catalysed cycloaddition (Initiall coordination of alkyne and azide give intermediate **A**, oxidative coupling give ruthenacycle **B** or **C** and reductive elimination leads to product).[15,17]

It is reported in literature that the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddtion reactions are not generally affected by the steric and electronic properties of the groups close to the reactive centers of azide and alkyne. For example variously substituted terminal alkynes usually react well with organic azides carrying a primary, secondary, or tertiary group; electron rich or electron deficient group; and aromatic, aliphatic or heteroaromatic substituent.[13]

While regioselectivity and catalytic efficiency is considerably affected by the nature of azide component in Ru-catalyzed 1,3-dipolar cycloaddtion reaction but independent of nature of alkyne.[15] In [3+2]-cycloadditions of alkyl azide and sterically or electronically biased alkynes for the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles, the regioselectivity is predominantly controlled by the alkyne substitution pattern.[17]

More than a decade ago, a terminal alkyne with high density of reactive functional groups, 3,3,4,4-tetraethoxybut-1-yne (TEB) was prepared in Professor Sydnes laboratory.[18] Since then this terminal alkyne has been found to be a versatile starting material for the synthesis of a range of molecules and its potential to undergo a wide range of reactions have been explored to a great extent.[19,20,21,22] An important reason for this is the presence of high density of reactive functional groups which can participate in a number of reactions under various conditions.

As a part of our recent interest in the synthesis of 1,2,3-triazoles, we decided to explore the reactivity and scope of two highly functionalized polar terminal alkynes, the ketal 3,3,4,4-tetraethoxybut-1-yne (TEB) and the corresponding ketone 1,1-diethoxybut-3-yn-2-one (keto-TEB)[23] by reacting them with benzyl azide to make triazoles. We expected that addition of benzyl azide to TEB and keto-TEB in the presence of Cu(I) salt should result in a faster reaction, less by-product formation and regioselective formation of 1,4-disubstituted 1,2,3-triazoles, whereas reactions carried out in the presence of Ru-catalyst should furnish corresponding 1,5-disubstituted analogues only. During this course of study we came across a number of interesting results which are discussed in subsequent sections.

2.1.1 Synthesis of highly functionalized alkynes

TEB was synthesized in four steps starting from non-acetylenic precursor ethyl vinyl ether as shown in Scheme 2.6.

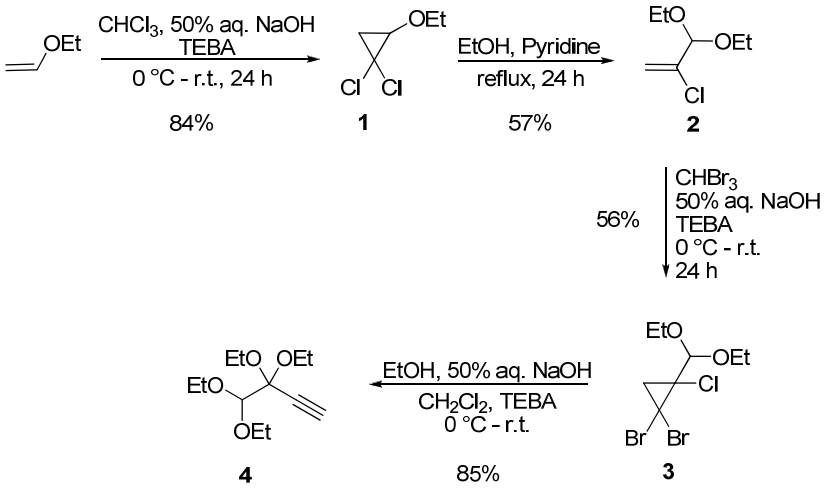
The synthesis of 1,1-dichloro-2-ethoxycyclopropane (**1**) by the addition of dichlorocarbene to ethyl vinyl ether was a simple straight forward reaction with high yield (84%). Under Makosza's phase-transfer condition,[24] chloroform was reacted with 50% aqueous sodium hydroxide to generate dichlorocarbene that undergoes cyclopropanation with ethyl vinyl ether. The triethylbenzylammonium chloride (TEBA) was used as a phase transfer catalyst in this addition reaction.

The synthesis of 2-chloro-3,3-diethoxyprop-1-ene (**2**) from **1** was achieved in moderate yield (57%) by thermally induced ring opening reaction using ethanol in the presence of pyridine, a method first reported by Skattebøl[25] and later modified and improved by Kvernenes *et al*.[26]

Using Makosza's phase-transfer method, the cyclopropanation of **2** was performed to generate 1,1-dibromo-2-chloro-2-(diethoxymethyl) cyclopropane (**3**) in moderate yield (56%), where dibromocarbene was produced from a large excess of bromoform. The unreacted bromoform is recovered by distillation and recycled. The relatively lower yield is attributed to extremely tedious work-up condition due to the formation of highly stable emulsion.

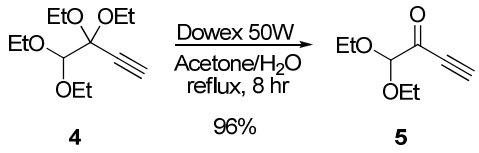
The ring opening reaction of **3** in a mixture of ethanol, 50% aqueous sodium hydroxide in the presence of TEBA as phase-transfer catalyst and dichloromethane as co-solvent took place smoothly and produced 3,3,4,4-tetraethoxybut-1-yne (TEB) (**4**) as the only product in high yield (85%).

The synthesis is simple, reliable and inexpensive since bromoform, the most expensive reagent is recycled.



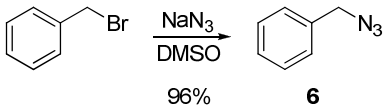
Scheme 2.6 Four step synthesis of TEB

The ketal in TEB was hydrolysed under slightly acidic conditions by using Dowex 50W as acid catalyst in moist acetone to furnish 1,1-diethoxybut-3-yn-2-one (**5**)[23] essentially in quantitative yield (96%) (Scheme 2.7). It has been noticed that older batches of Dowex 50W has a weaker catalytic efficiency in deketalization reaction.



Scheme 2.7 Deketalization of TEB

Benzyl azide was prepared by nucleophilic substitution of benzyl bromide using NaN_3 in dimethyl sulfoxide at ambient temperature according to the literature.[27]

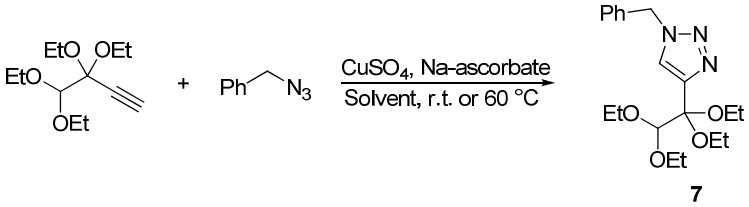


Scheme 2.8 Synthesis of benzyl azide

2.1.2 Copper-catalyzed cycloaddition reaction

The addition of benzyl azide to ketal **4** was first studied. Experiments were first carried out in CH_3CN, DMF and DMSO in the absence of Cu(I) catalyst at temperatures ranging from 60 ^oC to 110 ^oC, but cycloadducts were neither isolated nor detected. It was surprising because when Sheehan and Robinson reacted polar substituent bearing terminal alkyne, 3-phenylprop-2-ynal with phenyl azide an approximately 5:2 mixture of the 1,5- and 1,4-diphenyl-1,2,3-triazoles was obtained in 90% total yield.[28] Similarly, Huisgen and co-workers reported that the reaction of methyl propynoate with the same azide under similar conditions produced the expected 1,4- and 1,5-disubstituted triazoles in a 7:1 ratio.[29] To our surprise the result was the same when reactions were performed in aqueous *tert*-butyl alcohol containing Cu(I) generated *in situ* from copper(II) sulfate and sodium ascorbate, reaction conditions commonly used to obtain 1,4-disubstituted 1,2,3-triazoles by azide addition.[30-6] The outcome was the same when the temperature was raised to 60 ^oC and the solvent was changed to aqueous DMF (Table 1, entry 5). However, when dry acetonitrile or mixtures of water with chloroform, dichloromethane or dimethyl sulfoxide were used as solvents and $CuSO_4$/sodium ascorbate was applied as catalyst, triazole formation took place. The only product formed was 1-benzyl-4-(1,1,2,2-

tetraethoxyethyl)-1*H*-1,2,3-triazole (**7**) (Scheme 2.9) as substantiated by spectroscopic data and an X-ray crystallography structure determination (see Figure 2.1 and Table 2), which revealed that the bond lengths and angles were close to literature values for similar compounds.[31-35] In all cases the yield was not better than moderate even after 48 hrs at both room temperature and 60 °C, but generally somewhat higher at the higher temperature (Table 1). The rest of the reaction mixture was in essence unreacted starting material.



7

Scheme 2.9 Cycloaddition under *in situ* Cu(I)-catalysis

Table 1 Isolated yield of triazole **7**, after 48 hrs at two temperatures

Entry	Solvent	Room temperature	60 °C
1	CH_3CN	44%	58%
2	H_2O/CH_3Cl (1:3)	41%	51%
3	H_2O/DMSO (1:3)	61%	69%
4	H_2O/CH_2Cl_2 (1:3)	55%	[a]
5	H_2O/DMF	none	none

[a] The reaction was not run since dichloromethane boils below 60 °C

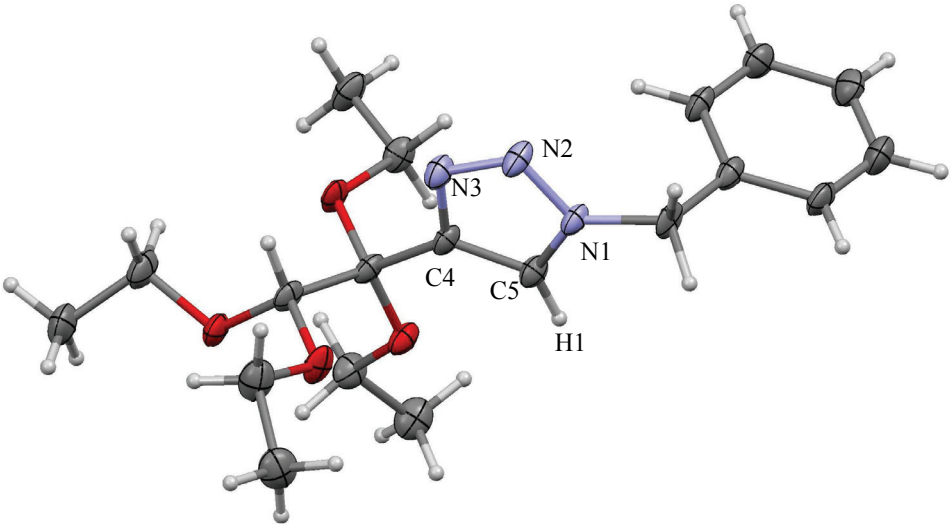


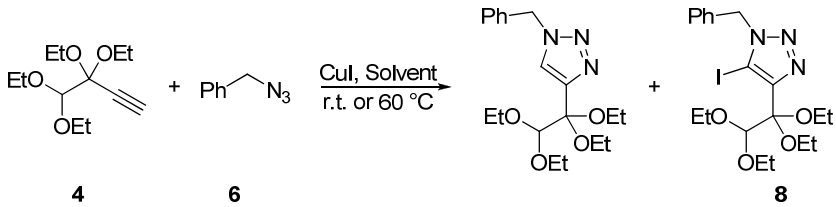
Figure 2.1 Crystal structure of compound **7**

Table 2 Endocyclic bond lengths (Å) and angles (º) for the triazole ring in **7**[36]

Atoms	Bond length	Atoms	Angle
N(1)-N(2)	1.346(6)	N(2)-N(1)-C(5)	111.4(4),
N(1)-C(5)	1.356(7)	N(3)-C(4)-C(5)	108.5(5)
C(4)-N(3)	1.353(7)	N(3)-C(4)-C(6)	121.8(4),
C(4)-C(5)	1.382(7)	N(3)-N(2)-N(1)	106.6(4),
N(2)-N(3)	1.324(6)	N(1)-C(5)-C(4)	104.1(5),
C(5)-H1	0.9500	N(1)-C(5)-H1	128.0
		N(2)-N(3)-C(4)	109.4(4).

Crystal system: monoclinic, Density: 1.225 Mg/m^3, Volume: 1970.3(12) $Å^3$, Unit cell dimentions: a = 6.429(2), b = 41.716(14), c = 7.486(3) Å, α= 90°, β= 101.092(5)°, γ = 90°

An alternative cuprous salt that is often used to facilitate azide-alkyne cycloaddition, is copper(I) iodide which is used in the presence or absence of a base.[37] When this salt was employed instead of $CuSO_4$/sodium ascorbate system, the yield of **7** from **4** generally increased under most conditions, although the best yield (71%, see Table 3) was only slightly higher than the best yield obtained with the $CuSO_4$-ascorbate catalyst (69%, see Table 1). Again, 1,4-disubstituted 1,2,3-triazole **7** was obtained in better yield at 60 ^oC than at room temperature. Interestingly, no product was detected when the reaction was carried out in water mixed with either dichloromethane or chloroform (Table 3, entry 4 and 5), an observation which clearly indicates that chlorinated solvents for one reason or another prevent triazole formation when CuI is used as catalyst. Li *et al*.[38] found that the poor solubility of CuI in halogenated solvent retards the cycloaddition reaction. This is not really the case as observed in other cycloadditions (Table 4, entry 9 and 10). Another notable feature is the consistent formation of an additional, minor product, which finally turned out to be 1-benzyl-5-iodo-4-(1,1,2,2-tetraethoxyethyl)-1*H*-1,2,3-triazole (**8**) as additionally confirmed by an independent known synthetic route (Scheme 2.11).



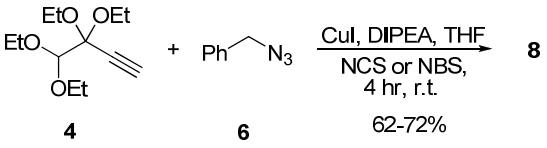
4 **6** **8**

Scheme 2.10 Cycloaddition with CuI as catalyst

Table 3 Isolated yields of triazole **7** and 5-iodotriazole **8** after 48 hrs

Entry	Solvent	Room temperature		60 °C	
		7	**8**	**7**	**8**
1	CH_3CN	68%	6%	71%	5%
2	H_2O/DMSO (1:3)	69%	3%	61%	3%
3	H_2O/DMF (1:3)	42%	5%	62%	7%
4	H_2O/CH_2Cl_2	none		None	
5	H_2O/CH_3Cl	none		None	

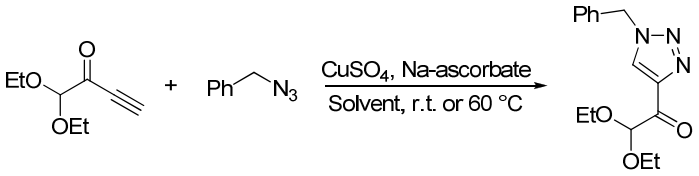
The yield of **8** was very low when CuI was applied in the absence of base (< 7%, see Table 3), but when the reaction was performed with CuI in the presence of diisopropylethylamine (DIPEA) and either *N*-chlorosuccinimide (NCS) or *N*-bromosuccinimide (NBS) as electrophilic iodinating reagents,[38] triazole **7** was not formed whereas 5-iodotriazole **8** was obtained in a respectable yield (72% and 62% yield, respectively) (Scheme 2.11).



Scheme 2.11 Synthesis of 5-Iodo-isomer

Copper-catalyzed addition of benzyl azide to ketoalkyne **5** was then performed. On the basis of a paper published by Girard *et al*.[39] who studied the addition of the same

azide to various alkynes containing polar substituents under similar conditions, we expected regiospecific formation of the analogous 1,4-disubstituted 1,2,3-triazole in moderate to good yield. That was indeed observed when $CuSO_4$/sodium ascorbate was used as catalyst system (Table 4); the only product obtained, in up to 70% yield (entry 5), was 1-(1-benzyl-1*H*-1,2,3-triazole-4-yl)-2,2-diethoxyethanone (**9**), which structure was elucidated by spectroscopic analyses and finally also unequivocally substantiated by a high-yield (90%) independent synthesis through deketalization of **7** (Scheme 2.13).



5 **6** **9**

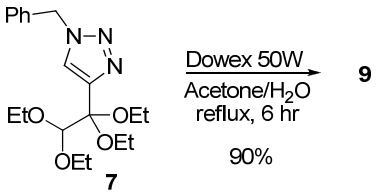
Scheme 2.12 Cycloaddition of ketoalkyne and benzyl azide

When addition of benzyl azide to keto-TEB **5** was carried out under CuI catalysis, the outcome of the reaction changed somewhat. 1,4-Disubstituted triazole **9** was still the predominant product (Table 4, entry 6), but in addition the corresponding 1,5-disubstituted isomer, *viz*. 1-(1-benzyl-1*H*-1,2,3-triazole-5-yl)-2,2-diethoxyethanone (**10**), was obtained (Scheme 2.14) in up to 10% yield (Table 4, entry 8). Furthermore, unlike TEB **4** the corresponding ketone **5** appeared not to furnish any iodotriazole, and by analyzing the crude reaction mixture with respect to the iodoketo corresponding to iodoketal **8**, *viz*. 1-(1-benzyl-5-iodo-1*H*-1,2,3-triazole-4-yl)-2,2-diethoxyethanone (**11**) prepared by deketalization of **8** (Scheme 2.15), it was unambiguously proved that iodide **11** was not formed under the conditions that furnished **8** from **4**.

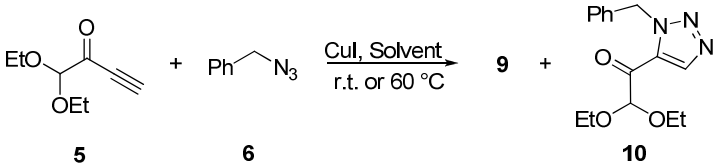
Table 4 Isolated yields of triazoles **9** and **10** in 48 hr.

Entry	Catalyst	Solvent	Room temperature		60 °C	
			9	**10**	**9**	**10**
1	$CuSO_4$/Ascorbate	CH_3CN	59%		61%	
2		H_2O/DMSO (1:3)	61%		69%	
3		H_2O/DMF (1:3)	51%		60%	
4		H_2O/CH_3Cl (1:3)	48%		52%	
5		H_2O/CH_2Cl_2 (1:3)	70%		[a]	
6	CuI	CH_3CN	61%	3%	70%	3%
7		H_2O/DMSO (1:3)	54%	3%	61%	2%
8		H_2O/DMF (1:3)	52%	10%	61%	4%
9		H_2O/CH_3Cl (1:3)	58%	3%	54%	5%
10		H_2O/CH_2Cl_2 (1:3)	59%	0%	[a]	

[a] The reaction was not run since dichloromethane boils below 60 °C.



Scheme 2.13 Deketalization reaction



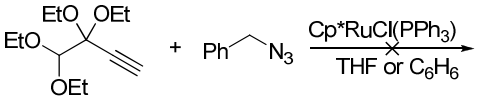
Scheme 2.14 Cycloaddition with CuI as catalyst

Scheme 2.15 Deketalization reaction of 5-*I*-triazole

It is concluded that the reactivity exhibited by TEB **4** and keto-TEB **5** is essentially identical when the $CuSO_4$/sodium ascorbate catalyst system is applied, and this indicates that, under these conditions, the cycloaddition is barely sensitive to the functional groups' different ability to both conjugate with the neighbouring C-C triple bond and form complexes with the copper species involved in reaction. However, when CuI is the catalyst one similarity and two differences are observed. The similarity is that both alkynes give the corresponding 1,4-disubstituted 1,2,3-triazole as the main product (60-70% yield) along with one by-product (typically in 3-7% yield). The differences are the structures of the by-products produced in the two cases; whereas the by-product in the case of acetylenic ketal **4** is the 5-iodinated derivative of the main product, the by-product from acetylenic ketone **5** is the iodine-free 1,5-disubstituted structural isomer of the main product.

2.1.3 Ruthenium-catalyzed cycloadditions

The formation of 1,5-disubstituted triazole **10** as a by-product when keto-TEB **5** was reacted with benzyl azide in the presence of CuI indicates that **10** might be formed in higher yields if the reaction is carried out under conditions that are known to favour 1,5-disubstituted-1,2,3-triazole formation over 1,4-disubstituted-1,2,3-triazole formation in such addition reactions. In order to favour dominance of the former Cu(I) salt was replaced by a ruthenium complex, bis(triphenylphosphine) pentamethylcyclopentadienyl ruthenium(II) chloride ($Cp^*RuCl(PPh_3)_2$) and reactions were performed in THF and benzene.[15] After having run the reaction between benzyl azide and phenylacetylene under $Cp^*RuCl(PPh_3)_2$ catalysis several times as described in the literature and obtained 1-benzyl-5-phenyl-1,2,3-triazole (**12**) as the only product in consistently better than 85% yield (Table 5, entry 1) ketal **4** was reacted with benzyl azide under the same conditions (Scheme 2.16). To our surprise no reaction occurred as observed from chromatographic and spectroscopic analyses, and when the reaction mixture was worked up in the usual way, both reactants were recovered in high yield (Table 5, entries 2 and 3).



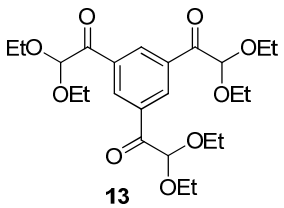
4 **6**

Scheme 2.16 Cycloaddition for 1,5-disubstituted 1,2,3-triazole

Table 5 Outcome of syntheses performed to obtain 1,5-disubstituted 1,2,3-triazoles

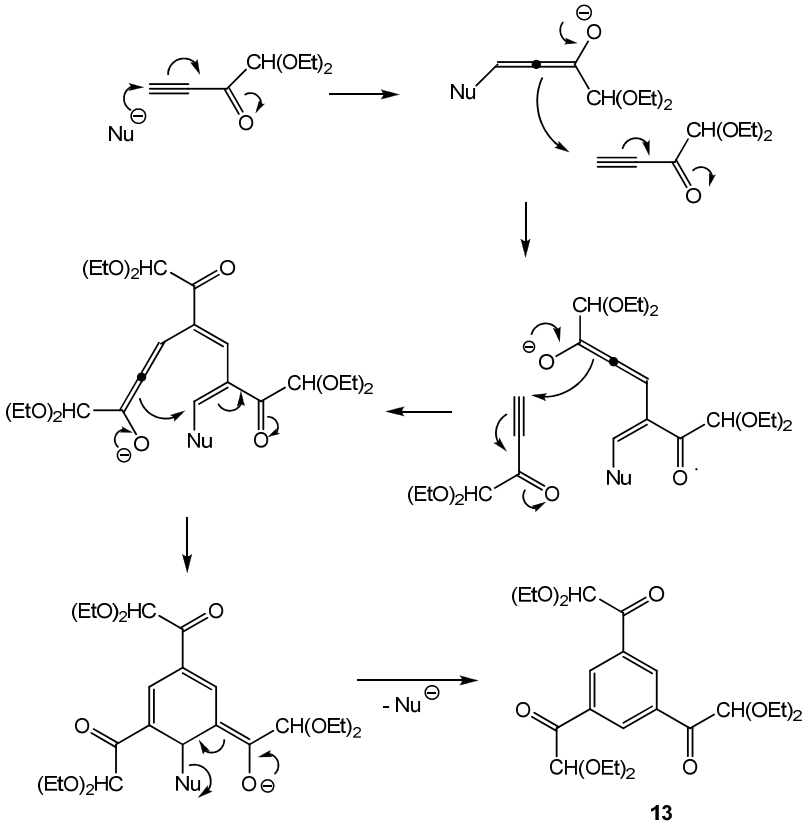
Entry	Alkyne	Reaction conditions	Isolated compounds (yield)
1	Ph—≡	Cp*RuCl(PPh_3)$_2$, THF, 65 ºC, 3 h	**12** (86%)
2	**4**	Cp*RuCl(PPh_3)$_2$, THF, 65 ºC, 24 h	**4** (95%) and **6** (96%)
3		Cp*RuCl(PPh_3)$_2$, C_6H_6, 80 ºC, 24 h	**4** (94%) and **6** (93%)
4	**5**	Cp*RuCl(PPh_3)$_2$, THF, 65 ºC, 4 h	**13** (55%) and **6** (91%)
5		Cp*RuCl(PPh_3)$_2$, C_6H_6, 80 ºC, 3 h	**13** (60%) and **6** (88%)

When the substrate was changed to keto-TEB **5**, TLC analysis showed that a reaction took place. Subsequent work-up revealed that all of **5** had been consumed and been converted to one product which appeared not to be a triazole, but 1,3,5-tris(2,2-diethoxyacetyl)benzene (**13**) that was obtained in 55% and 60% yield at 65 ^{o}C and 80 ^{o}C, respectively (Table 5, entries 4 and 5). This trimer of **5** has previously been obtained by treating **5** with aqueous solutions of sodium bicarbonate.[40] The formation of **13** is not really surprising because ruthenium complexes have proved to facilitate cyclotrimerization of electron-deficient alkynes [41, 42,42] (also see Section 2.3). The mechanism for the reaction has not been unraveled, but a suggestion is depicted in Scheme 2.17.



13

Figure 2.2 Trimer produced in Ru-catalyzed reaction

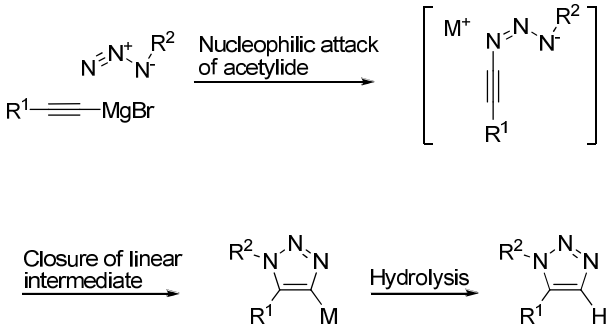


Scheme 2.17 A proposed mechanism for the formation of **13** Nu^- denotes an unknown nucleophilic species derived from $Cp^*RuCl(PPh_3)_2$.

Thus, the different behaviour of TEB and Keto-TEB toward $Cp^*RuCl(PPh_3)_2$ is quite likely due to increased reactivity associated with conjugative effects between the triple bond and the carbonyl group, but it cannot be ruled out that when TEB is reacted, the catalyst is so much deactivated by some sort of complexation with some or all of the four oxygen atoms in the tetraethoxyethyl moiety that TEB is rendered unreactive even after 24 hr.

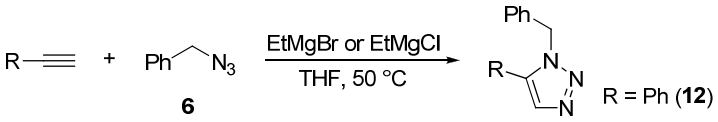
2.1.4 1,5-Disubstituted 1,2,3-triazoles via addition of bromomagnesium acetylides to azides

Regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles from terminal alkynes has also been achieved by adding bromomagnesium acetylides to organic azides.[43,14] The proposed mechanism begins with the nucleophilic attack of acetylide on terminal nitrogen atom of the azide, followed by spontaneous closure of the intermediate to 4-metallotriazole which after hydolysis gives triazole



Scheme 2.18 Proposed mechanism for synthesis of 1,5-disubstituted 1,2,3-triazoles[14]

After having conducted the reaction between benzyl azide and the acetylide from phenylacetylene[14] several times and isolated 1-benzyl-5-phenyl-1,2,3-triazole (**12**) as the only product in 93% yield the acetylide from TEB **4** was reacted with benzyl azide in exactly the same way (Scheme 2.19). To our disappointment the reaction failed to generate any 1,2,3-triazole; instead both benzyl azide and TEB **4** were recovered in almost quantitative (98% TEB and 97% BnAz) yield even after 24 hr (Table 6).



Scheme 2.19 Addition of halomagnesium acetylides to azide

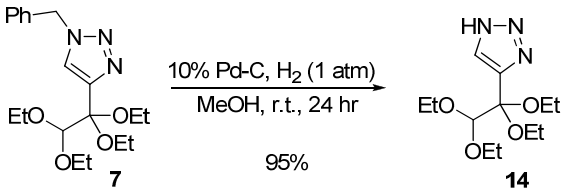
Table 6 1,5-disubstituted 1,2,3-triazoles via addition of halomagnesium acetylides

Entry	**R**	Reaction conditions	(%yield)
1	Ph	EtMgBr, THF, NH_4Cl, 50 ºC	(**12**) 93%
2	$C(OEt)_2CH(OEt)_2$	EtMgBr, THF, NH_4Cl, 50 ºC	-
3	$C(OEt)_2CH(OEt)_2$	EtMgCl, THF, NH_4Cl, 50 ºC	-

2.2 Debenzylation of *N*-benzyl 4- and 5-substituted 1,2,3-triazles

The benzyl group has found wide applications as a protecting group for amines and *N*-debenzylation is an important conversion for the deprotection. The Pd-C catalyzed hydrogenolysis is one of the most studied reactions for *N*-debenzylation of benzylamines. This reaction is however normally found to occur for basic compounds. In addition to some reasonably described methodologies,[44,45,46] *N*-unsubstituted, i.e *N*H-1,2,3-triazoles can also be prepared by hydrogenolysis of *N*-benzylsubstituted 1,2,3-triazoles in the presence of palladium on carbon. A report by Wiley *et al*.[47] on the use of the benzyl group as a *N*-protecting group for the synthesis of 1,2,3-triazoles describes the requirement for an elevated temperature and high hydrogen pressure for the debenzylation of 1-benzyl-4,5-disubstituted-1,2,3-triazoles. However, another report suggests the use of atmospheric hydrogen pressure to facilitate the removal of a *N*-benzyl group from C4- or C5-mono substituted or 4,5-disubstituted 1,2,3-triazoles.[48]

We found that *N*-benzylsubstituted 1,2,3-triazole **7** could be debenzylated by catalytic hydrogenolysis over 10% Pd-C in methanol for 24 hr to provide 4-(1,1,2,2-tetraethoxyethyl)-1*H*-1,2,3-triazole (**14**) in 95% yield (Scheme 2.20).



Scheme 2.20 Debenzylation of triazole **7**

According to the literature reports, hydrogenolysis of benzylamines can be facilitated by the addition of hydrochloric acid to protonate the amine.[49] Keeping this in view, when the previous reaction (Scheme 2.20) was repeated with the addition of two drops of concentrated HCl, the ketal functionality was converted to the ketone, giving **9** (64%) and a red-brown polymeric material after 24 hrs and no debenzylation was observed.

A novel procedure recently developed by Cheng *et al.* describes the accelerated hydrogenolysis of benzylamines by HCl released *in situ* in the hydrodechlorination of 1,1,2-trichloroethane.[50] Following this protocol, 1,2,3-triazole **7** was completely debenzylated after only two hours to produce the *N*H-1,2,3-triazole **14** in 97% yield. This increase in the rate of the reaction prompted us to explore whether other substituted 1-benzyl 1,2,3-triazoles could be debenzylated following this protocol.

Towards this end, a number of 1,4-disubstituted 1,2,3-triazoles were synthesized by copper-catalyzed addition of benzyl azide to various alkynes and $CuSO_4$/sodium ascorbate was used as catalyst system while corresponding 1,5-disubstituted 1,2,3-triazoles were prepared by Ru(II)-catalysis using Cp*RuCl$(PPh_3)_2$ in THF or C_6H_6 as described in previous sections.[51] The reaction times and yields for the individual triazole syntheses are summarized in Table 7. As previously discussed, 1,5-disubstituted 1,2,3-triazoles from alkyne **4** and **5** were not formed at all (Section 2.1) and Ru-catalyzed reaction between methyl propiolate and benzyl azide produced a fraction of **15b** along with trimethyl benzene-1,3,5-tricarboxylate **(15c)** (Figure 2.3).

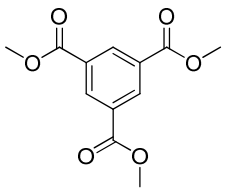
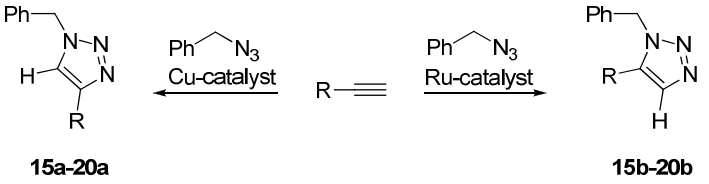


Figure 2.3 Trimer of methyl propiolate **15c**



15a-20a **15b-20b**

Scheme 2.21 Synthesis of 1,4-and 1,5-disubstituted 1,2,3-triazoles

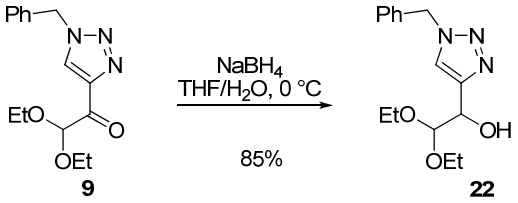
Table 7 1,4-and 1,5-disubstituted 1,2,3-triazoles from various alkynes

Entry	**R**	1,4-isomer[a]			1,5-isomer[b]		
		Triazole	(%) Yield	Time (hr)	Triazole	(%) Yield	Time (hr)
1	CH_3OCO	**15a**	99	12	**15b**	3	4
2	Ph	**12a**	99	12	**12**	86	3
3	$PhCH_2$	**16a**	95	12	**16b**	-	-
4	CH_3OCH_2	**17a**	99	20	**17b**	76	4
5	$PhOCH_2$	**18a**	95	12	**18b**	97	4
6	$CH(OEt)_2$	**19a**	98	12	**19b**	79	4
7	CH_3CHOH	**20a**	97	24	**20b**	42-70	3

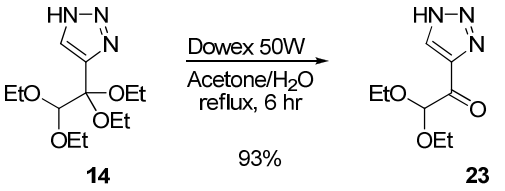
Conditions: a) CH_2Cl_2/H_2O (3:1) and $CuSO_4$/sodium ascorbate; b) $Cp^*RuCl(PPh_3)_2$,C_6H_6 at 80 ºC or in THF at 65 ºC

While 1,4-disubstituted 1,2,3-triazole **7** was cleanly debenzylated to give **14**, the 1,2,3-triazole **9** underwent a reduction in addition to the debenzylation, to give the secondary alcohol, 2,2-diethoxy-1-(1*H*-1,2,3-triazol-4-yl)ethanol **(21)** in high yield

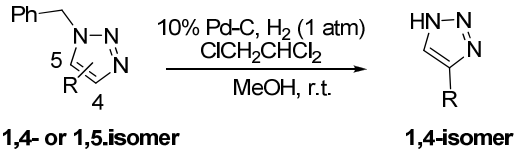
(Table 8). Direct debenzylation of 1-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-2,2-diethoxyethanol **(22)**, prepared by $NaBH_4$-mediated reduction of **9** (Scheme 2.22), afforded **21** in 97% isolated yield after 9 hr reaction time (Table 8, entry 2). However, the expected ketone, 2,2-diethoxy-1-(1*H*-1,2,3-triazol-4-yl)ethanone **(23)** from 1,2,3-triazole **9** was alternatively synthesized by the deketalization of **14** in high yield (93%) in 6 hr (Scheme 2.23).



Scheme 2.22 Reduction of triazole **9**

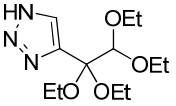
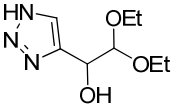
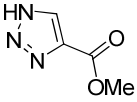
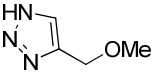
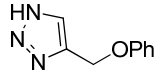
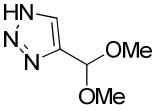
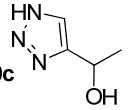


Scheme 2.23 Deketalization of *N*H-1,2,3-triazole **14**



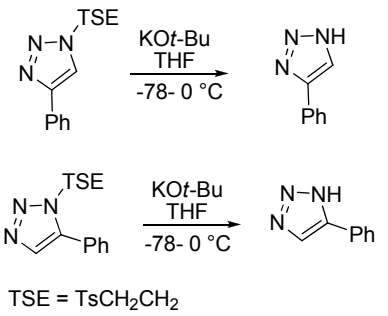
Scheme 2.24 *N*-debenzylation of 1,4- and 1,5-disubstituted 1,2,3-triazoles

Table 8 Debenzylation of 1,2,3-triazoles[a]

Entry	Substrate	Time (h)	Yield (%)	Product
1	**7**	2	97	**14** 
2	**9**	24	85	**21** 
	22	9	97	
3	**15a**	36	96	**15c** 
4	**12a**	24	no reaction	
5	**12**	24	no reaction	
6	**16a**	24	no reaction	
7	**17a**	28	95	**17c** 
	17b	21	94	
8	**18a**	24	30	**18c** 
	18b	24	94	
9	**19a**	24	94	**24** 
	19b	24	94	
10	**20a**	24	96	**20c** 
	20b	24	94	

a) Conditions: 10% Pd-C, $ClCH_2CHCl_2$, MeOH, r.t.

Further, hydrogenolysis of the 1,4-isomer **15a** equipped with methoxy carbonyl substitutent gave 97% of debenzylated product in 36 hr (Table 8 , entry 3). However, when 1,4-disubstituted 1,2,3-triazole **12a**, **16a** and 1,5-disubstituted 1,2,3-triazole **12** were submitted to debenzylation conditions, to our surprise no reaction occurred even after 24 hr and starting material could be recovered in 95% yield in all cases (Table 11). Contrary to this, the 1,4- and 1,5-disubstituted 1,2,3-triazoles **17a** and **17b** were both readily debenzylated in 28 and 21 hr respectively (Table 8, entry 7) and the analytical data of products obtained from both isomers were identical in all respects. Which suggested the formation of only one isomer of *N*H-1,2,3-triazole either C4- or C5-substituted. Whereas, Yap and Weinreb[52] in 2006 has reported that TSE-protected 1,4- and 1,5-disubstituted 1,2,3-triazole produced C4- and C5-monosubstituted *N*H-1,2,3-triazle respectively after removing the TSE-protecting group under mildly basic conditions via a retro-Michael reaction (Scheme 2.25). This fact was not in consistent with our results.



Scheme 2.25 Removal of TSE-protecting group by Yap and Wienreb[52]

According to Dabbagh *et al.*[53] the C-monosubstituted 1,2,3-triazole exhibits tautomerism: the (N)H hydrogen atom can be attached to the 1st, 2nd or 3rd nitrogen atom. For C-monosubstituted *N*H-1,2,3-triazoles, the N1-H-C4 tautomer (Figure 2.4) is generally described as being more stable than the N3-H-C5 tautomer, with the N2-

H being the most stable tautomer. It has also been suggested that the relative stability of the C5-substituted 1,2,3-triazloe tautomerism is strongly influenced by intramolecular interactions between substituent and protons located either at N1 or N3 atom. The nature of substituent, electron withdrawing or donating and possibility of hydrogen bonding play an important role in this regard.[54]

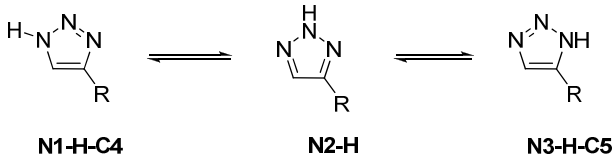


Figure 2.4 Tautomers of C-monosubstituted *N*H-1,2,3-triazoles.

Based on experimental and theoretical studies, Abboud *et al*.[55] reported that in gas phase, 2*H* tautomers **b** always predominates, while in aquous solution, both 1*H* and 2*H* tautomers- **a** and **b** are present equally. In solid state C-monosubstituted *N*H-1,2,3-triazoles can be **a** or **b** with an equal probability (Figure 2.5).

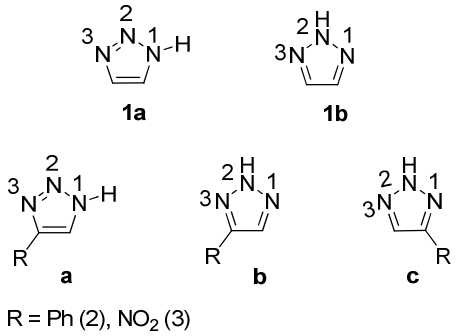


Figure 2.5 Tautomers of *N*H-1,2,3-triazoles.

Under debenzylation conditions, the conversion of triazole **18a** was low, most likely due to its low solubility in methanol, and only 30% of 4-(phenoxymethyl)-1*H*-1,2,3-triazole **(18c)** could be isolated even after 24 hr reaction time (confirmed by GC-MS) and 39% in 48 hr when reaction was run in ethanol. Interestingly, the C5-substituted isomer **18b** was fully converted to **18c** under identical conditions in 24 hr reaction time. We were also able to obtain a single crystal X-ray structure from **18c** (Figure 2.6). In the solid state an intermolecular hydrogen bond with the triazole NH as the donor and a triazole N(2) as the acceptor, was observed. The hydrogen bond length was measured to 2.1 Å with an N-H-N angle of 148.4 º. From the crystal structure it is clear that for the present case, the N1-H-C4 tautomer (see Figure 2.4) is the preferred tautomer in the solid phase. The N1-N2-N3 bond angle was found to be 107.8 º, which is typical for this tautomeric form.[55] However, for the N2-H tautomer, this bond angle is typically found to be around 116 º.

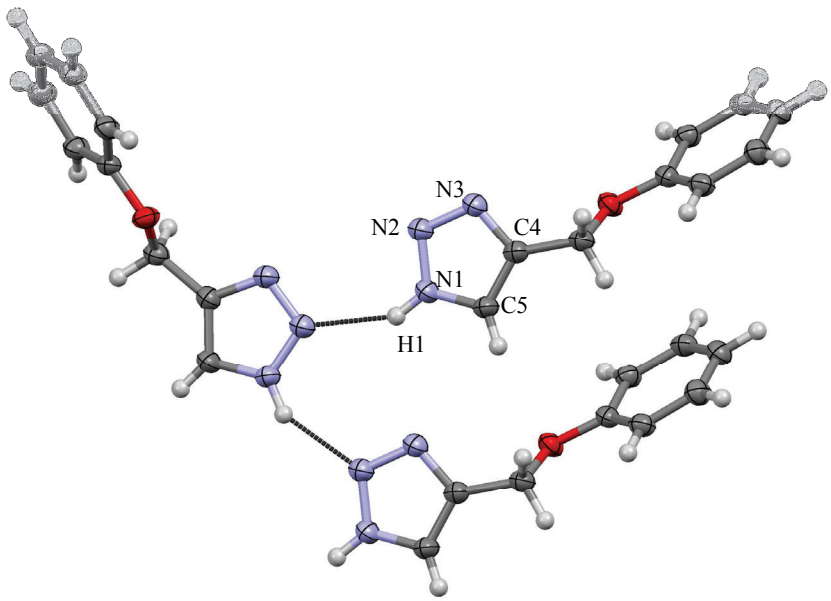


Figure 2.6 Single crystal structure of **18c** with intermolecular hydrogen bonding.

Table 9 Endocyclic bond lengths (Å) and angles (°) for the triazole ring in **18c**[56]

Atoms	Bond length	Atoms	Angle
N(1)-N(2)	1.338	N(2)-N(1)-C(5)	110.75
N(1)-C(5)	1.342	N(3)-C(4)-C(5)	108.58
C(4)-N(3)	1.365	N(3)-C(4)-C(6)	121.32
C(4)-C(5)	1.365	N(3)-N(2)-N(1)	107.76
N(2)-N(3)	1.324	N(1)-C(5)-C(4)	105.12
C(5)-H(2)	0.974	N(1)-C(5)-H2	123.37
N(1)-H(1)	0.877	N(2)-N(3)-C(4)	107.78
		C(5)-N(1)-H(1)	127.71

Unit cell dimentions: a = 14.227 (10), b = 5.348 (4), c = 11.087 (8) Å, α= 90°, β= 92.437 (8)°, γ = 90° (The bond length and angles have been compared with literature values).[55,53,33, 57]

In line with the reactivity described so far, the C4-alkoxy substituted **19a** and C5-alkoxy substituted **19b** were efficiently debenzylated to a *N*H-1,2,3-triazole in excellent yield (Table 8, entry 9), but interestingly the ethoxy groups were replaced with methoxy groups giving 4-(diethoxymethyl)-1*H*-1,2,3-triazole **(24)** instead of **19c** as the product. The progress of this reaction was followed by GC-MS; it was found that the exchange of alkoxy groups and debenzylation occurred at the same time as only two peaks were present in the chromatogram; one reactant peak with ethoxy groups (at 27.95 min) and one product peak with methoxy groups (at 14.49 min) (Figure 2.7).

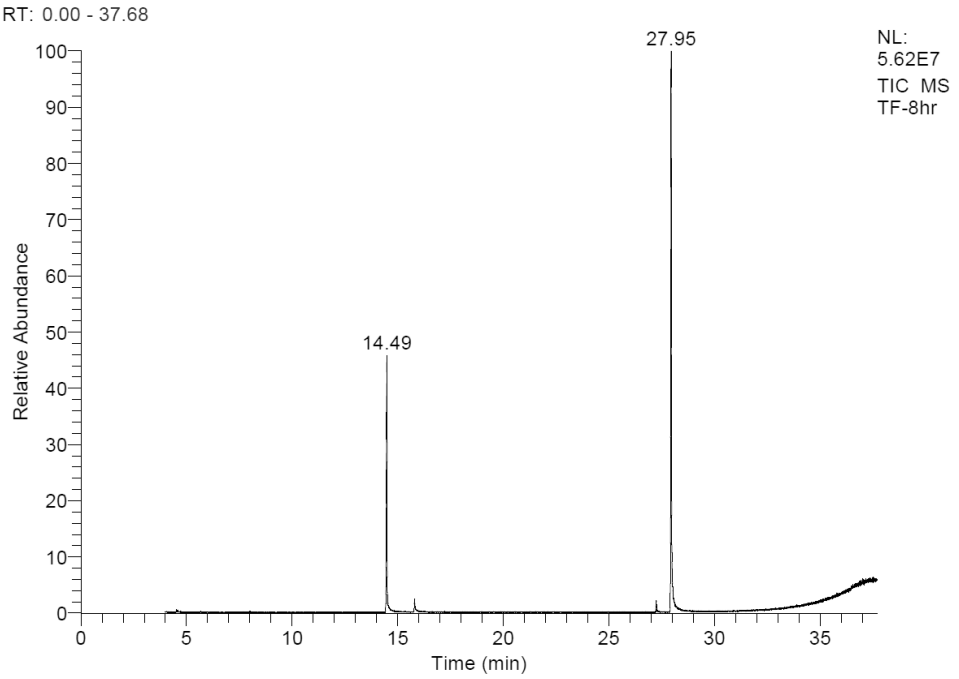


Figure 2.7 GC-chromatogram of debenzylation of **19b** after 8 hr

Further, it was found that **24** was unstable as it was converted into 1*H*-1,2,3-triazole-4-carbaldehyde **(25)** upon standing in the fume hood for few days (see Experimental section).

In 2003 Ozimiński *et al.*[54] reported on the basis of DFT studies that the electron withdrawing or donating effect of substituent at position C5(4) is not the only intramolecular effect that stabilize the 1,2,3-triazole ring. Indeed, the possibility for intramolecular interactions (both repulsive and attractive) between substituent and proton present either at N1 or N3 atom play vital role in tautomer stabilization.

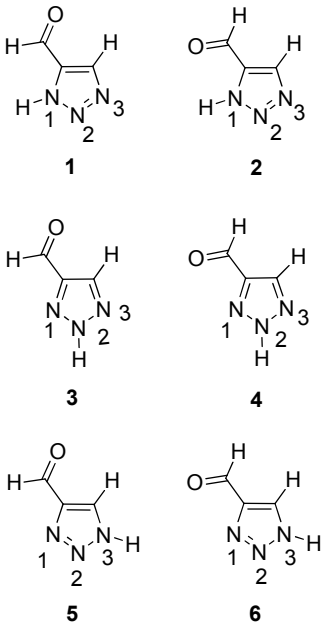


Figure 2.8 5-aldo-1,2,3-triazoles on rotation of –CHO substituent[54]

In the above case (Figure 2.8), from DFT calculations the most stable form appeared to be that with an intramolecular hydrogen bond present in the system, in gas phase: the C-H or C=O moieties of aldehyde group with the N1 or N1-H moiety of triazole ring (structure 3). However, in our case, the x-ray analysis of a single crystal of **25** revealed that also for this monosubstituted 1,2,3-triazole the N1-H-C4 tautomer is the most stable in the solid phase (Figure 2.9). In this case, the N1-N2-N3 bond angle was also found to be 106.9º, typical for N1-H-C4 tautomer. The intermolecular hydrogen bonding was evident also for this crystal structure. In this case, the triazole NH forms hydrogen bonds with both the N3 and the carbonyl oxygen atom acting as hydrogen bond acceptors. The bond lengths were measured to 2.3 Å and 2.2 Å for the the O-H and N-H bonds respectively with N-H-N and N-H-O bond angles of 141.8 Å and 139.3 Å respectively.

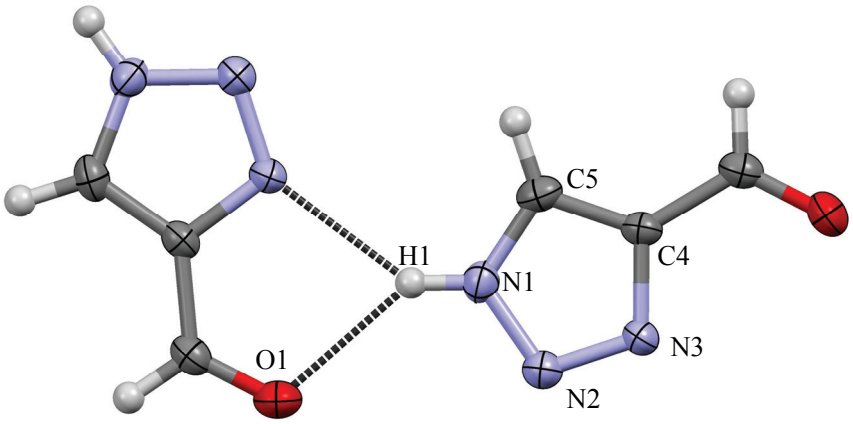


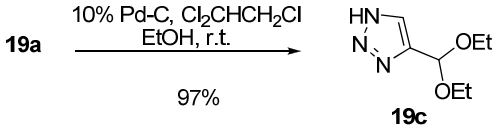
Figure 2.9 X-ray crystal structure of **25**

Table 10 Endocyclic bond lengths (Å) and angles (°) for the triazole ring in **25**[58]

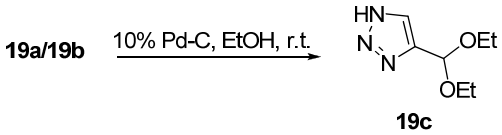
Atoms	Bond length	Atoms	Angle
N(1)-N(2)	1.350	N(2)-N(1)-C(5)	111.34
N(1)-C(5)	1.338	N(3)-C(4)-C(5)	108.49
C(4)-N(3)	1.369	N(3)-N(2)-N(1)	106.92
C(4)-C(5)	1.362	N(1)-C(5)-C(4)	104.53
N(2)-N(3)	1.303	N(1)-C(5)-H	127.77
C(5)-H(2)	0.950	N(2)-N(3)-C(4)	108.72
N(1)-H(1)	0.880	C(5)-N(1)-H(1)	124.30

Crystal system: monoclinic, Density: 1.573 Mg/m^3, Volume: 205.0(10) Å^3, Unit cell dimentions: a = 3.6581(10), b = 10.204(3), c = 5.4918(16) Å, α= 90°, β= 90.154(3)°, γ = 90° (The bond length and angles have been compared with literature values).[55,53,33, 57]

In order to avoid the replacement of ethoxy groups in methanol, the debenzylation reaction of **19a** was repeated using ethanol as the solvent, a clean conversion to **19c** was observed in 12 hr (Scheme 2.26). However, debenzylation reaction produced **19c** in near quantitative yield in 62 and 68 hr when **19a** and **19b** were submitted to debenylation in ethanol in the absence of trichloroethane (Scheme 2.27).



Scheme 2.26 Debenzylation of **19a** in ethanol



Scheme 2.27 Debenzylation in ethanol without trichloroethane

The conversion of **17a**, **17b**, **19b** in methanol and **19a** in ethanol to their corresponding *N*H-1,2,3-triazoles have been studied on GC-MS (Figure 2.10). These reactions found to be very slow in first 10 hr (less than 15% conversion) except the conversion of **19a** which is completed in 12 hr, faster than any other. However, **19a** completed its conversion in 24 hr when reaction was run in methanol (not shown in Figure 2.10).

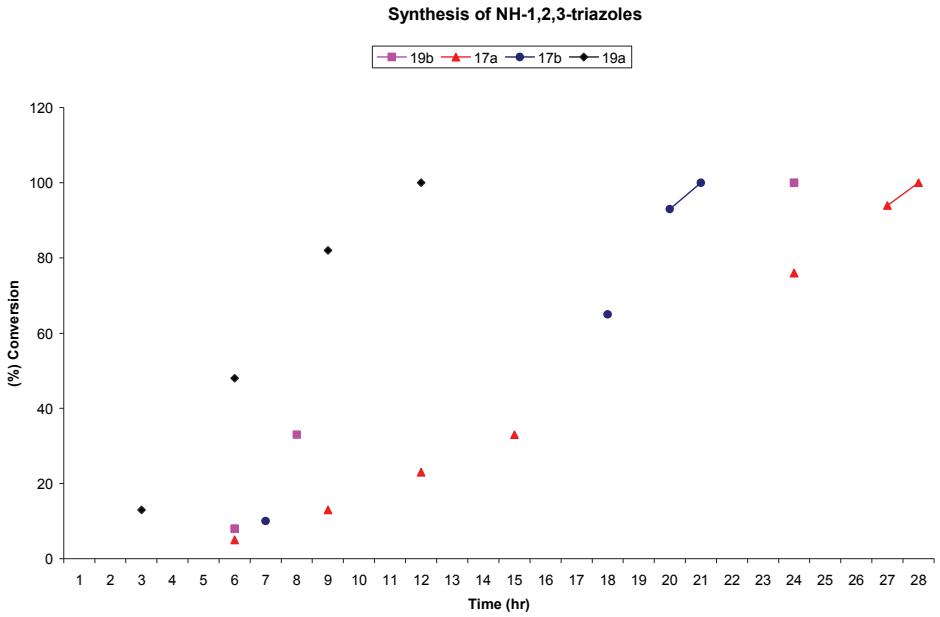
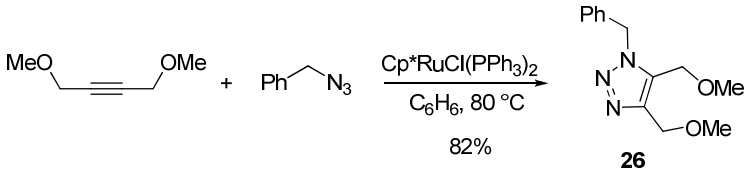


Figure 2.10 Synthesis of *N*H-1,2,3-triazoles studied on GC-MS

Since both the 1,4- and 1,5-disubstituted 1,2,3-triazoles were found to be susceptible to the debenzylation reaction, as long as the C4/C5-substituent contained oxygen atoms, we were interested to see if this was also the case for 4,5-disubstituted 1-benzyl 1,2,3-triazoles. Thus, 1-benzyl-4,5-bis(methoxymethyl)-1*H*-1,2,3-triazole **(26)**, which has the same C4/C5-substituent as **17a** and **17b** was prepared from 1,4-dimethoxybut-2-yne and benzyl azide using Cp*RuCl(PPh_3)$_2$ as the catalyst in refluxing benzene (Scheme 2.28)

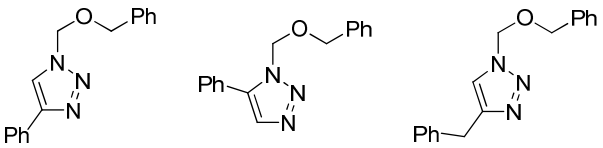


Scheme 2.28 Synthesis of 4,5-disubstituted 1-benzyl 1,2,3-triazole

To our dismay, the 1,4,5-trisubstituted 1,2,3-triazole **26**, did not undergo a debenzylation reaction during 24 hr, and the starting material could be recovered in near quantitative yield (Table 11).

In an earlier account in 2008, Kalsiaki *et al.*[59] found that triazole **27** could be converted to the corresponding *N*H-1,2,3-triazole through simple hydrogenation using 10% Pd-C in MeOH. However, this sluggish reaction required 7 days to go to completion. We consider that trichloroethane also for this reaction could act as an accelerant, and for this very purpose 1,2,3-triazole **27**, **28** and **29** were prepared to explore it further.

The required organic azide was prepared from benzyl chloromethyl ether following the procedure described in literature. Similarly, 1,4- disubstituted 1,2,3-triazoles **27**, **29** and the 1,5-disubstituted 1,2,3-triazole **28** were synthesized according to the previously described Cu(I) and Ru(II)-catalysis (Figure 2.11). Interestingly, it was observed that *N*-alkoxy substituted triazoles **27**, **28** and **29** were not converted to *N*H-1,2,3-triazoles after submission to the debenzylation conditions for 24 hr and in all cases the starting materials could be recovered in near quantitative yield (Table 11).



(27) 77% **(28)** 34% **(29)** 91%

Figure 2.11 Synthesis of *N*-Alkoxy substituted 1,2,3-triazoles

Table 11 1,2,3-Triazoles which did not undergo debenzylation.

Entry	Substrate	(%) St. material recovered	Time (h)
1	**12a**	95	24
2	**12**	96	24
3	**16a**	98	24
4	**26**	98	24
5	**27**	98	24
6	**28**	98	24
7	**29**	98	24

It is concluded that C4-monosubstituted *N*H-1,2,3-triazoles can be obtained from 4- and 5-substituted 1-benzyl 1,2,3-triazoles in excellent yields by hydrogenation over 10% Pd-C and 1,1,2-trichloroethane in methanol provided the substituent on the triazole C-atom contains at least one alkoxy group.

2.3 Summery

It has been observed that the cycloaddions of benzyl azide to highly functionalized terminal alkynes under Cu(I)-catalysis and Ru(II)-catalysis are largely influenced in terms of regioselectivity and efficacy by the nature of alkyne, substitution next to the C-C triple bond is important in this regard as observed from the reactivity of alkyne **4** and **5**.

Similarly, synthesis of C4-monosubstituted *N*H-1,2,3-triazoles by the debenzylation of 4- and 5-substituted 1-benzyl 1,2,3-triazoles found to be dependent on the presence of alkoxy group on C4 or C5 of the triazole ring but independent of the presence of alkoxy group on N-atom. It is found that the HCl driven hydrogenolysis is facilited by the alkoxy group at C4 or C5 in 1-benzyl 1,2,3-triazoles. Further, alkoxy group at C4 or C5 also helps to stabilize C4-alkoxy substituted *N*H-1,2,3-triazole tautomer.

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Chapter 3

Synthesis of piperidine-based building blocks

3.1 Introduction

Proteases were once considered to function primarily as "enzymes of digestion", but are now recognized as the largest and most diverse class of enzymes.[1] Four main classes of proteases include aspartic, serine, cysteine and metallo, are critical for their control over protein synthesis, and function enable them to regulate physiological processes such as digestion, growth, differentiation, wound healing and apoptosis.[2] Proteases are also critical for disease propagation, and inhibitors of such proteases are emerging with promising therapeutic uses.[2] In recent years, the scientific interest in protease inhibitors has been enormous both in private industry and in academia. Numerous protease inhibitors are currently in development in the pharmaceutical industry. A number of these belong to the group of aspartic proteases which are involved in key processes that are related to several human disease.[3,4,5] Currently, different aspartic proteases are being targeted for the development of new medicines for use in the treatments of a range of conditions including malaria (plasmepsins), hypertension (renin), Alzheimer's disease (β-secretase) and HIV/AIDS (HIV-1-protease).[6,7]

The function of aspartic proteases depends on the presence of two aspartic acid residues in the active site (Figure 3.1). A water molecule is bound between the two catalytic Asp residues, and through a "push-pull" general acid-base mechanism the water molecule acts as a nucleophile that attacks the carbonyl of the peptide bond to be broken (scissile peptide bond).[8,9]

Most aspartic proteases recognize and bind a 6-10 amino-acid stretch of their substrates,[8] but the enzymatic cleavage of the substrate depends on several key events to occur. The enzyme active site is covered by a flap region (Figure 3.3 A), and to allow for substrate entry into the active site, this flap must first be opened, and then

closed again over the substrate in the catalytic cleft during enzyme catalysis.[9] To allow for diffusion of products from the active site the flap region needs to re-open after the substrate hydrolysis has occurred.

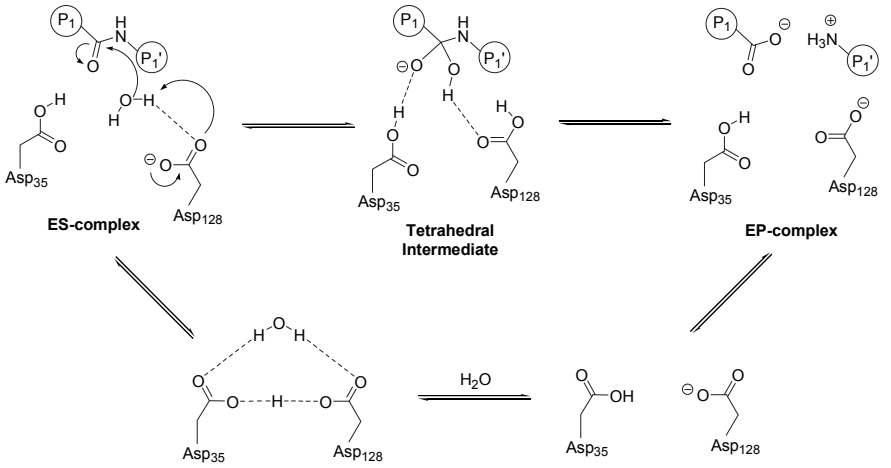


Figure 3.1 General acid-base catalytic mechanism for aspartic proteases (porcine pepsin numbering)

Due to peptidic nature, early protease inhibitors were often found to have poor oral absorption, low bioavailability and metabolic instability, and further development of these compounds into non-peptide peptidomimetic drugs has been necessary.[10] In the search for tight binding inhibitors, structure-based drug design has proved to be an effective tool. Access to protease-inhibitor crystal structures, has opened the way for reduction of the molecular weight of inhibitors as well as reducing the peptidic features, and allowed for designed selectivities in lead inhibitors.[2]

The aspartic protease renin is secreted by special kidney cells via three responses, a decrease in arterial blood pressure, decrease in the NaCl level in ultra-filtrate of the nephron and following sympathetic nervous system activity. It plays an important role in controlling the blood pressure. An overactive renin-angiotensin system leads to

vasoconstriction and retention of sodium and water, causing hypertention. Renin inhibitors can be used for the treatment of hypertension.[11, 12] Several renin inhibitors with low molecular weight, less peptidic character and improved bioavailability have been reported.[13]

In recent years, piperidines have proven to be efficient scaffolds for the development of novel non-peptide aspartic protease inhibitors.[6,7,10] In this project we planed to elaborate on these findings, and develop novel inhibitors with a central piperidine moiety.

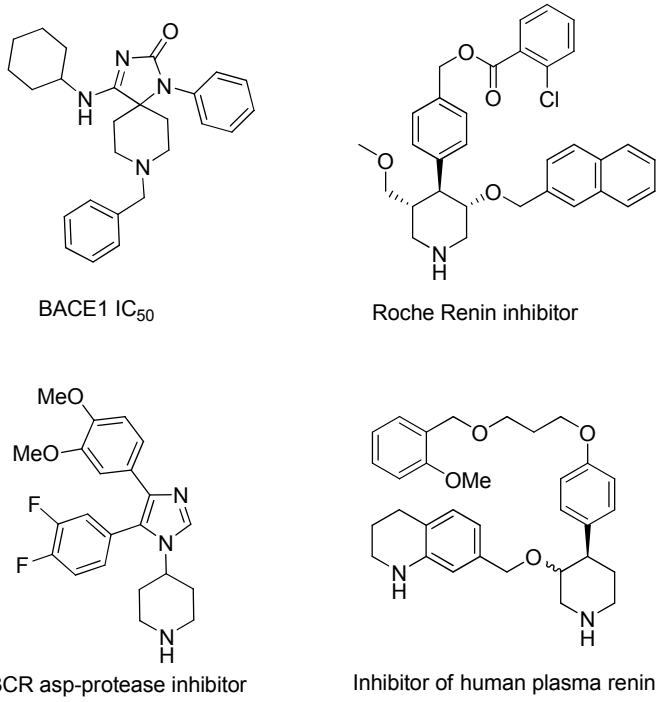


Figure 3.2 Piperidine aspartyl protease inhibitors[6,14,13]

An X-ray crystal structure of a piperidine inhibitor bound to renin, revealed a different binding mode of inhibitor compared to peptide based inhibitors (Figure 3.3 B).[14] This new concept of a central piperidine as a scaffold in the development of

aspartic protease inhibitors has lead to several tight binding compounds used in clinical testing.[15]

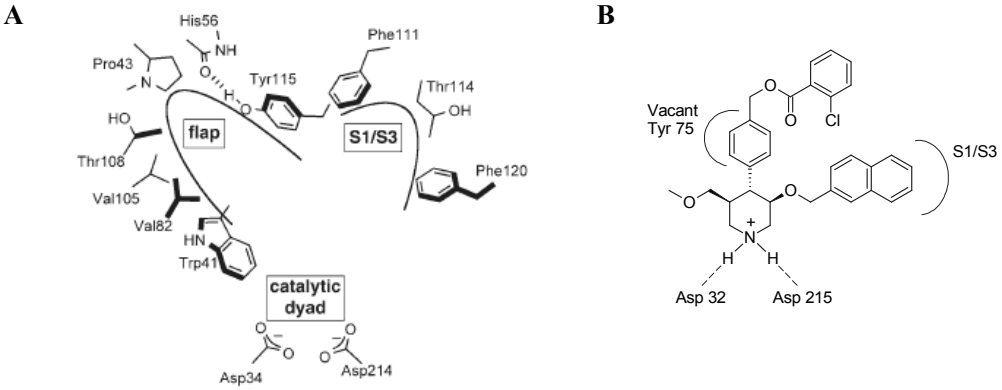


Figure 3.3 A) Schematic diagram of the active site conformation of Plasmepsin II (left) when bound to a "diamine-clamp" inhibitor[16] and B) Binding mode of piperidine inhibitor to renin.

The protonated nitrogen of the piperidine is bound between the two catalytically active aspartic acid residues (Asp32 and Asp215 in the case of renin, see Figure 3.3 B), thereby displacing the water molecule necessary for peptide bond cleavage (Figure 3.1). Further, the 4-substituent displaces a tyrosine residue which is positioned on the flap that normally closes the active site (Tyr75 in the case of renin). The 3-substituent binds in a hydrophobic S1/S3 super pocket. A similar binding of "diamine-clamp" inhibitors and acylguanidine inhibitors to plasmempsins (Figure 3.3 A) and β-secretase, respectively has recently been reported.[16,17]

Purpose of the project

Based on the aforementioned facts, 3-alkoxypiperidines with a 1,2,3-triazole-containing substituent in position 4 (Figure 3.4) seem to constitute a promising group of novel non-peptide aspartic protease inhibitors. The purpose of this project has been to find out how promising these derivatives are in this respect.

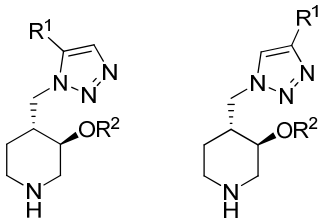
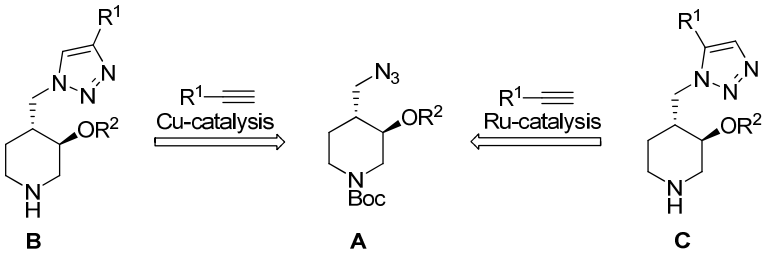


Figure 3.4 Target molecules

In this context, in the course of our efforts to prepare 1,2,3-triazloes and in the development of 3,4-disubstituted piperidine as building blocks,[18] we envisage that piperidine **A** could be a useful building block for the synthesis of a series of novel piperidines.

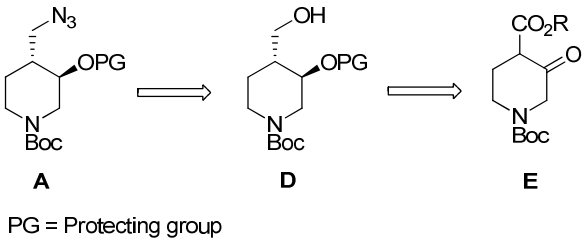


Scheme 3.1 Synthetic plan for piperidine based building block

Different polar groups could be introduced at R1 position under Cu(I) and Ru(II)-catalyzed 1,3-dipolar cycloadditions to enhance the inhibiting properties of these piperidine-based inhibitors. In order to modulate the binding ability, we envisioned that different groups could be introduced at as the R2 substituent through *O*-alkylation. This would require that a synthetic route to building block **A** is established, and the use of the building block towards the synthesis of representative inhibitors **B** and **C**.

3.2 Synthesis of piperidine-based building block

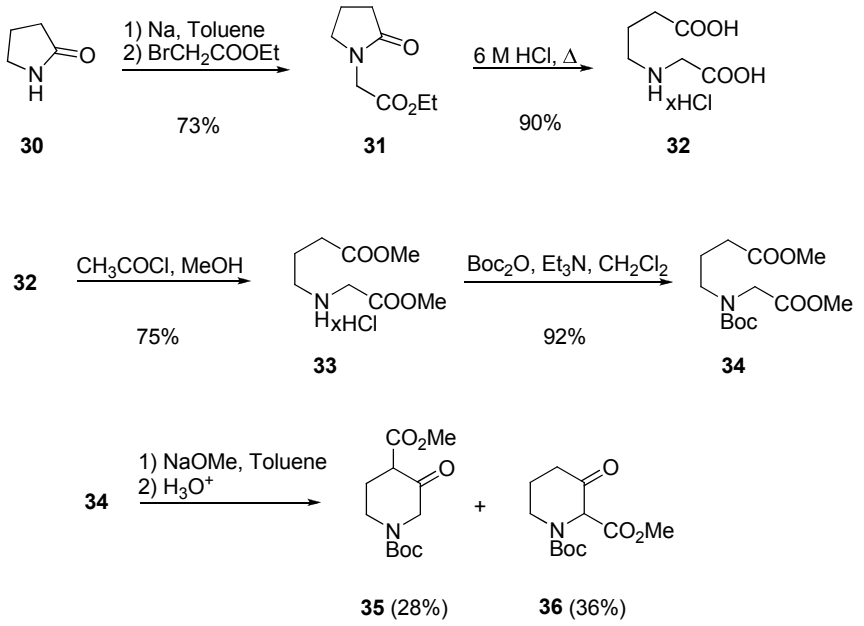
3.2.1 Synthesis of starting material



Scheme 3.2 Retrosynthesis for **A**

We envisioned that building block **A** could be prepared from the corresponding alcohol **D**, which should be assesible from keto ester **E** (Scheme 3.2).

In order to obtain starting material, we followed the synthetic route described by Knight *et al.*[19] which relies on Dieckmann cyclization to establish the piperidine ring. The *N*-alkylation of pyrrolidin-2-one **(30)** by ethyl bromoacetate provided ethyl 2-(2-oxopyrrolidin-1-yl)acetate **(31)**, which was hydrolysed to give 4-(carboxymethylamino)butanoic acid hydrochloride **(32)** in high yield. The subsequent esterification led to methyl 4-(2-methoxy-2-oxoethylamino)butanoate hydrochloride **(33)** (Scheme 3.3).

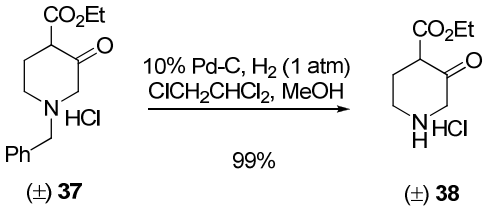


Scheme 3.3 Synthesis of starting material

In the following step, protection of the piperidine N-atom with a Boc protecting group gave methyl 4-(*tert*-butoxycarbonyl(2-methoxy-2-oxoethyl)amino)butanoate **(34)**. Finally, Dieckmann cyclization led to 1-*tert*-butyl 4-methyl 3-oxopiperidine-1,4-dicarboxylate **(35)** in 28% yield and 1-*tert*-butyl 2-methyl 3-oxopiperidine-1,2-dicarboxylate **(36)** in 36% yield (Scheme 3.3). Attempts to receive required starting material **35** in higher yield failed.

According to Zhang *et al.*[20], commercially available ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride **(37)** could be debenzylated in 4 hr. However, this Pd-C catalyzed hydrogenation reaction requires an elevated hydrogen pressure (4.9 atm) to go to completion. We managed to produce ethyl 3-oxopiperidine-4-carboxylate hydrochloride **(38)** in 2 hr by Pd-C catalyzed *N*-debenzylation of **37**, by following a novel procedure reported by Cheng *et al.*[21] in 2009 (Scheme 3.4). The trichloroalkane undergoes a chemoselective monodehydrochlorination to release HCl which

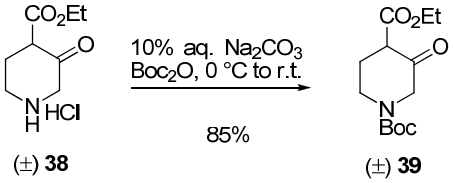
accelerates the normal hydrogenolysis process even at room temperature and atmospheric pressure.[21]



(±) **37** (±) **38**

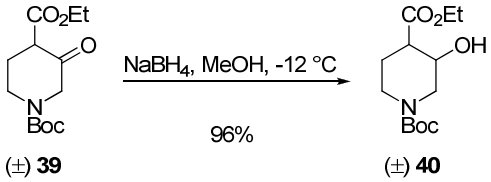
Scheme 3.4 Removal of benzyl group

In the next step, the protection of amine in **38** was accomplished to generate 1-*tert*-butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate **(39)** in 85% yield (Scheme 3.5).[22]



(±) **38** (±) **39**

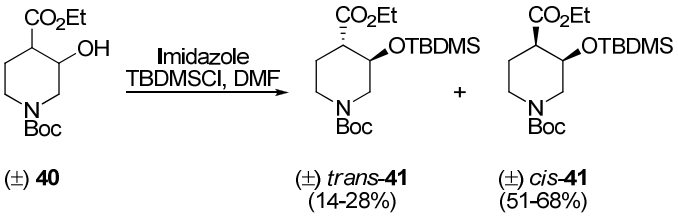
Scheme 3.5 Protection of amine functionality



(±) **39** (±) **40**

Scheme 3.6 Reduction of ketone

Subsequently, the keto ester **39** was reduced with 1.1 equivalents of $NaBH_4$ in methanol to give an inseparable mixture of diastereomeric hydroxyl ester **40** in excellent yield (96%) in 1 hr (Scheme 3.6). All attempts to achieve a satisfying separation of the two diastereomers using silica gel chromatography failed. From the complex proton spectrum, it was not possible to elucidate the *cis*/*trans* ratio of **40**, however, Hanessian *et al*.[23] has earlier repoted a 4:1 ratio of *cis*/*trans* in 96% yield after 3 hr when 0.6 equivalents of $NaBH_4$ was utilized in EtOH as solvent at room temperature for the reduction of **39**.

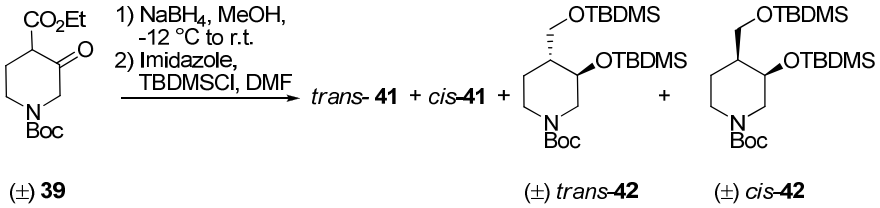


Scheme 3.7 TBDMS protection of hydroxyl functionality

The *cis*/*trans* mixture of **40** was subjected to TBDMS protection of the secondary alcohol, and the products, *trans*-1-*tert*-butyl 4-ethyl 3-(*tert*-butyldimethylsilyloxy)piperidine-1,4-dicarboxylate **(***trans*-**41)** and *cis*-1-*tert*-butyl 4-ethyl 3-(*tert*-butyldimethylsilyloxy)piperidine-1,4-dicarboxylate **(***cis*-**41)** were easily separated by flash column chromatography (Scheme 3.7). In early experiments, *trans* **41** and *cis* **41** were obtained in variable ratios from 1:1.8 to 1:4.9 with combined yields of 79-82%.

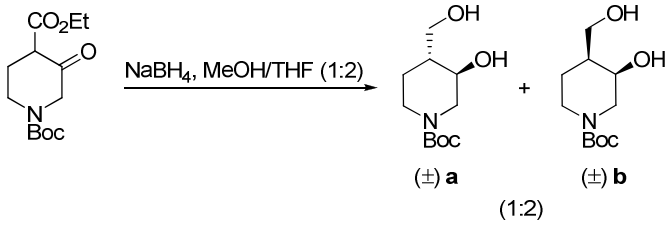
During exploratory experiments (reduction of **39** and subsequent TBDMS protection), interestingly, two new non polar fractions were detected in addition to *trans*-**41** and *cis*-**41** as indicated by thin layer chromatography. It turned out that the ester group of **39** also to some extent has been reduced, and the two new products that were formed

were found to be *trans/cis-tert*-butyl 3-(*tert*-butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)piperidine-1-carboxylate **(***trans*-**42** and *cis*-**42)**. The structural and stereochemical features of *trans*-**42** and *cis*-**42** were elucidated by spectroscopic analyses and finally also unequivocally substantiated by a high yield independent syntheses at later stages (see Scheme 3.19 and 3.20). Due to the formation of the protected diols, the ratio between *trans*-**41** and *cis*-**41** was also found to be disturbed and inconsistent (Scheme 3.8 and Table 3.1).

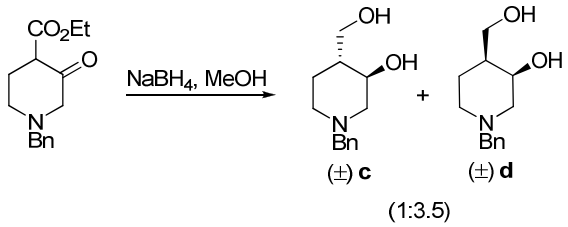


Scheme 3.8 Reduction of ketone **39** and subsequent TBDMS protection

Indeed, the production of diols during the reduction of **39** by $NaBH_4$ in methanol was not surprising. Gohimukkula *et al.*[24] have also found that an inseparable mixture of *cis* and *trans* diols in a 2:1 ratio were formed as the only products when **39** was reduced by using $NaBH_4$ in a mixture of THF and methanol as a solvent. Unfortunately, incomplete experimental details were reported (Scheme 3.9).



Scheme 3.9 Synthesis of *cis* and *trans* diols[24]

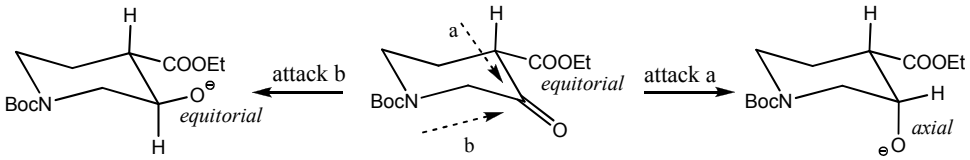


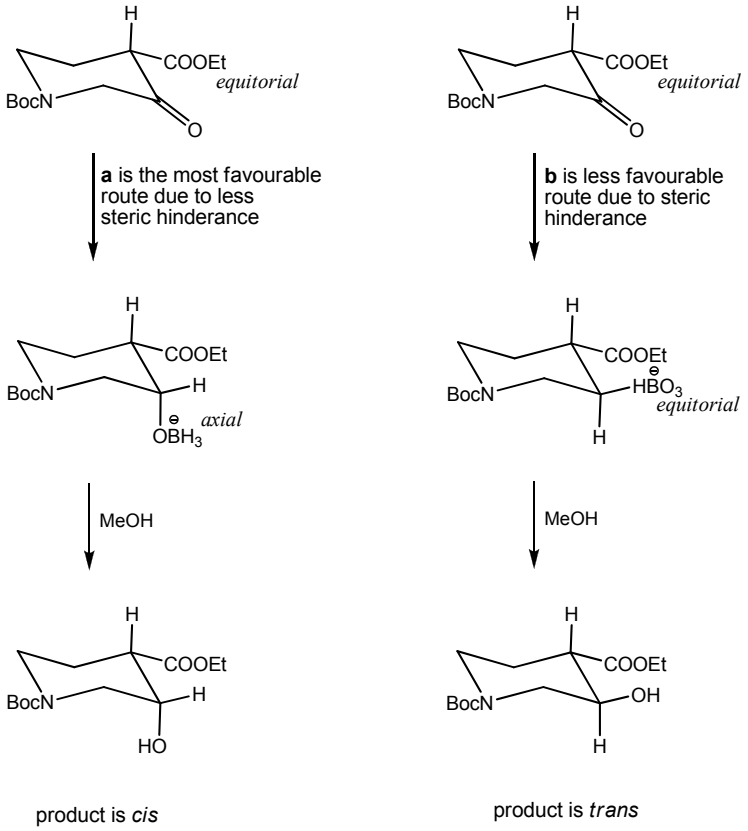
Scheme 3.10 Synthesis of diols (*cis* and *trans*)[25,26]

Similarly, an earlier account by Lewis *et al.*[25], described the reduction of *N*-benzyl 3-oxo-4-carboxylate using 20 mol equivalents of $NaBH_4$ in MeOH at room temperature in 24 hr to give *trans*-**c** (22%) *cis*-**d** (77%) diols, which were separable using silica gel chromatography (Scheme 3.10). Sørensen *et al.*[26], reported to obtain a mixture of **c** and **d** in a ratio of 1:3.7 in a combined yield of 80% after employing 12 equivalents of $NaBH_4$ in the reduction. Separation of the *cis* and *trans* isomers was achieved using preparative HPLC. Gijsen *et al.*[27] have argued that due to the enolic nature of the 3,4-piperidine bond in β-keto esters like **39**, invariably a mixture of *cis* and *trans* diastereomers is produced with *cis* isomer as the expected major product. Keeping in mind the aforementioned literature reports, we could expect the formation of diols during the reduction of **39**. However, we have used only 1.1 mol equivalents of metal hydride and we have observed interesting variations in product ratios separated after the TBDMS protection step (Table 3.1).

In initial experiments, the formation of *cis* ester **41** dominated over the corresponding *trans* ester **41** in the reduction step (Table 3.1, entery 1 and 2). In both cases, the reactions were found to give as the major product the piperidine derivative with a *cis* relation between the ester group at C-4 and the hydroxyl group at C-3. We considered that the reduction took preferentially place by route **a**, i.e. from the opposite side of the Boc group (Scheme 3.11). The reason for this selectivity could be

There are two ways of attack for any cyclohexanone in general





Scheme 3.11 A possible mechanism for the predominance of *cis* product

explained by steric restrictions imposed on the system by the bulky Boc group which hinderes the hydride attack by route **b**. The dominance of *cis* ester **41** increased at the expense of *trans*-**41** when reaction was performed at a higher concentration (Table 3.1, entry 3). This suggests that in solution with high concentration, the intermolecular interaction become more pronounce, increase the steric restriction for attacking hydride which then predominantly attack from path **a**. A possible mechanism for the attack of sodium borohydride for the reduction of keto moity in **39** is depicted in Scheme 3.11.[28,29]

Table 3.1 Summery of reduction of **39** and subsequent TBDMS protection

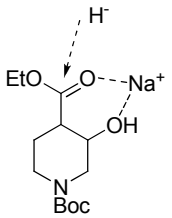
	Scale step 1[a]		mole eq.	Time	Temp.	Yield (%)	Yield (%) step 2[b]			
	(mmoles, conc.)		$NaBH_4$	step 1	step 1	**40**	*t*-**41**	*c*-**41**	*t*-**42**	*c*-**42**
1	5.54	0.185 M	1.10	40 min	-12 ºC	79	28	51	n.d	n.d
2	28.5	0.204 M	1.02	1 hr	-12 ºC	96	14	68	n.d	n.d
3	18.42	0.263 M	1.10	2 hr	-12 to -10 ºC	99 (crude)	5	70	n.d	n.d
4	26.1	0.522 M	1.10	2 hr	-15 to -12 ºC	74	8	72	18	trace
5	18.11	0.453 M	1.10	4 hr	-15 to -10 ºC	61	2	48	48	trace
6	1.69	0.338 M	1.10	24 hr	-12 ºC 1st hr then r.t.	91 (crude)	18	61	15	trace
7	0.76	0.475 M	2.00	4 hr	-12 to -10 ºC	96	7	61	27	trace

a) Keto-ester **39** in Methanol. b) TBDMS protection step

The reduction of ketones by metal hydrides which can yield diastereomeric alcohols, has been studied extensively on acyclic, cyclic and polycyclic compounds. [30,31,32]

Dauben *et al*.[33] has evaluated two interpretations of the stereochemical results of the hydride reduction; product development control and steric approach control. The former effect would favour the more stable product whereas the latter would favour the least hindered approach. Our results suggest that the reaction is more governed by steric approach factors leading to *cis* product and not to thermodynamically more stable *trans* product with equatorial hydroxyl group.

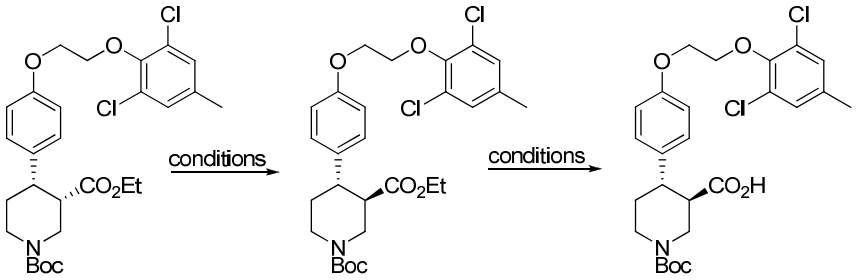
While in further experiment with double concentration, the generation of double protected *trans* diol **42** and a fraction of *cis* diol **42** along with the dominant product *cis* ester **41** seems to be controlled by intramolecular hydrogen bonding between the ester group and hydroxyl moiety (or OBH_3^-) that determines the route of hydride attack on ester group leading to *trans* diol. According to Våbeno *et al*.[34] chelation control could be important to explain the stereochemical outcome of reduction reactions in favour of *trans*-diastereomer. Chelation control involves the coordination of chelating atom (M), often boron or other ions in reducing agent. Generally, monovalent counter ions such as Na^+ or Li^+ are not expected to produce stable chelates. However, $NaBH_4$ in EtOH has been reported to show a slight chelation effect.[34] So, we could expect in our case, *O,O*-chelation between carbonyl oxygen, oxygen of hydroxyl group and the metal ion, resulting in a six membered ring structure which could have blocked one face of the carbonyl and directed the hydride attack from the opposite side leading stereoselectively to the *trans* diol (Scheme 3.12). This could be the reason that almost only *trans* diol **42** was formed with only traces of *cis* diol **42** (Table 3.1).



Scheme 3.12 A possibile chelation of Na^+

From the Table 3.1 it is evident that the *trans* diol is produced faster than the *cis* diol. Also, epimerization occurred during the formation of *trans* diol **42** from *cis* hydroxy ester **41** since *trans* **42** and *cis* **41** were isolated in a 1:1 ratio after TBDMS protection (Table 3.1, entry 5). However, with the generation of *trans* diol **42**, the *cis*/*trans* ratios of *cis* products (*cis* **41** and *cis* **42**) and *trans* products (*trans* **41** and *trans* **42**) were found to nearly 2:1 (Entry 6 and 7) which were 4.9:1 and 14:1 (Entry 2 and 3), a clear indication of epimerization of the α-carbon atom, i.e. C-4 of the piperidine. We suggest that chelation effect or epimerization or both factors are responsible for the formation of almost only *trans* diol **42** from the *cis* ester **41**.

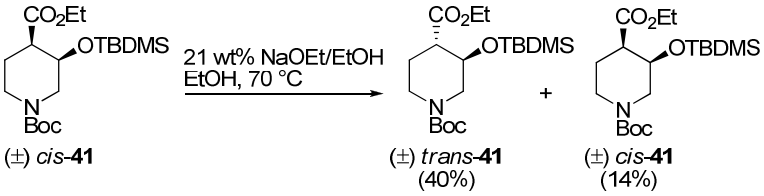
Our interests in *trans* ester **41**, obtained in lower yield, prompted us to explore the possibility to convert the *cis* **41** into the *trans* **41**. In the first exploratory experiment, the *cis* isomer was treated with 2 equivalents of anhydrous K_2CO_3 in ethanol at room temperature. The reaction progress was monitored by thin layer chromatography up to 48 hr however, only the starting material was recovered in quantitative yield. For epimerization,[35] a recent report by Molinaro *et al*. [36] successfully describes the epimerization of the α-carbon atom, i.e. C-4 of the piperidine. For this purpose, NaOEt was used and depending on the source of NaOEt different *cis*/*trans* ratios were reported (Scheme 3.13).



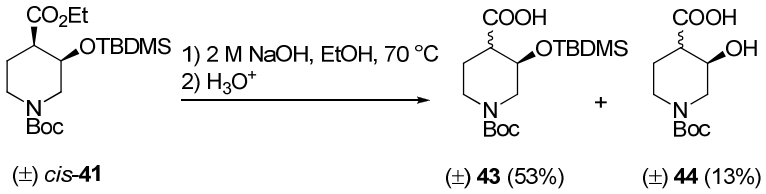
Entry	Conditions	**f** *trans*/*cis* ratio	**g** *trans*/*cis* ratio
1	21 wt% NaOEt/EtOH, EtOH, 70 °C	14:1	
2	5 equiv 2 M NaOH, EtOH, 70 °C	n.a.	10:1
3	1) 21 wt% NaOEt/EtOH, EtOH, 70 °C 2) 5 equiv 2 M NaOH, EtOH, 70 °C	14:1	99:1

Scheme 3.13 Epimerization/saponification described by Molinaro *et al*.[36]

Following this procedure, the epimerization was repeated using 5 equivalents of commercially available 21 wt% NaOEt/EtOH in EtOH at 70 ºC for 1 hr. The *trans*/*cis* ratio was found to be 2.9:1; but the combined yield of the isomers was only 54%. However, no much change was observed when reaction was allowed to run even for 4 hr (Scheme 3.14). Whereas, the *cis* to *trans* conversion was expected to be high as described by the report, 14:1 in favor of *trans* isomer (Scheme 3.13).



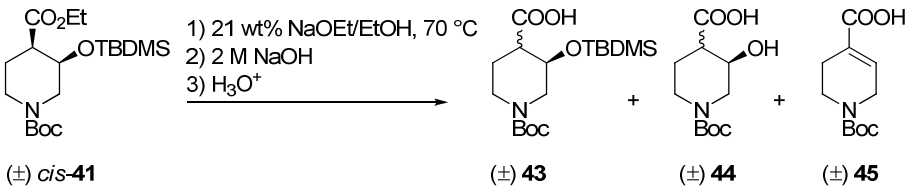
Scheme 3.14 conversion of *cis* to *trans*



Scheme 3.15 Direct epimerization/saponification

In a second approach, a direct epimerization/saponification using 5 equivalents of 2 M NaOH in ethanol at 70 ºC was also performed. This gave an inseparable mixture of *cis*/*trans*-1-(*tert*-butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)piperidine-4-carboxylic acid **(43)** in addition to a mixture of *cis*/*trans*-1-(*tert*-butoxycarbonyl)-3-hydroxypiperidine-4-carboxylic acid **(44)** with loss of the TBDMS group, were separated by flash column chromatography. However, again the combined yield obtained in this reaction was not more than 66% (Scheme 3.15). The TBDMS group was presumably lost during acidic work up.

As a third approach, a sequential epimerization with a solution of 21wt% NaOEt/EtOH followed by saponification with 5 equivalents of 2 M NaOH, was also employed (Scheme 3.16). It has been demonstrated that under these conditions, the *trans* ester converts to *trans* carboxylic acid faster than the *cis* isomer, and in parallel, the *cis* ester would still equilibrate to the thermodynamically stable *trans* isomer, finally providing a better *trans*/*cis* ratio of carboxylic acids up to 99:1.[36]



Scheme 3.16 Epimerization and saponification

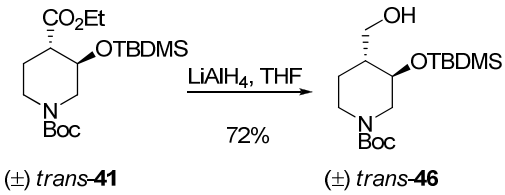
Table 3.2 Epimerization and saponification at different pH

Entry	pH	Yield (%)		
		43	**44**	**45**
1	2-3	18	29	5
2	5	74	21	0

It was found that at lower pH (2-3 in work up) the yield of **43** decreased notably and generation of **44** increased due to the cleavage of the acid sensitive TBDMS group and additionally a new fraction 1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridine-4-carboxylic acid **(45)** was recovered in 5% as maximum (Table 3.2). Formation of **45** has also been reported to occur by Hanessian *et al.* [23] in a similar reaction.

In order to avoid the cleavage of the TBDMS group and the formation of **44** and **45**, the pH was adjusted to 5 during work up by using 0.5 M HCl solution (Table 3.2, entry 2). We were able to isolate **43** in relatively high yield (74%), however still with a significant cleavage of the TBDMS group as 21% of **45** was also isolated (Table 3.2).

Proceeding further, the reduction of the ester group in *trans* ester **41** to its corresponding alcohol (a crystalline solid), *trans*- *tert*-butyl 3-(*tert*-butyldimethylsilyloxy)-4-(hydroxymethyl)piperidine-1-carboxylate **(***trans*-**46)** was accomplished using lithium aluminium hydride in THF (Scheme 3.17, Figure 3.5).



(±) *trans*-**41** (±) *trans*-**46**

Scheme 3.17 Reduction of *trans* ester **41**

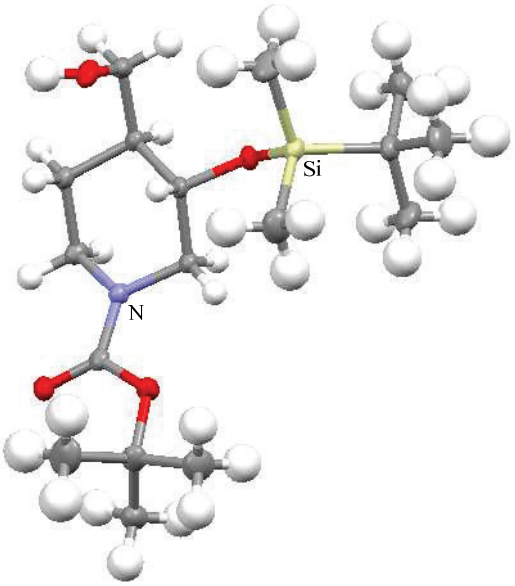


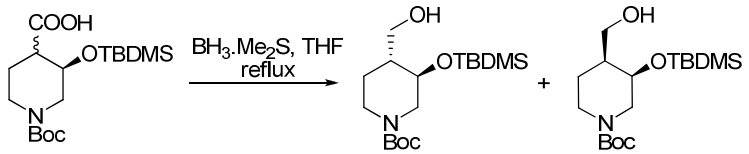
Figure 3.5 X-ray structure of *trans* alcohol **46**

Likewise, a number of attempts were made to reduce the carboxylic acid group of **43** into the alcohol. In fact, the required alcohol was not produced under below mentioned reaction conditions (Table 3.3).

Table 3.3 Failed attempts to generate alcohol from **43**

Entry	Reaction conditions	Isolated yield
1	$LiAlH_4$, dry THF, -35 ºC, 2 hr	-
2	$LiAlH_4$, dry THF, 0 ºC to reflux, 3 hr	-
3	DIBAL, dry THF, reflux, 5 hr	-
4	$NaBH_4/BF_3{\cdot}Et_2O$, dry THF, reflux, 24 hr[37]	7%

Following the procedure reported by Kato *et al.*[38] borane-methyl sulfide complex (BMS) was employed in THF at 0 ºC to reduce the carboxylic acid group of **43**, again a fraction of *trans* alcohol **46** was isolated and the rest was solely the starting material as confirmed by thin layer chromatography and spectroscopic analyses. However, when the reaction mixture was refluxed for 4 hr, the *trans* alcohol **46** as crystalline solid and *cis* alcohol **46** as clear oil were easily isolated by silica gel chromatography (Scheme 3.18). In fact, the *cis/trans* ratio of alcohols found to be dependent on the origin of carboxylic acid **43** (Table 3.4, entry 1 and 2).



(±) **43** (±) *trans*-**46** (±) *cis*-**46**

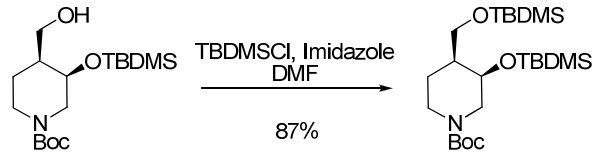
Scheme 3.18 Reduction of carboxylic acid **43** with BMS

Table 3.4 (%) Yield of *cis* and *trans* alcohol

Entry	Source of carboxylic acid **43**	(%Yield) *t*-**46**	(%Yield) *c*-**46**
1	1) 21 wt% NaOEt/EtOH, EtOH, 70 ºC, 2) 2 M NaOH, 70 ºC	62	32
2	2 M NaOH, 70 ºC	16	74

Indeed, as expected, the first approach (Table 3.4, entry 1) proved that carboxylic acid **43** contained more *trans* isomer than the *cis* isomer but not that much as suggested by literature (*trans*/*cis* ratio of carboxylic acid is reported as 99:1 determined by HPLC assay).[36] However, in our case, we received an inseparable mixture of *cis* and *trans* carboxylic acid **43** (Scheme 3.16) which after reduction with BMS produced *trans* and *cis* alcohol in 1.9:1 ratio which may correspond to *trans*/*cis* ratio in carboxylic acid **43**. While in second approach (Table 3.4, entry 2) the predominance of *cis* alcohol **46** (*cis* to *trans* ratio 4.6:1) suggested that during the formation of carboxylic acid **43** (Scheme 3.15), the *cis* ester **41** epimerizes only to a small extent and converted directly into *cis* carboxylic acid which subsequently produced *cis* alcohol as dominant isomer when reduced with BMS. So, by using the 21 wt% NaOEt/EtOH and 2 M NaOH approach and subsequent reduction with BMS, we were able to generate *trans* alcohol **46** in comparatively better yield for further explorations.

For confirmatory purposes, the primary hydroxyl group of *cis* **46** was protected using TBDMSCl and imidazole in DMF. The independently synthesized sample of double protected diol found to be same as *cis* **42** (Scheme 3.8) as substantiated by spectroscopic analyses (Scheme 3.19).

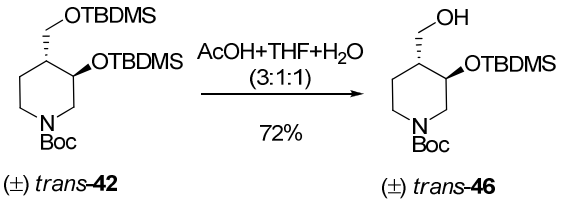


(±) *cis*-**46** (±) *cis*-**42**

Scheme 3.19 Synthesis of doubly protected diol *cis* **42**

Secondly, selective cleavage of a primary TBDMS group in protected diol *trans* **42** was achieved by applying an earlier reported procedure.[39] The resulting mono-TBDMS compound was isolated as a crystalline solid in 72% yield and found to be

the *trans* alcohol **46** and the rest was starting material (Scheme 3.20). Thus, the *trans* diol **42** found out to be exclusively the *trans* isomer (Actually, this experiment confirmed the stereochemistry of *trans* **42**).

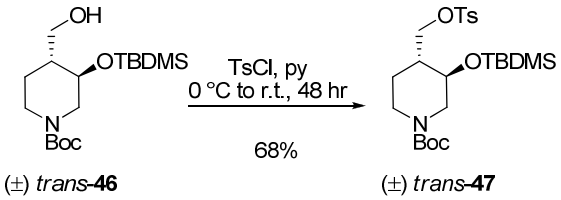


(±) *trans*-**42** (±) *trans*-**46**

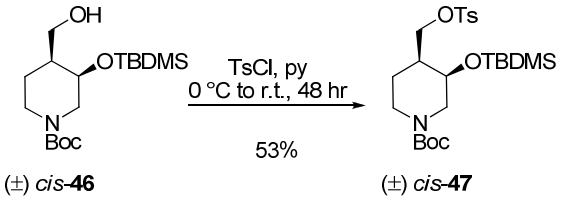
Scheme 3.20 Selective deprotection of primary TBDMS group

3.2.2 Synthesis of tosylates

In order to proceed further, both alcohol *trans* **46** and *cis* **46** were converted to their corresponding tosylates,[40, 41] namely *trans*/*cis*-*tert*-butyl 3-(*tert*-butyldimethylsilyloxy)-4-(tosyloxymethyl)piperidine-1-carboxylate **(***trans*-**47** and *cis*-**47)** using *p*-toluenesulfonyl chloride in pyridine. The tosylate formation found to be a slow process, in both cases, the maximum isolated yield of *trans*-tosylate was 68% and *cis*-tosylate 53% after 48 hr and the unreacted starting material *trans* **46** and *cis* **46** were recovered in each case (Scheme 3.21 and 3.22).



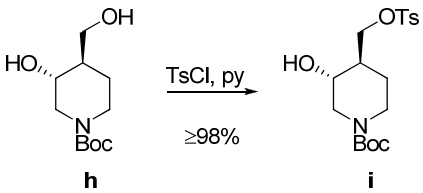
Scheme 3.21 Synthesis of tosylate from alcohol *trans* **46**



Scheme 3.22 Synthesis of tosylate from alcohol *cis* **46**

The slow tosylate formation is might be due to the steric hindrance caused by the presence of a bulky TBDMS group close to the primary hydroxyl group in *trans* **46** and *cis* **46**. This idea is further strengthened by a tosylation reaction reported by Gijsen *et al*.[27] where they have managed to convert a primary hydroxyl group in diol into tosylate in excellent yield (98%) in 1 hr (Scheme 3.23).

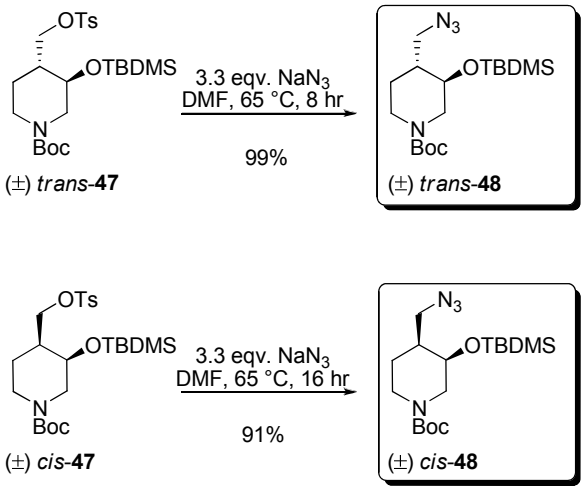
In our case, we wanted to keep secondary hydroxyl group protected with TBDMS group, due to future use of the Grignard-type reaction use to synthesize 1,5-disubstituted 1,2,3-triazoles. In retrospect, the tosyation would selectively have worked better without the TBDMS group. However, separation of *cis* and *trans* isomers was not possible without TBDMS-protection (Scheme 3.7 and 3.8).



Scheme 3.23 Tosylate formation from diol[27]

3.2.3 Synthesis of azides

In the next step, both tosylates, *trans* **47** and *cis* **47** were converted to their corresponding azides,[42] *trans*/*cis*-*tert*-butyl 4-(azidomethyl)-3-(*tert*-butyldimethylsilyloxy)piperidine-1-carboxylate **(***trans*-**48** and *cis*-**48)** using NaN_3 in DMF in excellent yield of 99% and 91% respectively.[43] However, the conversion of *trans* tosylate to *trans* azide found to be almost two times faster than the conversion of *cis* tosylate to *cis* azide, as observed by thin layer chromatography analyses (Scheme 3.24).



Scheme 3.24 Synthesis of piperidine based azides as new building blocks

Organic azides are energy rich molecules, heat and shock sensitive and can decompose explosively with the slightest input of external energy. Caution should be exercised when designing target azides and using them. The following equation[44] gives some general guidelines to consider when working with organic azides.

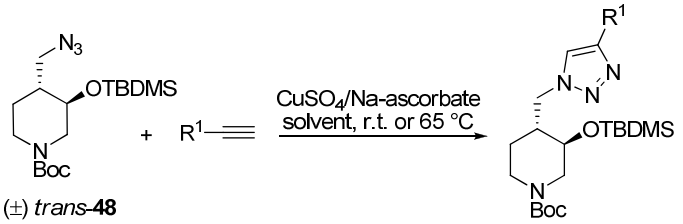
$$(N_C + N_O) / N_N \geq 3$$

The total number of nitrogen atoms in organic azide should not exceed that of carbon. Azides with a C/N ratio greater than one but no more than three can be synthesized and isolated, but by no means should these molecules be stored in their highest purity. Rather, they should be stored as solutions below room temperature. Under no circumstances should organic azide with C/N ratio less than one be isolated.[45]

Alternatively, the "rule of six:" six carbons (or other atoms of about the same size) per energetic functional group (nitro, diazo, azide etc.) should provide enough dilution to render the compound relatively safe to work with under appropriate safety procedures.[44]

3.3 Piperidine based organic azide and Cu-catalyzed 1,3- dipolar cycloadditions

With the aim of forming piperidine based 1,4-disubstituted 1,2,3-triazoles selectively, the *trans* azide **48** was added to alkynes under Cu(I)-catalyzed 1,3-dipolar cycloadditions (Scheme 3.25). For this purpose, Cu(II) sulphate and sodium ascorbate were used to generate *in situ* Cu(I) which could catalyze the cycloaddition reaction (Scheme 3.25 and Chapter 2).[43,18]

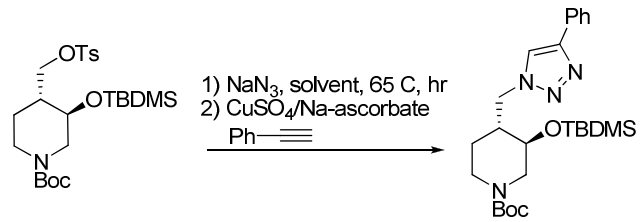


Scheme 3.25 Cu-catalyzed cycloadditions

Table 3.5 Isolated yields of 1,4-disubstituted 1,2,3-triazoles

Entry	R^1	Conditions	1,2,3-triazole	(%)Yield
1	Ph	THF/H_2O (1:1), r.t., 48 hr	**49**	64
2	Ph	Dioxane/H_2O (3:1), 65 ºC, overnight		93
3	CH_3OCO	Dioxane/H_2O (3:1), 65 ºC, 12 hr	**50**	96

As mentioned earlier, organic azides are potentially unstable and difficult to handle due to potential explosion danger, thus their *in situ* generation is considered to be advantageous.[45] However, in our case, we found both *trans* **48** and *cis* **48** to be stable azides and thus easy to handle, but still we were interested to generate azide *in situ* from *trans* tosyale **47** during copper-catalyzed 1,3-dipolar cycloaddition reactions (Scheme 3.26).



(±) *trans*-**47** **49**

Scheme 3.26 Cu-catalyzed cycloadditions using *in situ* azide

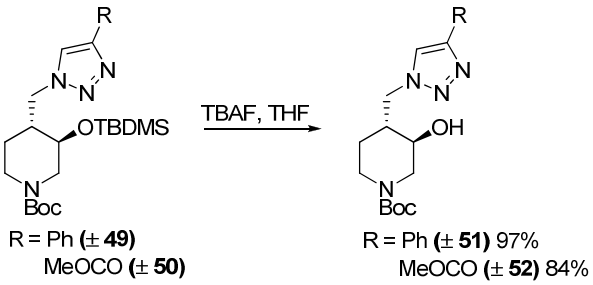
Table 3.6 Isolated Yields of **49** prepared from *in situ* azide

Entry	Solvent	Temp (ºC)	Time (h)	(%) Yield **49**
1	DMF	65	30	53
2	DMSO	65	30	26
3	$CHCl_3$/EtOH/H_2O (9:1:1)	r.t.	40	-

In case of reaction in DMF or in DMSO, first the tosylate was stirred with sodium azide at 65 ºC for 5-6 hrs to form the azide then phenyl acetylene and the copper

catalyst were added and stirring continued for 24 hr (Table 3.6, entery 1and 2). In both cases, at the end of reaction, the unreacted azide *trans* **48** was recovered along with **49**. However, when the reaction was performed in $CHCl_3$/EtOH/H_2O at room temperature, unreacted tosylate was recovered in quantitative yield.

In order to synthesize 1,4-disubstituted 1,2,3-triazoles containing 3,4-disubstituted piperidines as central moiety, at first, the acid sensitive TBDMS group was removed. Both the 1,4-disubstituted 1,2,3-triazoles, **49** and **50** were treated with TBAF in dry THF, stirred overnight at room temperature to receive corresponding unprotected 1,2,3-triazoles **51** and **52** respectively (Scheme 3.27).[46,47]



Scheme 3.27 Removal of protecting group

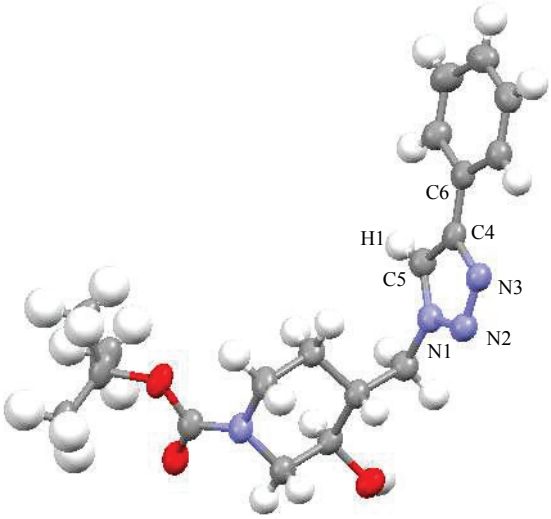


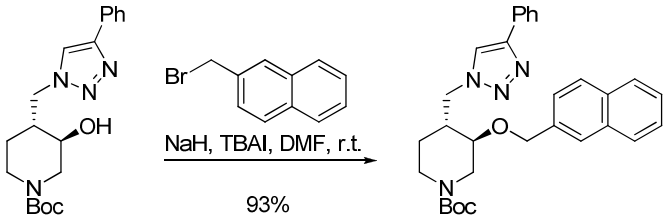
Figure 3.6 Crystal Structure of **51**

Table 3.7 Endocyclic bond lengths (Å) and angles (º) for the triazole ring in **51**

Atoms	Bond length	Atoms	Angle
N(1)-N(2)	1.337	N(2)-N(1)-C(5)	111.32
N(1)-C(5)	1.324	N(3)-C(4)-C(5)	106.62
C(4)-N(3)	1.358	N(3)-C(4)-C(6)	124.12
C(4)-C(5)	1.376	N(3)-N(2)-N(1)	106.46
N(2)-N(3)	1.317	N(1)-C(5)-C(4)	105.84
C(5)-H1	0.951	N(1)-C(5)-H1	127.07
		N(2)-N(3)-C(4)	109.75

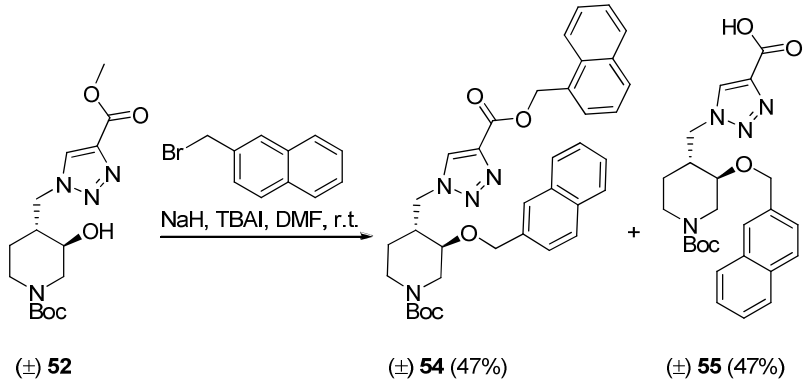
Crystal system: monoclinic, Density: 1.238 Mg/m^3, Volume: 1922.8(5) $Å^3$, Unit cell dimentions: a = 14.051(2), b = 11.1079(17), c = 13.266(2) Å, α= 90°, β= 111.779(2)°, γ = 90°

Proceeding further, the introduction of side chain at hydroxyl group in **51** and **52** by *O*-alkylation was attempted using NaH, TBAI and 2-bromomethylnephthalene, following a reported procedure.[48] The *O*-alkylation on **51** proceeded well to furnish **53** in excellent yield (Scheme 3.28).



Scheme 3.28 *O*-alkylation step

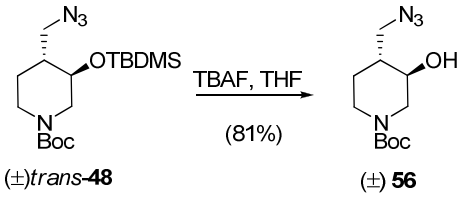
However, when attempts were made for the *O*-alkyation on triazole **52** under same conditions, two new products were isolated after flash column chromatography (Scheme 3.29).



Scheme 3.29 Attempted *O*-alkylation of **52**

Basic hydrolysis of ester functionality generated carboxylate anion which attacked on bromide of 2-bromomethylnephthalene under nucleophilic substitution reaction to produce **54**. While carboxylate anion under acidic work up produced **55** (Scheme 3.29).[49,50]

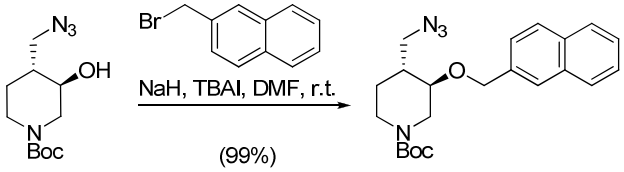
In order to avoid the formation of unwanted **54** and **55** we decided to apply an alternative route. For this purpose, the protecting group TBDMS in *trans* azide **48** was removed to generate *trans*-*tert*-butyl 4-(azidomethyl)-3-hydroxypiperidine-1-carboxylate **(56)** (Scheme 3.30).



(±)*trans*-**48** (±) **56**

Scheme 3.30 Removal of TBDMS

In the subsequent step, the hydroxyl group in newly synthesized *trans* azide **56** underwent *O*-alkylation to produce *trans*-*tert*-butyl 4-(azidomethyl)-3-(naphthalene-2-ylmethoxy)piperidine-1-carboxylate **(57)** in excellent yield (Scheme 3.31).

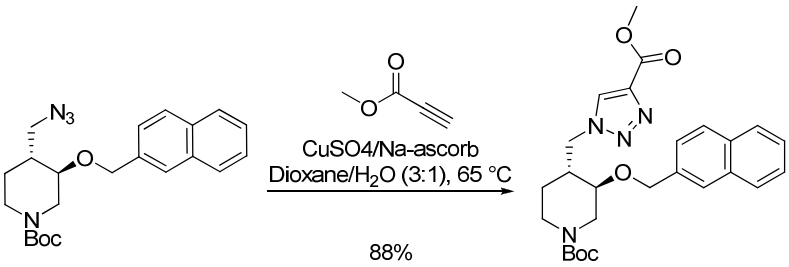


(±) **56** (±) **57**

Scheme 3.31 *O*-alkyation of *trans*-azide **56**

Now with the formation of alkoxy substituted *trans* azide **57**, we were in a position to use this for the synthesize of 1,4- or 1,5-disubstituted 1,2,3-triazoles under Cu-catalyzed or Ru-catalyzed 1,3-dipolar cycloadditions.

The copper-catalyzed 1,3-dipolar cycloaddition of *trans* azide **57** and methyl propiolate under previously mentioned conditions afforded 1,4-disubstituted 1,2,3-triazole **58** (Scheme 3.32).

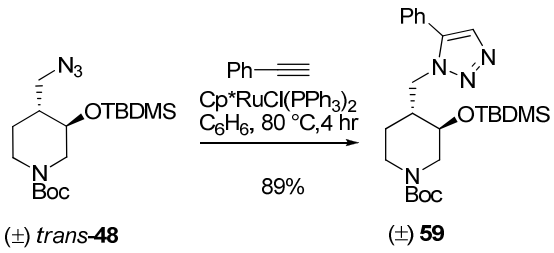


(±) **57** (±) **58**

Scheme 3.32 Cu-catalyzed cycloaddition of **57** and methyl propiolate

3.4 Piperidine based organic azide and Ru-catalyzed 1,3- dipolar cycloadditions

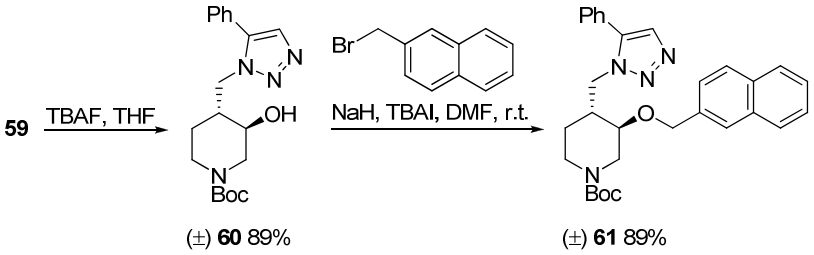
To further explore the reactivity of *trans* azide **48**, a representative 1,5-disubstituted 1,2,3-triazole, *trans*-*tert*-butyl 3-(*tert*-butyldimethylsilyloxy)-4-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate **(59)** was synthesized by reacting *trans* **48** and phenyl acetylene under Ru-catalyzed 1,3-dipolar cycloaddition (Scheme 3.33 and Chapter 2).



(±) *trans*-**48** (±) **59**

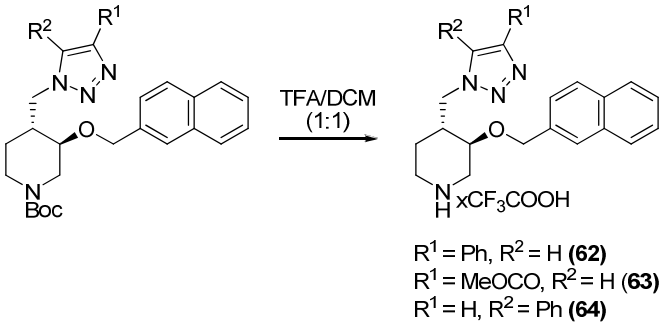
Scheme 3.33 Ru-catalyzed 1,3-dipolar cycloaddition

In the subsequent step, the protecting group, TBDMS of **59** was removed by previously mentioned procedure (Scheme 3.27 and 3.30) to give *trans*-*tert*-butyl 3-hydroxy-4-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate **(60)** (Scheme 3.34). Further, **60** was subjected to *O*-alkylation reaction under aforementioned conditions (Scheme 3.28 and 3.31) to afford **61** in high yield (Scheme 3.34).



Scheme 3.34 TBDMS removal and subsequent *O*-alkylation

Finally, in order to remove the Boc group, the 1,4-disubstituted 1,2,3-triazoles **53** and **58**, and 1,5-disubstituted 1,2,3-triazole **61** were stirred with TFA in dichloromethane for 30 min and subsequently purified by preparative HPLC before bio-assay.



Scheme 3.35 Removal of Boc group

3.5 Renin assay

The 1,4-disubstituted 1,2,3-triazoles **62** and **63** and 1,5-disubstituted 1,2,3-triazole **64** were tested to inhibit the renin activity.

The 1,5-disubstituted 1,2,3-triazole **64** was found comparatively more efficient to inhibit renin activity than its counterpart 1,4-disubstituted 1,2,3-triazole **62**. Whereas, the 1,4-disubstituted 1,2,3-triazole **63** was found to be the least efficient to show inhibition activity compared to other two 1,2,3-triazoles (Table 3.8).

Table 3.8 Inhibition activity % towards renin, 5 μM compound concentration

	Renin
Compound	5 uM[a]
62	18.1
63	11.2
64	23.6

[a] 3 parallels, all parallels diverge no more than 11.5 % from the mean value in average

3.6 Summery

A synthetic route has been developed for the preparation of *cis* and *trans* 3,4-disubstituted piperidine as building blocks for the synthesis of a series of novel piperidines.

During the synthesis of *cis* and *trans* 3,4-disubstituted piperidines, the epimerization leading to the generation of diol *cis* **42** and conversion of *cis* ester **41** into *trans* **41** has been studied although more experiments are required for complete understanding.

Further, *trans* 3,4-disubstituted piperidine building block was employed for the synthesis of representative 1,4- and 1,5-disubstituted 1,2,3-triazoles under Cu(I)- and Ru(II)-catalyzed 1,3-dipolar cycloadditions. These triazoles when tested as renin inhibitors, showed considerable inhibition property.

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Chapter 4

Concluding remarks

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In the first part of the project, 1,4-disubstituted 1,2,3-triazoles have been generated by reacting benzyl azide with two densely functionalized terminal alkynes, 3,3,4,4-tetraethoxybut-1-yne (TEB) and 1,1-diethoxy-but-3-yn-2-one (keto-TEB), in moderate to good yields in different solvent systems. However, we were unable to generate corresponding 1,5-disubstituted 1,2,3-triazoles when $Cp^*RuCl(PPh_3)_2$ was used as catalyst. The result was same for the TEB, when 1,5-disubstituted 1,2,3-triazole synthesis via the addition of bromomagnesium acetylide to azide was attempted. We suggest that some other Ru-catalysts should be evaluated for the synthesis of 1,5-disubstituted 1,2,3-triazoles from these functionalized alkynes.

N-Unsubstituted 1,2,3-triazoles (1*H*-1,2,3-triazoles) were prepared by using *in situ* HCl accelerated catalytic hydrogenolysis over 10% Pd-C to remove *N*-benzyl substituent. When debenzylation reaction was further explored, it was observed that only the 1-benzyl 1,2,3-triazloes with at least one alkoxy substituent at C-atom of triazole ring underwent deprotection. Further research should be directed to investigate the role of alkoxy group, firstly in the debenzylation of 1-benzyl 1,2,3-triazoles and secondly in the stabilization of C4-monosubstituted 1,2,3-triazoles.

As a second part of the project, we have been able to establish a synthetic route for *cis* and *trans* 3,4-disubstituted piperidine as building blocks for the synthesis of a series of novel piperidines. Proceeding further, *trans* 3,4-disubstituted piperidine building block was used for the synthesis of 1,4- and 1,5-disubstituted 1,2,3-triazoles. These

piperidines with a triazolyl-methyl substituents showed considerable inhibition activity when applied as renin inhibitors.

Keeping this in mind, further evaluation should be carried out by introducing different substituents at C4 or C5 of the triazole ring to enhance the inhibition properties. Structure-based drug design could help for the selection of substituents at C4 or C5 for the improvement of these inhibitors. Likewise, attempts should be directed to modulate the binding ability of these inhibitors by introducing different groups at C3 of the piperidine ring through *O*-alkylation. This could lead to the synthesis of novel aspartic protease inhibitors.

Chapter 5

Experimental

Experimental

5.1 General

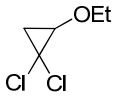
All chemicals were purchased from Sigma-Aldrich and were used without any further purification. Dry solvents were prepared by using mBraun SPS-800 solvent purification system. All anhydrous reactions were performed under inert atmosphere either by argon or nitrogen gases. TLC analyses were carried out using Silica gel (60 F_{254}) on aluminium sheets with mixtures of appropriate solvents as the mobile phase and visualization was made possible by staining with 2% ninhydrin in EtOH or ethanolic acidic phosphomolymdic acid solutions as appropriate. Purification by flash column chromatography was performed using Merk 60 Kieselgel (230-400 mesh) as the stationary phase and mixtures of hexanes and ethyl acetate as the mobile phase.

Melting points were determined by using Stuart Scientific SMP3 melting point apparatus and are uncorrected.

Infra-red spectra were recorded on a Nicolet Impact 410 infrared spectrophotometer or Nicolet 380 FT-IR spectrophotometer and the intensities are given as weak (w), medium (m), strong (s) and broad (br). The NMR spectra were recorded on a Bruker Spectrospin DPX-400 MHz spectrometer; the chemical shifts are reported in ppm relative to Me_4Si, the coupling constants (*J*) in Hz, and the multiplicity as singlet (s), doublet (d), triplet (t) and multiplet (m). ^{13}C NMR signals marked with * were recognized from cross peaks in respective HSQC spectra. The mass spectra were obtained on a JEOL AccuTOF T100GC, operated in the DART mode and MS-ESI were obtained on Thermo electron LTQ Orbitrap. GC-MS analyses were performed

on Trace Ultra GC coupled with a DSQII quardpole MS detector from Thermo Scientific. Purification by reversed-phase high performance liquid chromatography (RP-HPLC) was performed using a C_{18}-column (Ascentis® C18, 5 µm, 21.2x250 mm, Supelco Corp., Bellefonte, PA, USA) with a mixture of water and acetonitrile (both containing 0.1 % TFA) as mobile phase and UV detection at 220 nm. Analytical RP-HPLC was performed using a C_{18}-column (Ascentis® C18, 5 µm, 4.6x250 mm, Supelco Corp., Bellefonte, PA, USA).

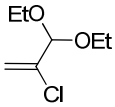
1,1-Dichloro-2-ethoxycyclopropane (1)



The title compound was prepared in 84% yield according to already published procedure. The spectroscopic data were in agreement with literature values.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.1, 3H), 1.51 (dd, *J* = 8.2, 5.1, 1H), 1.56 (t, *J* = 8.5, 1H), 3.53 (dd, *J* = 8.2, 5.1, 1H), 3.65-3.90 (m, 2H).

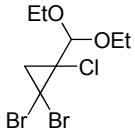
2-Chloro-3,3-diethoxyprop-1-ene (2)



The title compound was prepared in 57% yield according to already published procedure. The spectroscopic data were in agreement with literature.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.1, 6H), 3.46 – 3.72 (m, 4H), 3.65-3.90 (m, 2H), 4.85 (t, *J* = 8.6, 1H), 5.46 (m, 1H), 5.68 (t, *J* = 1.2, 1H)

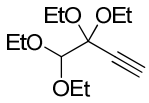
1,1-Dibromo-2-chloro-2-(diethoxymethyl) cyclopropane (3)



The title compound was prepared in 56% yield according to already published procedure. The spectroscopic data were in agreement with literature.[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15-1.30 (m, 6H), 1.93 (d, J = 9.4, 1H), 2.06 (d, J = 9.4, 1H), 3.48 – 3.84 (m, 4H), 4.50 (s, 1H).

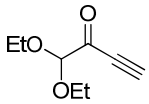
3,3,4,4-Tetraethoxybut-1-yne (4)



The title compound was prepared in 85% yield according to already published procedure. The spectroscopic data were in agreement with literature.[2,3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17-1.30 (m, 12H), 2.60 (s, 1H), 3.63 – 3.84 (m, 8H), 4.40 (s, 1H).

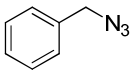
1,1-Diethoxybut-3-yn-2-one (5)



The title compound was prepared in 96% yield according to already published procedure. The spectroscopic data were in agreement with literature.[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, *J* = 7.1, 6H), 2.65 (s, 1H), 3.62 – 3.90 (m, 8H), 4.67 (s, 1H).

(Aazidomethyl)benzene (6)

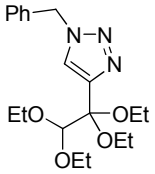


The title compound was prepared in 96% yield according to already published procedure. The spectroscopic data were in agreement with literature. [4]

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.35 (s, 2H), 7.26-7.42 (m, 5H).

5.2 Synthesis of 1,2,3-triazoles

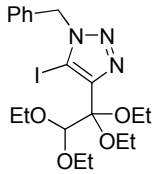
1-Benzyl-4-(1,1,2,2-tetraethoxyethyl)-1*H*-1,2,3-triazole (7)



The ketal **4** (0.230 g, 1 mmol), benzyl azide (0.147 g, 1.1 mmol), $CuSO_4{\cdot}5H_2O$ (9.3 mg, 0.04 mmol)/sodium ascorbate (22 mg, 0.11 mmol) were suspended in a water/DMSO (1:3) (4 ml).The mixture was stirred vigorously at 60 ºC for 48 hr. After extraction with EtOAc (10 ml x 3), combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **7** (0.220 g, 74%); colorless solid, mp 74-75.5 ˚C; R_f = 0.35; IR: 3154 (s), 2986 (s), 2940 (m), 2886 (m), 2366 (m), 2334 (w), 1613 (w), 1499 (w), 1458 (m), 1371 (m), 1188 (s), 1125 (s), 1084 (s), 979 (m), 928 (m), 842 (m), 728 (s), 687 (m) cm^{-1}; ^{1}H NMR (400 MHz,

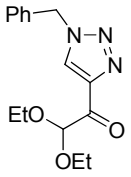
MeOD): δ 1.08 (t, *J* = 7.0 Hz, 6H), 1.66 (t, *J* = 7.0 Hz, 6H), 3.41-3.71 (m, 8H), 4.72 (s, 1H), 5.57 (s, 2H), 7.29-7.36 (m, 5H), 7.82 (s, 1H); ^{13}C NMR (101 MHz, MeOD): δ 14.6, 14.7, 53.9, 57.9, 65.5, 99.9, 104.7, 125.5, 128.1, 128.6, 129.1, 136.0, 147.3; HRMS (DART): *m/z* $[M+H]^+$ calcd. for $C_{19}H_{30}N_3O_4$: 364.2236 found 364.2233.

1-Benzyl-5-iodo-4-(1,1,2,2-tetraethoxyethyl)-1*H*-1,2,3-triazole (8)



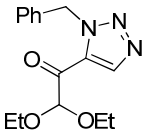
Ketal **4** (0.230 g, 1 mmol), benzyl azide (0.146 g, 1.1 mmol), CuI (0.209 g, 1.1 mmol), diisopropyl-ethylamine (DIPEA) (0.129 g, 1 mmol), and *N*-chlorosuccinimide (NCS) (0.160 g, 1.2 mmol) were dissolved in THF (5 ml), and the resulting mixture was stirred vigorously at r.t for 4 hr. After extraction with EtOAc (10 ml x 3), combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **8** (0.352 g, 72%). When the reaction was repeated using *N*-bromosuccinimide (NBS) (0.213 g, 1.2 mmol) instead of NCS the yield of **8** dropped (0.302 g, 62%). yellowish crystalline solid; mp 83-84 ˚C; R_f = 0.60; IR: 2979 (s), 2931 (m), 2899 (w), 2358 (s), 2340 (m), 1653 (m), 1557 (m), 1440 (m), 1241 (m), 1209 (m), 1173 (w), 1121 (s), 1077 (s), 973 (s), 929 (m), 724 (s) cm^{-1} ; ^{1}H NMR (400 MHz, MeOD): δ 1.12 (t, *J* = 7.0 Hz, 6H), 1.24 (t, *J* = 7.0 Hz, 6H), 3.51-3.71 (m, 8H), 4.73 (s, 1H), 5.68 (s, 2H), 7.19-7.32 (m, 5H); ^{13}C NMR (101 MHz, MeOD): δ 14.3, 14.4, 53.6, 57.6, 65.2, 99.6, 104.4, 125.2, 127.8, 128.3, 128.7, 135.7, 147.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{19}H_{29}N_3O_4I$: 490.1197 found 490.1195.

1-(1-Benzyl-1*H*-1,2,3-triazole-4-yl)-2,2-diethoxyethanone (9)



The ketone **5** (0.156 g, 1 mmol), benzyl azide (0.147 g, 1.1 mmol) and CuI (19 mg, 0.1 mmol) were suspended in acetonitrile (3 ml).The mixture was stirred vigorously at 60 ºC for 48 hr and 2 ml water was added. After extraction with CH_2Cl_2 (5 ml x 3), combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **9** (0.240 g, 70%) and **10** (25 mg, 3%) ; For **9**; yellowish oil; R_f = 0.27; IR: 3127 (m), 3027 (w), 2975 (s), 2923 (m), 2891 (m), 1701 (s), 1529 (s), 1490 (m), 1457 (m), 1369 (m), 1321 (w), 1241 (s), 1113 (m), 1065 (m), 917 (w), 828 (m), 716 (s), 700 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.0 Hz, 6H), 3.65-3.81 (m, 4H), 5.45 (s, 1H), 5.57 (s, 2H), 7.29-7.40 (m, 5H) 8.12 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.7, 54.9, 64.0, 100.9, 128.3, 128.9, 129.7, 129.8, 134.1, 145.1, 187.7; HRMS (DART): *m/z* $[M+H]^+$ calcd. for $C_{15}H_{20}N_3O_3$: 290.1504 found 290.1525.

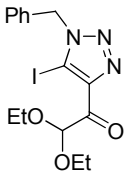
1-(1-Benzyl-1*H*-1,2,3-triazole-5-yl)-2,2-diethoxyethanone (10)



For **10**; greenish oil; R_f = 0.51 (Hex/EtOAc, 7:3); IR (film): 3047 (w), 2987 (s), 2943 (w), 2891 (w), 1709 (s), 1505 (w), 1449 (m), 1333 (m), 1245 (w), 1125 (m), 1073 (s), 921 (w), 724 (s), 700 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, J = 7.0 Hz, 3H), 3.51-3.69 (m, 4H), 4.93 (s, 1H), 5.29 (s, 2H), 7.30-7.32 (m, 5H), 8.47 (s, 1H);

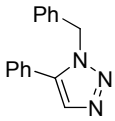
^{13}C NMR (101 MHz, $CDCl_3$): δ 15.5, 54.4, 64.0, 103.0, 128.6, 128.8, 129.2, 130.4, 135.4, 140.6, 186.0; HRMS (DART): *m/z* $[M+H]^+$ calcd. for $C_{15}H_{20}N_3O_3$: 290.1504 found 290.1501.

1-(1-Benzyl-5-iodo-1*H*-1,2,3-triazole-4-yl)-2,2-diethoxyethanone (11)



The Iodoketal **8** (0.489 g, 1.0 mmol) was dissolved in a mixture of acetone (18 ml) and water (0.5 ml) and Dowex 50W (0.260 g) was subsequently added. The mixture was heated at reflux for 6 hr and was then filtered, dried ($MgSO_4$) and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **11** (0.353 g, 85%); brownish oil; R_f = 0.50; IR: 3600 (m), 2975 (m), 2931 (w), 2891 (w), 1713 (s), 1497 (s), 1461 (w), 1445 (m), 1421(m), 1097 (w), 1065 (s), 980 (m), 920 (m), 710 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 8.0 Hz, 6H), 3.80-3.84 (m, 4H), 5.66 (s, 2H), 5.90 (s, 1H), 7.31-7.38 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.8, 54.6, 63.8, 98.6, 128.6, 128.8, 129.2, 129.3, 129.5, 133.9, 187.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{19}N_3O_3I$: 416.0465 found 416.0466.

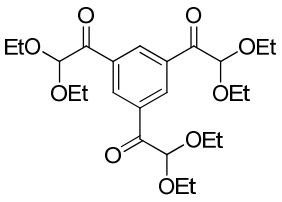
1-Benzyl-5-phenyl-1,2,3-triazole (12)



The title compound was prepared in 86% yield using Ru-catalyst according to already published procedure. The spectroscopic data were in agreement with literature.[5]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (s, 2H), 7.05-7.07 (m, 2H), 7.23-7.28 (m, 5H), 7.38-7.45 (m, 3H), 7.73 (s, 1H).

1,3,5-tris(2,2-diethoxyacetyl)benzene (13)



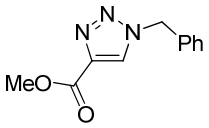
The title compound was received in 60% yield. The spectroscopic data were in agreement with literature.[6]

^{1}H MNR (400 MHZ, $CDCl_3$): δ 3.96 (s, 12H), 8.83 (s, 3H).

General procedure for Cu-catalyzed cycloadditions (compound 15a-20a)

Terminal alkyne (1.0 mmol), benzyl azide (1.1 mmol) and $CuSO_4.5H_2O$ (9.3 mg, 0.04 mmol)/sodium ascorbate (22 mg, 0.11 mmol) were suspended in 4 ml of water/CH_2Cl_2 (1:3). The reaction mixture was stirred vigorously at r.t for 12-48 hr (Table 1). After extraction with dichloromethane (10 ml x 3), the combined organic layers were dried over $MgSO_4$, the drying agent was removed by filtration and the filtrate was concentrated under vacuum. Purification of the crude product using flash column chromatography eluting with mixtures of hexanes and ethyl acetate provided 1,4-disubstituted 1,2,3- triazoles.

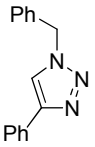
Methyl 1-benzyl-1*H*-1,2,3-triazol-4-carboxylate (15a)



The title compound was prepared from methyl propiolate (84 mg 1.0 mmol) and benzyl azide (0.146 g, 1.1 mmol) according to the general procedure. Crystalline solid; Yield: 0.215 g (99%). The spectroscopic data were in accordance with those reported in the literature.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 5.58 (s, 2H), 7.69 – 7.26 (m, 5H), 7.97 (s, 1H).

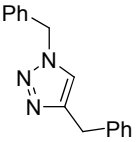
1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (12a)



The title compound was prepared from phenyl acetylene (0.102 g 1.0 mmol) and benzyl azide (0.146 g, 1.1 mmol) according to the general procedure. Crystalline solid; Yield: 0.233 g (99%). Analytical data were in accordance with those reported in the literature.[8]

^{1}H MNR (400 MHZ, $CDCl_3$): δ 5.58 (s, 2H), 7.30-7.42 (m, 8H), 7.67 (s, 1H), 7.81 (d, J = 8.7 Hz, 2H).

1,4-Dibenzyl-1*H*-1,2,3-triazole (16a)

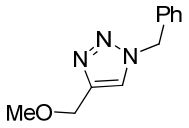


The title compound was prepared from prop-2-ynylbenzene (0.116 g 1.0 mmol) and benzyl azide (0.146 g, 1.1 mmol) according to the general procedure.

Light yellow crystalline solid; Yield: 0.237 g (95%). Analytical data were in accordance with those reported in the literature.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 (s, 2H), 5.46 (s, 2H), 7.16 – 7.53 (m, 11H).

1-Benzyl-4-(methoxymethyl)-1*H*-1,2,3-triazole (17a)

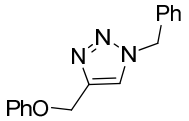


The title compound was prepared from methyl propargyl ether (70 mg 1.0 mmol) and benzyl azide (0.146 mg, 1.1 mmol) according to the general procedure.

Light yellow oil; Yield: 0.201 g (99%). Analytical data were in accordance with those reported in the literature.[10]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.39 (s, 3H), 4.55 (s, 2H), 5.52 (s, 2H), 7.26-7.37 (m, 5H), 7.46 (s, 1H).

1-Benzyl-4-(phenoxymethyl)-1*H*-1,2,3-triazole (18a)

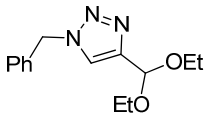


The title compound was prepared from phenyl propargyl ether (0.145 g 1.0 mmol) and benzyl azide (0.146 g, 1.1 mmol) according to the general procedure.

Colorless crystals; Yield: 0.251 g (95%). Analytical data were in accordance with those reported in the literature.[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.19 (s, 2H), 5.54 (s, 2H), 6.95-6.98 (m, 3H), 7.28-7.30 (m, 5H), 7.37-7.39 (m, 2H), 7.53 (s, 1H).

1-Benzyl-4-(diethoxymethyl)-1*H*-1,2,3-triazole (19a)

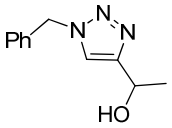


The title compound was prepared from 3,3-diethoxy-1-propyne (0.128 g 1.0 mmol) and benzyl azide (0.146 g, 1.1 mmol) according to the general procedure.

Crystalline solid; Yield: 0.255 g (98%). Analytical data were in accordance with those reported in the literature.[11]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, *J* = 7.2 Hz, 6H), 3.54-3.70 (m, 4H), 5.51 (s, 2H), 5.59 (s, 1H), 7.26-7.36 (m, 5H), 7.49 (s, 1H).

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)ethanol (20a)

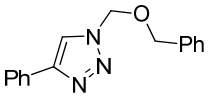


The title compound was prepared from 3-butyn-2-ol (70 mg 1.0 mmol) and benzyl azide (0.146 g, 1.1 mmol) according to the general procedure.

Crystalline solid; Yield: 0.197 g (97%). Analytical data were in accordance with those reported in the literature.[12]

^{1}H MNR (400 MHZ, $CDCl_3$): δ 1.50 (d, *J* = 6.4 Hz, 3H), 4.93-4.97 (q, *J* = 7.2 Hz, 1H), 5.57 (s, 2H), 7.31-7.36 (m, 5H), 7.83 (s, 1H).

1-(Benzyloxymethyl)-4-phenyl-1*H*-1,2,3-triazole (27)

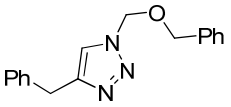


The title compound was prepared from phenyl acetylene (0.102 g 1.0 mmol) and ((azidomethoxy)methyl)benzene (0.179 g, 1.1 mmol) according to the general

procedure. Colorless crystals; Yield: 0.203 g (77%). Analytical data were in accordance with those reported in the literature.[13]

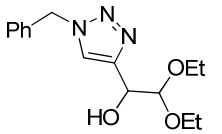
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (s, 2H), 5.79 (s, 2H), 7.32-7.39 (m, 6H), 7.45 (t, *J* = 7.2, 2H), 7.86 (d, *J* = 7.6, 2H), 7.95 (s, 1H).

4-Benzyl-1-(benzyloxymethyl)-1*H*-1,2,3-triazole (29)



The title compound was prepared from prop-2-ynylbenzene (0.116 g 1.0 mmol) and ((azidomethoxy)methyl)benzene (0.179 g, 1.1mmol) according to the general procedure. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 8:2) afforded the title compound. Thick semisolid; Yield: 0.253 g (91%); R_f = 0.11 (hexanes-EtOAc, 8:2); IR: 3062 (w), 3028 (w), 2872 (w), 1602 (w), 1548 (w), 1493 (m), 1454 (m), 1434 (w), 1379 (m), 1346 (w), 1302 (w), 1222 (m), 1096 (s), 1048 (s), 1026 (s), 797 (w), 755 (s), 737 (m), 725 (s), 694 (s) cm^{-1}; ^{1}H NMR (400 MHz, MeOD): δ 4.06 (s, 2H), 4.54 (s, 2H), 5.73 (s, 2H), 7.19-7.31 (m, 10H), 7.79 (s, 1H); ^{13}C NMR (101 MHz, MeOD): δ = 32.5, 72.4, 79.2, 123.9, 127.5, 129.1, 129.4, 129.6, 138.0, 140.3, 149.2;; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{17}N_3ONa$: 302.1264; found 302.1269.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-2,2-diethoxyethanol (22)



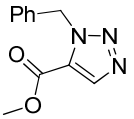
To a solution of ketone **9** (0.396 g, 1.37 mmol) in THF/H_2O (9:1, 10 ml) at 0 ˚C was added $NaBH_4$ (26 mg, 0.69 mmol) in one portion. After 30 minutes the starting material had been consumed and 0.1 M HCl (3 ml) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x15 ml) and the combined organic layers were dried over

$MgSO_4$. The drying agent was removed by filtration and the filtrate was concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 1:1) provided the title compound. Colorless oil; Yield: 0.340 g (85%); R_f = 0.14 (hexanes-EtOAc, 1:1); IR: 3388 (br), 2975 (m), 2882 (w), 1737 (s), 1497 (w), 1455 (w), 1333 (w), 1221 (w), 1119 (s), 1050 (s), 804 (w), 713 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 2.88 (d, *J* = 4.4 Hz, 1H) 3.52-3.56 (m, 2H), 3.69-3.81 (m, 2H), 4.72 (d, *J* = 4.8, 1H), 4.86 (t, *J* = 4.4, 1H), 5.52 (s, 2H), 7.25-7.27 (m, 2H), 7.35-7.37 (m, 3H), 7.48 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.4, 15.5, 54.4, 64.2, 64.3, 104.1, 128.3, 128.9, 129.3, 134.8, 147.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{21}N_3O_3$: 292.1656 found 292.1658.

General procedure for Ru-catalyzed cycloadditions (15b-21b)

Alkyne (1-1.8 mmol), organic azide (0.99-1.1 mmol) and $Cp^*RuCl(PPh_3)_2$ (1 mol %) were dissolved in 8-10 ml of anhydrous C_6H_6 (or anhydrous THF). The resulting mixture was heated to at 80 ºC (or 65 ºC for THF) and stirred vigorously for 3-4 h (Table 1). After cooling to room temperature, the solvent was removed under vacuum. Purification of the crude product using flash column chromatography with mixtures of hexanes and ethyl acetate provided 1,5-disubstituted 1,2,3- triazoles.

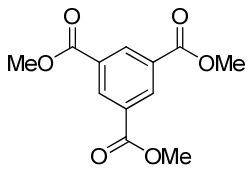
Methyl 1-benzyl-1*H*-1,2,3-triazol-5-carboxylate (15b)



The title compound was prepared from methyl propiolate (84 mg, 1 mmol) and benzyl azide (0.146 g, 1.1 mmol) according to the general procedure for Ru-catalyzed cycloadditions using C_6H_6 at 80 ºC.

Clear oil; Yield: 7 mg (3%). Analytical data were in accordance with those reported in the literature.[14]

Trimethyl benzene-1,3,5-tricarboxylate (15C)

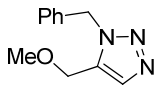


The title compound was isolated after reacting methyl propiolate with benzyl azide following the general protocol for Ru-catalyzed cycloadditions.

Yield: 72 mg, (97%). Analytical data were in accordance with those reported in the literature.[15]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 9H), 8.83 (s, 3H).

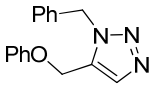
1-Benzyl-5-(methoxymethyl)-1*H*-1,2,3-triazole (17b)



The title compound was prepared from methyl propargyl ether (70 mg, 1 mmol) and benzyl azide (0.146 g, 1.1 mmol) according to the general procedure for Ru-catalyzed cycloadditions using C_6H_6 at 80 ºC; Red-brown oil; Yield: 0.154 g (76%); R_f = 0.22 (hexanes-EtOAc, 7:3); IR: 3032 (w), 2930 (w), 2825 (w), 1605 (w), 1593 (w), 1497 (m), 1455 (s), 1331 (m), 1220 (m), 1190 (m), 1103 (s), 1084 (s), 1029 (m), 980 (m), 954 (m), 906 (m), 836 (m), 755 (m), 717 (s), 694 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.27 (s, 3H), 4.34 (s, 2H), 5.62 (s, 2H), 7.22-7.35 (m, 5H), 7.65 (s, 1H).

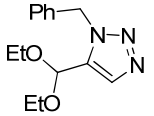
^{13}C NMR (101 MHz, $CDCl_3$): δ 52.6, 58.3, 62.6, 127.8, 128.6, 129.1, 133.3, 134.8, 134.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}N_3O$: 204.1131 found 204.1132.

1-Benzyl-5-(phenoxymethyl)-1*H*-1,2,3-triazole (18b)



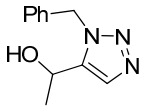
The title compound was prepared from phenyl propargyl ether (0.145 g, 1.1 mmol) and benzyl azide (0.133 g, 1 mmol) according to the general procedure for Ru-catalyzed cycloadditions using C_6H_6 at 80 ºC; Crystalline solid; Yield: 0.257 g (97%); R_f = 0.24 (hexanes-EtOAc, 7:3); mp 121.0-122.4 ºC; IR: 3132 (w), 2921 (w), 2871 (w), 1737 (w), 1712 (w), 1598 (m), 1584 (m), 1494 (s), 1486 (s), 1428 (m), 1382 (m), 1330 (m), 1237 (s), 1218 (s), 1177 (m), 1119 (m), 1053 (s), 1029 (s), 1005 (s), 987 (m), 855 (m), 753 (s), 690 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.90 (s, 2H), 5.69 (s, 2H), 6.83 (d, *J* = 7.6, 2H), 7.02 (t, *J* = 7.2, 1H), 7.17-7.19 (m, 2H), 7.27-7.31 (m, 5H) 7.73 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 52.8, 58.5, 114.8, 122.2, 127.8, 128.7, 129.1, 129.9, 132.4, 134.6, 134.8, 157.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{16}H_{16}N_3O$: 266.1288 found 266.1290.

1-Benzyl-5-(diethoxymethyl)-1*H*-1,2,3-triazole (19b)



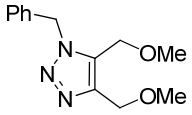
The title compound was prepared from 3,3-diethoxy-1-propyne (0.230 g, 1.8 mmol) and benzyl azide (0.132 g, 0.99 mmol) according to the general procedure for Ru-catalyzed cycloadditions using C_6H_6 at 80 ºC; Red brown oil; Yield: 0.206 g (79%); R_f = 0.50 (hexanes-EtOAc, 7:3); IR: 2975 (m), 2930 (w), 2883 (w), 1606 (w), 1552 (w), 1497 (w), 1455 (m), 1370 (w), 1231 (w), 1185 (w), 1109 (s), 1048 (s), 983 (m), 915 (m), 842 (m), 720 (s) 694 (s), 577 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.2 Hz, 6H), 3.41-3.50 (m, 4H), 5.41 (s, 1H), 5.62 (s, 2H), 7.21-7.30 (m, 5H), 7.69 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.0, 52.6, 61.5, 94.6, 127.7, 128.4, 128.9, 134.2, 135.0, 135.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{20}N_3O_2$: 262.1550 found 262.1552.

1-(1-Benzyl-1*H*-1,2,3-triazol-5-yl)ethanol (20c)



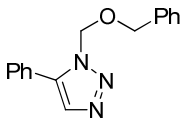
The title compound was prepared from 3-butyn-2-ol (70 mg, 1 mmol) and benzyl azide (0.133 g, 1 mmol) according to the general procedure for Ru-catalyzed cycloadditions using C_6H_6 at 80 ºC; Yellowish oil; Yield: 0.143 g (70%); R_f = 0.22 (hexanes-EtOAc, 1:1); IR: 3263 (br), 2976 (m), 2931 (w), 1496 (m), 1455 (s), 1373 (w), 1294 (w), 1233 (m), 1181 (w), 1113 (s), 1076 (s), 1027 (s), 984 (m), 889 (m), 833 (m), 715 (s), 693 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.2 Hz, 6H), 3.41-3.50 (m, 4H), 5.41 (s, 1H), 5.62 (s, 2H), 7.21-7.30 (m, 5H), 7.69 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 22.5, 52.4, 60.3, 127.6, 128.5, 129.1, 131.7, 135.2, 140.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{11}H_{14}N_3O$: 204.1131 found 204.1133.

1-Benzyl-4,5-bis(methoxymethyl)-1*H*-1,2,3-triazole (26)



The title compound was prepared from 1,4-dimethoxybut-2-yne (0.114 g, 1 mmol) and benzyl azide (0.160 g, 1.2 mmol) according to the general procedure for Ru-catalyzed cycloadditions using C_6H_6 at 80 ºC; Red brown oil; Yield: 0.202 g (82%); R_f = 0.26 (hexanes-EtOAc, 1:1); IR: 2927 (w), 2820 (w), 1589 (w), 1497 (m), 1455 (m), 1436 (m), 1329 (w), 1191 (s), 1116 (s), 1080 (s), 1028 (w), 996 (m), 950 (m), 905 (m), 825 (w), 719 (s), 694 (s) 583 (w), 538 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.24 (s, 3H), 3.35 (s, 3H), 4.35 (s, 2H), 4.55 (s, 2H), 5.58 (s, 2H), 7.21-7.32 (m, 5H), 7.45-7.52 (m, 3H) 7.63-7.67 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 52.7, 58.1, 58.2, 61.6, 65.4, 127.7, 128.4, 128.9, 131.6, 134.8, 143.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{18}N_3O_2$: 248.1394 found 248.1396.

1-(Benzyloxymethyl)-5-phenyl-1*H*-1,2,3-triazole (28)



The title compound was prepared from phenyl acetylene (0.102 g, 1 mmol) and ((azidomethoxy)methyl)benzene (0.179 g, 1.1 mmol) in THF at 65 ˚C.

Red brown oil; Yield: 90 mg (34%); R_f = 0.50 (Hexanes-EtOAc, 7:3). Analytical data were in accordance with those reported in the literature.[16]

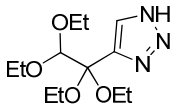
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75 (s, 2H), 5.73 (s, 2H), 7.33-7.37 (m, 5H), 7.48-7.51 (m, 3H) 7.64-7.66 (m, 2H) 7.83 (s, 1H).

5.3 Debenzylation of 1-benzyl 1,2,3-triazoles

General procedure for debenzylation

Into a solution of 1,2,3-triazole (0.88 mmol) in MeOH (25 ml) was added 10% Pd-C (36 mg) and the reaction mixture was affixed with hydrogen balloon (1 atm). After removing air, $ClCH_2CHCl_2$ (0.128 g, 0.96 mmol) was added. The reaction mixture was vigorously stirred at r.t. for 24 hr after which it was filtered through a pad of celite. Finally, the filtrate was concentrated to produce the title compound.

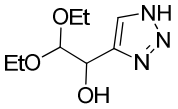
4-(1,1,2,2-Tetraethoxyethyl)-1*H*-1,2,3-triazole (14)



The title compound was prepared from **7** (0.181 g, 0.5 mmol) according to the general protocol for debenzylation.; Viscous colorless oil; Yield: 0.132 g (97%); R_f = 0.15

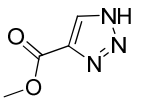
(hexanes-EtOAc, 7:3); IR: 3217 (br), 2975 (m), 2930 (w), 2890 (w), 1444 (w), 1373 (w), 1197 (w), 1117 (m), 1080 (s), 961 (m), 924 (w), 861 (w), 808 (w), 762 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, *J* = 7.2 Hz, 12H), 3.27-3.73 (m, 8H), 4.68 (s, 1H), 7.76 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.4, 57.7, 65.3, 99.5, 103.2, 133.0, 135.7; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{12}H_{23}N_3ONa$: 296.1581 found 296.1584.

2,2-Diethoxy-1-(1*H*-1,2,3-triazol-4-yl)ethanol (21)



The title compound was prepared from **22** (0.158 g, 0.54 mmol) according to the general protocol for debenzylation. Colorless oil; Yield: 0.105 g (97%); R_f = 0.21 (hexanes-EtOAc, 7:3); IR: 3147 (br), 2975 (m), 2930 (w), 2895 (w), 1444 (w), 1373 (w), 1117 (m), 1050 (s), 981 (m), 782 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.2 Hz, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), 3.48-3.83 (m, 4H), 4.65 (d, *J* = 5.6, 1H), 4.94 (d, *J* = 6, 1H), 7.73 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.3, 15.4, 64.1, 64.5, 67.8, 104.1, 133.8, 148.2; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_8H_{16}N_3O_3$: 202.1186 found 202.1185.

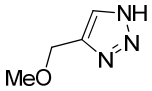
Methyl 1*H*-1,2,3-triazole-4-carboxylate (15c)



The title compound was prepared from **15a** (0.200 g, 0.92 mmol) according to the general protocol for debenzylation. Crystalline solid: Yield: 0.112 g (96%); mp 142.6-143.2 ºC; R_f = 0.18 (hexanes-EtOAc, 7:3); IR: 3135 (m), 2935 (m), 1727 (s), 1499 (m), 1431 (m), 1356 (s), 1242 (m), 1207 (s), 1019 (s), 864 (m), 778(s) 762 (w) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 3.89 (s, 3H), 8.33 (s, 1H); ^{13}C NMR (101 MHz,

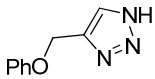
MeOD) δ 51.4, 130.8, 138.6, 161.6; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_4H_5O_2N_3Na$: 150.0274 found 150.0270.

4-(Methoxymethyl)-1*H*-1.2.3-triazole (17c)



The title compound was prepared from **17a** (0.175 g, 0.86 mmol) using the general protocol for debenzylation. Light yellow oil; Yield: 92 mg (95%); R_f = 0.20 (hexanes-EtOAc, 7:3); IR: 3132 (br), 2929 (m), 2825 (w), 1450 (m), 1385 (m), 1192 (m), 1087 (s), 1022 (w), 952 (w), 802 (m), 767 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.39 (s, 3H), 4.61 (s, 2H), 8.71 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 58.5, 65.5, 131.2, 143.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_4H_7N_3O$: 114.0662 found 114.0658.

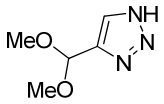
4-(Phenoxymethyl)-1*H*-1,2,3-triazole (18c)



The title compound was prepared from 1,5-disubstituted 1,2,3-triazole **18b** (0.232 g, 0.88 mmol) according to the general procedure for debenzylation. Colourless crystals; Yield: 0.145 g (94%); R_f = 0.50 (hexanes-EtOAc, 7:3). The analytical data were in accordance with those reported in the literature.[17]

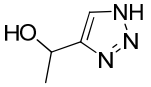
^1H NMR (500 MHz, MeOD) δ 5.19 (s, 1H), 6.94 (ddd, *J* = 7.5, 4.2, 1.0 Hz, 1H), 7.02 – 6.98 (m, 2H), 7.30 – 7.24 (m, 2H), 7.87 (s, 1H).

4-(Dimethoxymethyl)-1*H*-1,2,3-triazole (24)



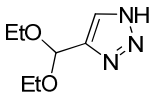
The title compound was prepared from **19b** (0.232 g, 0.89 mmol) according to the general protocol for debenzylation. Viscous oil; Yield: 0.120 g (94%); R_f = 0.40 (hexanes-EtOAc, 7:3); IR: 3137 (br), 2937 (w), 2833 (w), 1447 (w), 1320 (w), 1192 (m), 1100 (s), 1046 (s), 970 (s), 799 (s) cm^{-1}; ^1H NMR (400 MHz, MeOD): δ 3.30 (s, 6H), 5.59 (s, 1H), 7.73 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 52.9, 97.9, 130.5, 144.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_5H_{10}N_3O_2$: 166.0587 found 166.0588.

1-(1*H*-1,2,3-triazol-4-yl)ethanol (20c)



The title compound was prepared from **20a** (0.190 g, 0.94 mmol) according to the general protocol for debenzylation. Yellow oil; Yield: 0.102 g (96%); R_f = 0. 22 (hexanes-EtOAc, 1:1); IR: 3145 (br), 2977 (m), 2930 (w), 1697 (s), 1536 (w), 1479 (w), 1370 (w), 1325 (w), 1234 (w), 1051 (s), 965 (w), 925 (w), 827 (m), 681(m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, *J* = 6.4 Hz, 3H), 4.93-4.98 (q, *J* = 6.4 Hz, 1H), 7.65 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 22.6, 62.6, 126.6, 149.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_4H_8N_3O$: 114.0666 found 114.0659.

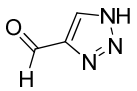
4-(Diethoxymethyl)-1*H*-1,2,3-triazole (19c)



The title compound was prepared from **19a** (0.248 g, 0.95 mmol) using the general protocol for debenzylation with EtOH as the solvent. Viscous oil; Yield 0.157 g (97%); R_f = 0.19 (hexanes-EtOAc, 7:3); IR: 3134 (br), 2976 (w), 2884 (w), 1445 (w), 1340 (w), 1103 (m), 1053 (s), 974 (w), 805 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ

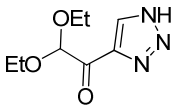
1.25 (t, *J* = 6.8 Hz, 3H), 3.60-3.69 (m, 4H), 5.76 (s, 1H), 7.76 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 15.4, 61.8, 96.5, 134.3, 148.1; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_7H_{13}N_3O_2Na$: 194.0900 found 194.0905.

1*H*-1,2,3-triazole-4-carbaldehyde (25)



While sitting in open air, **24** (0.120 g, 0.84 mmol) decomposed to give the title compound. Yellow crystalline solid; Yield 94 mg (97%); m.p 135.9- 136.5 ºC; IR: 3170 (br), 3126 (m), 2889 (w), 1693 (m), 1668 (s), 1530 (w), 1454 (w), 1399 (m), 1322 (s), 1237 (s), 1108 (m), 1028 (m), 829 (s), 764 (s), 636 (s) cm^{-1}; ^{1}H NMR (400 MHz, MeOD) δ 10.17, 11.58; ^{13}C NMR (101 MHz, MeOD) δ 127.8, 139.4, 194.75; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_3H_3N_3ONa$: 120.0163 found 120.0168.

2,2-Diethoxy-1-(1*H*-1,2,3-triazol-4-yl)ethanone (23)

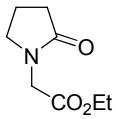


To a solution of *N*H-1,2,3-triazole **14** (0.119 g, 0.43 mmol) in a mixture of acetone (9 ml) and water (0.5 ml) was added Dowex 50W (16-40 mesh, 0.170 g). The mixture was heated at reflux for 6 hr before the Dowex resin was removed by filtration and acetone was removed The aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml) and thecombined organic layers were dried over $MgSO_4$. The drying agent was removed by filtration and the filtrate was concentrated. The crude product was purified using flash column chromatography (hexanes-EtOAc, 7:3) to give the title compound. Yellow oil; Yield: 79 mg (93%); R_f = 0.22 (hexane-EtOAc 7:3); IR: 3145 (br), 2977 (m), 2930 (w), 1697 (s), 1536 (w), 1479 (w), 1370 (w), 1325 (w), 1234 (w), 1051 (s), 965 (w), 925 (w), 827 (m), 681(m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.2 Hz, 6H), 3.68-3.81 (m, 4H), 5.38 (s, 1H), 8.49 (s, 1H); ^{13}C NMR (101 MHz,

$CDCl_3$): δ 15.3, 63.8, 101.3, 133.0, 142.3, 187.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_8H_{14}N_3O_3$: 200.1030 found 200.1033.

5.4 Synthesis of piperidine based building blocks

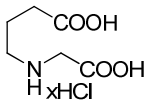
Ethyl 2-(2-oxopyrrolidin-1-yl)acetate (31)



The title compound was prepared in 73% yield according to already published procedure. The spectroscopic data were in agreement with literature.[18]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.3, 3H), 2.02-2.12 (m, 2H), 2.39 (t, 2H, *J* = 8), 3.50 (t, *J* = 7, 2H), 4.05 (s, 2H) 4.19 (q, *J* = 7, 2H).

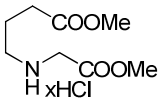
4-(Carboxymethylamino)butanoic acid hydrochloride (33)



The title compound was prepared in 90% yield according to already published procedure. The spectroscopic data were in agreement with literature.[18]

^{1}H NMR (400 MHz, D_2O): δ 1.58-172 (m, 2H), 2.21 (t, *J* = 7.2, 2H), 2.86 (t, *J* = 7.8, 2H), 3.67 (s, 2H).

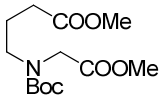
Methyl 4-(2-methoxy-2-oxoethylamino)butanoate hydrochloride (33)



The title compound was prepared in 75% yield according to already published procedure. The spectroscopic data were in agreement with literature.[18]

^{1}H NMR (400 MHz, MeOD): δ 2.01- 2.16 (m, 2H), 2.57 (t, *J* = 7.2, 2H), 3.15-3.25 (m, 2H), 3.71 (s, 3H), 3.87 (s, 3H), 4.10 (s, 2H), 5.48 (s, 1H).

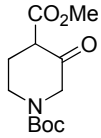
Methyl 4-(*tert*-butoxycarbonyl(2-methoxy-2-oxoethyl)amino)butanoate (34)



The title compound was prepared in 92% yield according to already published procedure. The spectroscopic data were in agreement with literature.[18]

. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 9H), 1.55-1.58 (m, 2H), 2.15 (t, *J* = 7.3, 2H), 3.13 (t, *J* = 6.8, 2H), 3.46 (s, 3H), 3.46 (s, 3H), 3.52 (s, 3H), 3.70 (s, 2H).

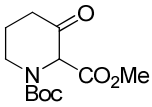
1-*tert*-Butyl 4-methyl 3-oxopiperidine-1,4-dicarboxylate (35)



The title compound was received in only 28% yield according to already published procedure. The spectroscopic data were in agreement with literature.[18]

^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 2.32-2.40 (m, 2H), 3.49 (t, *J* = 6, 2H), 3.78 (s, 3H), 4.03 (s, 2H), 12.00 (s, 1H).

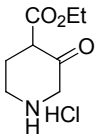
1-*tert*-Butyl 4-methyl 3-oxopiperidine-1,2-dicarboxylate (36)



The title compound was received in only 36% yield according to already published procedure. The spectroscopic data were in agreement with literature.[18]

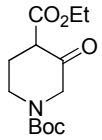
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.81-2.08 (m, 2H), 2.41-2.60 (m, 2H), 3.28-3.45 (m, 1H), 3.79 (s, 3H), 3.86-4.10 (m, 1H), 5.06 (s, 1H), 5.22 (s, 1H), 11.12 (s, 1H).

Ethyl 3-oxopiperidine-4-carboxylate hydrochloride (38)



A mixture of ethyl 1-benzyl-3-oxopiperidine-4-carboxylate hydrochloride **(37)** (10.395 g, 35.0 mmol), and 10% Pd-C (1.050 g) in methanol (350 ml) was affixed with hydrogen balloon (1 atm). Air was removed and $ClCH_2CHCl_2$ (3.23 ml, 35.0 mmol) was added. The solution was vigorously stirred at r.t. for 2 hr. The Pd-C catalyst was filtered off through a pad of celite. The filtrate was concentrated, residue was diluted with diethyl ether and evaporated to give **38** (7.443 g, 99%) as off-white crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 2.33 (t, *J* = 5.8 Hz, 2H), 2.58 (t, *J* = 5.8 Hz, 2H), 3.10 (s, 2H), 3.60 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 11.92 (s, 1H). The spectroscopic data were in agreement with literature [19]

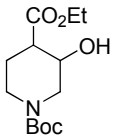
1-*tert*-Butyl 4-ethyl 3-oxopiperidine-1,4-dicarboxylate (39)



A mixture of **38** (7.045 g, 34.0 mmol) in 10% aq. Na_2CO_3 (30 ml) was cooled to 0 ˚C and di-*tert*-butyl dicarbonate (8.153 g, 37.4 mmol) was added in portions. The stirring was continued at 0 ˚C for 1 hr and then at r.t for overnight. The reddish brown mixture was extracted with diethyl ether (50 ml x 3). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 9:1) gave **39** (7.859 g, 85%) as yellow oil.

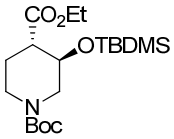
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.44 (s, 9H), 2.30 (d, *J* = 5.4 Hz, 2H), 3.46 (t, *J* = 5.7 Hz, 2H), 4.00 (s, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 12.05 (s, 1H). The spectroscopic data were in agreement with literature.[19]

1-*tert*-Butyl 4-ethyl 3-hydroxopiperidine-1,4-dicarboxylate (40)



A solution of **39** (7.737 g, 28.5 mmol) in methanol (140 ml) was cooled to -12 ˚C and $NaBH_4$ (1.097 g, 29.0 mmol) was added slowly over 10 min. After 1 hr, the reaction was quenched by slow addition of 10% citric acid (25 ml) and stirring was continued for 10 min at -10 ˚C and for 10 min at r.t. The aqueous layer was extracted with chloroform (50 ml x 3). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **40** as an inseprable mixture of isomers (7.527 g, 96%); Clear oil; R_f = 0.44; HRMS (ESI): *m/z* $[M+Na]^+$ calcd $C_{13}H_{23}O_5NNa$: 296.1468 found 296.1469.

***trans*-1-*tert*-Butyl 4-ethyl 3-(*tert*-butyldimethylsilyloxy)piperidine-1,4-dicarboxylate (*trans*-41)**



(±) *trans*-**41**

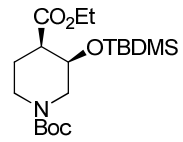
(A). A solution of **40** (obtained from exp. 4, see Table 3.1) (5.30 g, 19.56 mmol) in DMF (50 ml) was treated with imidazole (8.843 g, 58.68 mmol) and TBSCl (4.389 g, 64.55 mmol) at r.t. After 2 hr, 10% citric acid (20 ml) was added into the solution before extraction with EtOAc (30 ml x 3). The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 9:1) gave *trans*-**41** (0.580 g, 8%), *cis*-**41** (5.440 g, 72%), *trans*-**42** (1.588 g, 18%) and a fraction of *cis*-**42**.

Method (B). A solution of **40** (obtained from exp. 2, see Table 3.1) (7.520 g, 27.55 mmol) in DMF (50 ml) was treated with imidazole (6.175 g, 90.81 mmol) and TBSCl (12.408 g, 82.72 mmol) at r.t. After 4 hr, 10% citric acid (35 ml) was added into the solution before extraction with EtOAc (40 ml x 3). The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 9:1) gave *trans*-**41** (1.470 g, 14%) and *cis*-**41** (7.265 g, 68%).

For *trans*-**41**; Clear oil; R_f = 0.34; IR: 2959 (w), 2929 (m), 2896 (w), 2855 (m), 1735 (s), 1692 (s), 1463 (w), 1426 (s), 1363 (s), 1307 (m), 1243 (s), 1161 (s), 1124 (s), 1093 (w), 1032 (s), 932 (m), 829 (s), 775 (s), 699 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 – 0.22 (m, 6H), 0.84 (s, 9H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 1.60 – 1.64 (m, 1H), 1.82 (dd, *J* = 8.0 Hz, 1H), 2.35 – 2.46 (m, 1H), 2.56 (s, 1H), 2.67 (t, *J* = 12.0 Hz, 1H), 3.79 (s, 1H), 4.05 (d, *J* = 6.1 Hz, 1H), 4.10 – 4.14 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.1, 14.3, 17.9, 25.6, 25.7, 25.8, 27.6, 28.5, 42*, 49*, 51.1,

60.7, 68.7, 79.9, 154.5, 173.9; HRMS (ESI): *m/z* $[M+Na]^+$ calcd $C_{19}H_{37}NO_5NaSi$: 410.2333 found 410.2335.

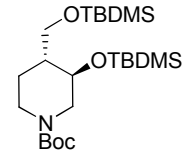
cis-1-_tert_-Butyl 4-ethyl 3-(_tert_-butyldimethylsilyloxy)piperidine-1,4-dicarboxylate (_cis_-41)



(±) *cis*-**41**

See description of synthesis of *trans*-**41** for experimental details. For *cis*-**41**; Clear oil; R_f = 0.22; ; IR: 2959 (w), 2929 (m), 2896 (w), 2855 (m), 1735 (s), 1692 (s), 1463 (w), 1426 (s), 1363 (s), 1307 (m), 1243 (s), 1161 (s), 1124 (s), 1093 (w), 1032 (s), 932 (m), 829 (s), 775 (s), 699 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 – 0.06 (m, 6H), 0.86 (s, 9H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 9H), 1.57 – 1.80 (m, 2H), 2.07 (qd, *J* = 8.2, 1H), 2.37 – 2.58 (m, 1H), 2.60 – 3.03 (m, 1H), 3.91 – 4.39 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 1.2, 14.3, 17.9, 21.7, 25.8, 28.5, 42*,47.1, 49*, 60.6, 66.6, 79.9, 154.5, 172.2; HRMS (ESI): *m/z* $[M+Na]^+$ calcd $C_{19}H_{38}NO_5Si$: 388.2519 found 388.2504.

***trans-tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-4-((*tert*-butyldimethylsilyloxy)methyl)piperidine-1-carboxylate (*trans*-42)**

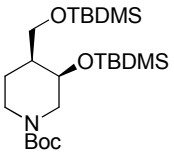


(±) *trans*-**42**

See description of synthesis of *trans*-**41** for experimental details. For *trans*-**42**; Clear oil; R_f = 0.89; IR: 2954 (w), 2928 (w), 2856 (w), 1698 (s), 1471 (w), 1364 (m), 1251 (m), 1169 (m), 1090 (s), 936 (m), 831 (s), 772 (s), 668 (m) cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 0.07 – 0.18 (m, 12H), 0.86 (s, 18H), 1.19 – 1.37 (m, 1H), 1.44 (s, 9H), 1.59 – 1.72 (m, 1H), 2.48 (br s, 1H), 2.55 – 2.61 (s, 1H), 3.38 (d, *J* = 4.0 Hz, 1H), 3.56 (dd, *J* = 7.2 Hz, 1H), 3.67 (br s, 1H), 3.90 – 4.04 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.1, 18.4, 25.9, 26.8, 27.2, 28.5, 44*, 46.6, 51*, 63.4, 67.9, 79.5, 154.8; HRMS (ESI): *m/z* $[M+Na]^+$ cald for $C_{23}H_{49}O_4NNaSi_2$: 482.3092 found 482.3096.

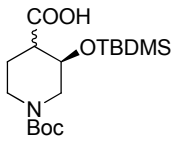
cis-tert-Butyl 3-(_tert_-butyldimethylsilyloxy)-4-((_tert_-butyldimethylsilyloxy)methyl)piperidine-1-carboxylate (_cis_-42)



(±) *cis*-**42**

See description of synthesis of *trans*-**41** for experimental details for method A. Method (B): A solution of *cis*-**46** (0.102 g, 0.30 mmol) in DMF (2 ml) was treated with imidazole (67 mg, 0.99 mmol) and TBSCl (0.136 g, 0.90 mmol) at r.t. After 1 hr, 10% citric acid (2 ml) was added into the solution before extraction with EtOAc (5 ml x 3). The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave *cis*-**42** (0.120 g, 87%); R_f = 0.55; Crystalline solid; mp 57.8- 59.3 ºC; IR: 2952 (w), 2926 (w), 2854 (w), 1681 (s), 1430 (m), 1363 (m), 1247 (m), 1169 (m), 1096 (m), 983 (w), 939 (w), 831 (s), 785 (s), 665 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.49 – -0.51 (m, 12H), 0.35 (s, 18H), 0.79 – 0.86 (m, 1H), 0.90 (s, 9H), 1.02 – 1.10 (m, 2H), 2.08 – 2.21 (m, 1H), 2.20 – 2.26 (m, 1H), 2.78 – 2.87 (m, 1H), 3.03 – 3.10 (m, 1H), 3.34 (d, *J* = 10.9 Hz, 1H), 3.40 – 3.47 (m, 1H), 3.56 – 3.66 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 0.1, 18.5, 22.6, 26.1, 28.6, 44.1, 50.5, 64.4, 79.5, 155.4; HRMS (ESI): *m/z* $[M+Na]^+$ cald for $C_{23}H_{49}O_4NNaSi_2$: 482.3092 found 482.3100.

***cis* and *trans*-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butyldimethylsilyloxy)piperidine-4-carboxylic acid (43)**



(±) **43**

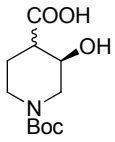
Method A: Into a solution of *cis*-**41** (5.406 g, 13.97 mmol) in EtOH (15 ml), NaOEt/EtOH 21 wt % (5.5 ml, 69.9 mmol) was added and heated to 70 ºC for 2 hr. NaOH (5.588, 139.6 mmol) was then added and stirred for 4 additional hr. Most of the EtOH was evaporated and EtOAc (5 ml) was added. At 0 ºC, 10% citric acid (5 ml) was added and extraction was done with EtOAc (10 ml x 3). The pH of aqueous layer was maintained to 2-3 with 0.5 M HCl solution. The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **43** (0.920 g, 18%), **44** (0.996 g, 29%) and **45** (0.160 g, 5%).

Method B: Into a solution of *cis*-**41** (0.201 g, 0.52 mmol) in EtOH (5 ml), NaOEt/EtOH 21 wt % (0.2 ml, 2.6 mmol) was added under nitrogen and heated to 70 ºC for 2 hr. NaOH (2M, 1.5 ml, 2.6 mmol) was then added and stirred for 2 additional hr. Most of the EtOH was evaporated and EtOAc (5 ml) was added. At 0 ºC, 10% citric acid (5 ml) was added and extraction was done with EtOAc (10 ml x 3). The pH of aqueous layer was maintained to 5 with 0.5 M HCl solution. The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **43** (0.138 g, 74%) and **44** (27 mg, 21%).

For **43**; Yellow oil; R_f = 0.36; IR: 3153 (w), 2929 (w), 2856 (w), 1737 (w), 1697(s), 1425 (m), 1366 (m), 1249 (m), 1158 (s), 1112 (m), 1005 (w), 959 (w), 890 (s), 774 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 – 0.28 (m, 6H), 0.83 – 0.96 (m, 9H), 1.26 (s, 1H), 1.46 (s, 9H), 1.65 (s, 1H), 1.96 – 2.19 (m, 1H), 2.46 (d, *J* = 8.5 Hz, 1H), 2.52 – 2.88 (m, 2H), 2.99 – 3.39 (m, 1H), 3.67 – 3.73 (m, 1H), 3.93 – 4.37 (m, 1H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ -5.0, 18.0, 25.8, 27.4, 28.5, 42*, 46.4, 49*, 50.7, 68.5, 80.2, 154.5, 177.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd $C_{17}H_{33}O_5NNaSi$: 382.2020 found 382.2024.

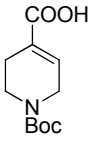
cis and _trans_-1-(_tert_-Butoxycarbonyl)-3-hydroxypiperidine-4-carboxylic acid (44)



(±) **44**

See description of synthesis of **43** for experimental details. For **44**; Yellow oil; IR: 3359 (w), 2976 (w), 2930 (w), 1661(s), 1417 (m), 1365 (m), 1239 (m), 1158 (s), 1129 (s), 1046 (w) 885 (w), 767 (w) cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 1.27 (s, 9H), 1.75 (dd, *J* = 8.2, 1H), 2.07 – 2.22 (m, 1H), 2.31 – 2.41 (m, 1H), 2.57 (br s, 1H), 3.45 – 3.55 (m, 1H), 3.76 – 3.81 (m, 1H), 3.83 – 3.95 (t, *J* = 13.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.8, 28.9, 43.7, 46.8, 51.4, 68.8, 81.5, 156.5, 178.8; HRMS (ESI): *m/z* $[M-H]^-$ calcd for $C_{11}H_{18}O_5N$: 244.1192 found 244.1190.

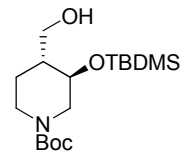
1-(_tert_-Butoxycarbonyl)-1,2,3,6-tetrahydropyridine-4-carboxylic acid (45)



(±) **45**

See description of synthesis of **43** for experimental details. For **45**; thick oil; ^1H NMR (400 MHz, MeOD) δ 1.17 – 1.33 (m, 1H), 1.48 (s, 9H), 1.98 (d, *J* = 5.3 Hz, 1H), 2.06 – 2.23 (m, 1H), 3.17 (s, 1H), 3.46 – 3.73 (m, 2H), 3.99 – 4.21 (m, 1H), 4.83 – 5.06 (m, 1H), 6.82 – 6.94 (m, 1H); ^{13}C NMR (101 MHz, MeOD) δ 23.9, 28.4, 37.4, 39.5, 81.4, 101.1, 127.5, 154.9, 171.3; HRMS (ESI): *m/z* $[M+Na]^+$ calcd $C_{11}H_{17}O_4NNa$: 250.1050 found 250.1053.

***trans-tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-4-(hydroxymethyl)piperidine-1-carboxylate (*trans*-46)**

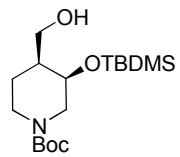


(±) *trans*-**46**

(Method A): A solution of *trans*-**41** (0.356 g, 09 mmol) in dry THF (5 ml) was treated with slow addition of $LiAlH_4$ (3 ml) at -35 ˚C. After 40 min, saturated solution of Rochelle's salt (10 ml) was added and stirring was continued for overnight at r.t. After extraction with EtOAc (10 ml x 3), organic layer was washed with brine, dried with $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave *trans*-**46** (227 mg, 72%).

(Method B): Into solution of borane dimethylsulfoxide complex (0.1 ml, 1.06 mmol) in dry THF (2 ml) **43** (0.190 g, 0.53 mmol dissolved in 3 ml dry THF) was added dropwise in 10 min and refluxed for 4 hr. Then cooled to r.t. and MeOH (3 ml) was added and solvent was removed under reduced pressure. The concentrated organic was redissolved in MeOH (5 ml x 2) and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 8:2) gave *trans*-**46** (0.114 g, 62%) and *cis*-**46** (58 mg, 32%). For *trans*-**46**; Crystalline solid; R_f = 0.56; IR: 3453 (s), 2957 (w), 2926 (m), 2854 (m), 1667 (s), 1470 (w), 1434 (m), 1365 (s), 1291 (s), 1255 (s), 1140 (s), 1076 (m), 1064 (m), 863 (s), 790 (s), 666 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.90 (s, 9H), 1.18 – 1.32 (m, 2H), 1.45 (s, 9H), 1.58 – 1.80 (m, 2H), 2.57 (m, 1H), 3.42 (s, 1H), 3.48 – 3.80 (m, 2H), 4.11 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ -4.8, 18.0, 25.9, 27.1, 28.6, 43*, 46.4, 51*, 65.9, 71.7, 79.8, 154.6; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{35}NO_4NaSi$: 368.2228 found 368.2229.

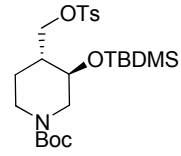
***cis-tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-4-(hydroxymethyl)piperidine-1-carboxylate (*cis*-46)**



(±) *cis*-**46**

See description of synthesis of *trans*-**46** by method B for experimental details. For *cis*-**46**; Clear oil; R_f = 0.38 (Hexanes-EtOAc, 8:2) ; IR: 3440 (s), 2957 (w), 2928 (m), 2855 (m), 1668 (s), 1462 (w), 1428 (s), 1365 (m), 1247 (s), 1165 (s), 1129 (m), 1091 (m), 1064 (m), 1032 (s), 935 (m), 835 (s), 713 (s), 732 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.83 (s, 9H), 1.38 (s, 9H), 1.47 – 1.86 (m, 2H), 2.18 (s, 1H), 2.69 – 2.98 (m, 2H), 3.48 (s, 1H), 3.62 (dd, *J* = 8.5 Hz, 1H), 3.78-4.02 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ -4.5, 18.1, 23.0, 25.9, 28.5, 42.4, 42.8, 49.8, 64.1, 66.5, 79.6, 155.3; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{35}NO_4NaSi$: 368.2228 found 100%.

***trans-tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-4-(tosyloxymethyl)piperidine-1-carboxylate (*trans*-47)**

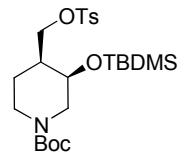


(±) *trans*-**47**

Into solution of *trans*-**46** (1.014 g, 2.94 mmol) in pyridine (6 ml), TsCl (0.673 g, 3.53 mmol) was added at 0 ºC and stirred for 4 hr, shifted to r.t. and stirred up to 48 hr. Then MeOH (10 ml) was added, stirred for 10 min and concentrated. After extraction with DCM (15 ml x 3), organic layer was washed with brine, dried with $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave *trans*-**47** (1.002 g, 68%); Thick oil; R_f = 0.38; IR;

2954 (w), 2928 (m), 2851 (m), 1692 (s), 1590 (w), 1419 (m), 1363 (s), 1252 (m), 1236 (w), 1174 (s), 1083 (w), 963 (m), 833 (s), 774 (s), 665 (s), 553 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.79 (s, 9H), 1.29 (m , 1H), 1.44 (s, 9H), 1.58-1.75 (m, 2H), 2.43 (s, 4H), 2.57 (m, 1H), 3.26 – 3.37 (m, 1H), 3.89 – 4.20 (m, 4H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 0.1, 17.9, 21.7, 25.7, 27.0, 28.5, 43*, 44.0, 51*, 67.6, 70.8, 79.9, 128.0, 129.9, 132.8, 144.9, 154.4; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{24}H_{41}NO_6NaSSi$: 522.2316 found 522.2307.

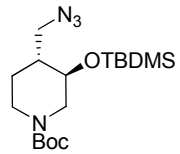
***cis-tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-4-(tosyloxymethyl)piperidine-1-carboxylate (*cis*-47)**



(±) *cis*-**47**

Into solution of *cis*-**46** (0.315 g, 0.91 mmol) in pyridine (3 ml), TsCl (0.209 g, 1.09 mmol) was added at 0 ºC and stirred for 4 hr, shifted to r.t and stirred up to 48 hr. Then MeOH (5 ml) was added, stirred for 10 min and concentrated and water was added (5 ml). After extraction with DCM (10 ml x 3), organic layer was washed with brine, dried with $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 8:2) gave *cis*-**47** (0.240 g, 53%); Clear oil; R_f = 0.62; IR: 2928 (w), 2855 (w), 1688 (s), 1426 (m), 1362 (s), 1250 (m), 1173 (s), 1141 (s), 1096 (m), 972 (m), 829 (s), 773 (s), 664 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -0.03 (s, 3H), 0.07 (s, 1H), 0.80 (s, 9H), 1.19 – 1.33 (m, 1H), 1.41 (s, 9H), 1.43 – 1.49 (m, 1H), 1.86 (m, 1H), 2.43 (s, 3H), 2.55 – 2.85 (m, 2H), 3.82 (br s, 1H), 3.92 – 4.00 (m, 2H), 4.05 – 4.21 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.0, 21.7, 22.2, 25.8, 28.5, 40.7, 42.2, 49.8, 64.6, 71.2, 79.8, 128.0, 129.9, 132.9, 144.9, 155.2; HRMS (ESI): *m/z* $[M+Na]^+$ cald for $C_{24}H_{41}O_6NNaSSi$: 522.2316 found 522.2321.

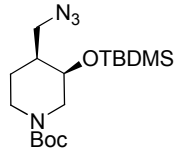
***trans-tert*-Butyl 4-(azidomethyl)-3-(*tert*-butyldimethylsilyloxy)piperidine-1-carboxylate (*trans*-48)**



(±) *trans*-**48**

A mixture of *trans*-**47** (0.558 g, 1.12 mmol) and NaN_3 (0.218 g, 3.36 mmol) in dry DMF (5 ml) was stirred under N_2 for 8hr at 65 ˚C. Water (5 ml) was added to the reaction mixture and the product was extracted with diethyl ether (10 ml x 3). The organic layer was washed, dried with anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 8:2) gave *trans*-**48** (0.412 g, 99%) as thick oil; R_f = 0.80; IR; 2955 (w), 2929 (m), 2857 (s), 2096 (s), 1694 (s), 1417 (s), 1365 (s), 1249 (m), 1163 (s), 1141 (s), 1081 (s), 960 (s), 868 (w), 832 (s), 774 (s), 667 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.40 – 1.24 (m, 2H), 1.45 (s, 9H), 1.70 – 1.80 (m, 1H), 2.47 (s, 1H), 2.63 (s, 1H), 3.33 (dd, *J* = 9.2 Hz, 2H), 3.52 (dd, *J* = 7.2 Hz, 1H), 4.12 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ -4.8, 18.1, 25.9, 27.9, 28.6, 43*, 44.6, 51*, 53.3, 68.8, 79.9, 154.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{34}O_3N_4NaSi$: 393.2292 found 393.2293.

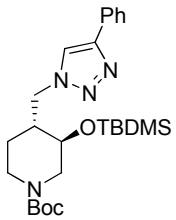
***cis-tert*-Butyl 4-(azidomethyl)-3-(*tert*-butyldimethylsilyloxy)piperidine-1-carboxylate (*cis*-48)**



(±) *cis*-**48**

A mixture of *cis*-**47** (0.212 g, 0.42 mmol) and NaN_3 (82 mg, 1.26 mmol) in dry DMF (5 ml) was stirred under N_2 for 16 hr at 65 ˚C. Then cooled to r.t., water (3 ml) was added to the reaction mixture and the product was extracted with diethyl ether (5 ml x 3). The organic layer was washed, dried with anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 8:2) gave *cis*-**48** (0.141 g, 91%); Clear oil; R_f = 0.55 (8:2); IR; 2928 (w), 2855 (m), 2096 (s), 1690 (s), 1426 (s), 1364 (s), 1243 (s), 1168 (s), 1133 (s), 1094 (w), 1039 (m), 985 (w), 837 (s), 776 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H), 0.87 (s, 9H), 1.43 (s, 9H), 1.51 – 1.70 (m, 2H), 2.68 – 2.74 (m, 1H), 2.74 – 2.80 (m, 1H), 3.15 – 3.21 (m, 1H), 3.25 – 3.31 (m, 1H), 3.78 – 3.83 (m, 1H), 3.89 – 4.09 (m, 1H), 4.16 (t, *J* = 14.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.2, 23.6, 25.9, 28.6, 41.1, 42.6, 50.1, 53.3, 65.3, 79.8, 155.3; HRMS (ESI): *m/z* $[M+Na]^+$ cald for $C_{17}H_{34}O_3N_4NaSi$: 393.2292 found 393.2288.

***trans-tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-4-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (49)**

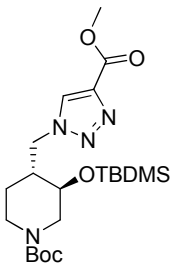


(±) **49**

A mixture of *trans*-**48** (0.250 g, 0.68 mmol), phenyl acetylene (0.108 g, 1.02 mmol), $CuSO_4$.$5H_2O$ (6 mg, 0.02 mmol) and Na-ascorbate (15 mg, 0.07 mmol) in dioxane/water (4 ml, 3:1) was stirred for overnight at 65 ºC. The extraction was done with ethyl acetate (10 ml x 3). The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 8:2) gave **49** (0.295 g, 93%); White powdery solid; mp 174-175 ºC; R_f = 0.55; IR: 2929 (w), 2855 (w), 1728 (s), 1681 (s),

1463 (w), 1426 (m), 1365 (m), 1241 (s), 1156 (s), 1074 (m), 833 (s), 778 (m), 763 (s), 693 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.95 (s, 9H), 1.23 – 1.27 (m, 2H), 1.44 (s, 9H), 1.98 – 2.04 (m, 1H), 2.50 – 2.56 (m, 2H), 3.38 – 3.41 (m, 1H), 4.04 (s, 1H), 4.22 (dd, *J* = 11.5, Hz, 2H), 4.73 (dd, *J* = 8.1 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.72 (s, 1H), 7.83 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ -3.4, 19.4, 27.2, 29.7, 43*, 46.9, 51*, 53.5, 71.0, 81.3, 121.2, 127.0, 129.5, 130.2, 131.8, 149.2; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{25}H_{40}O_3N_4NaSi$: 495.2762 found 495.2765.

trans-tert-Butyl 3-(_tert_-butyldimethylsilyloxy)-4-((4-methoxycarbonyl-1_H_-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (50)

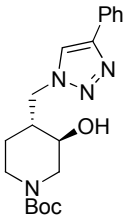


(±) **50**

A mixture of *trans*-**48** (0.408 g, 1.1 mmol), methyl propiolate (0.139 g, 1.65 mmol), $CuSO_4 \cdot 5H_2O$ (10 mg, 0.04 mmol) and Na-ascorbate (23 mg, 0.12 mmol) in dioxane/water (4 ml, 3:1) was stirred for 12 hr at 65 ºC. The extraction was done with ethyl acetate (10 ml x 3). The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **50** (0.479 g, 96%); White solid; mp 141-142.5 ºC; R_f = 0.29 (Hex/EtOAc, 7:3); IR: 3130 (w), 2974 (w), 2930 (w), 2861 (w), 1728 (m), 1688 (m), 1423 (m), 1365 (m), 1227 (m), 1155 (s), 1125 (m), 1042 (s), 954 (m), 872 (m), 775 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 6H), 0.91 (s, 9H), 1.13 – 1.26 (m, 2H), 1.43 (s, 9H), 1.78-2.02 (m, 1H), 2.40 – 2.53 (m, 2H), 3.36 (dt, *J* = 7.4 Hz, 1H), 3.94 (s, 3H), 4.06 (br s, 1H), 4.23 (dd, *J* = 11.5 Hz,

2H), 4.72 (dd, *J* = 8.2 Hz, 1H), 8.05 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 18.1, 25.9, 27.7, 28.5, 43*, 45.6, 50*, 52.3, 52.6, 69.8, 80.1, 128.0, 140.1, 154.3, 161.2; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{21}H_{38}O_5N_4NaSi$: 477.2504; found 477.2506.

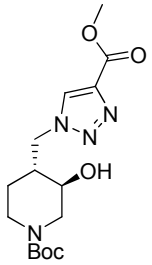
***trans-tert*-Butyl 3-hydroxy-4-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (51)**



(±) **51**

Into a solution of **49** (0.285 g, 0.60 mmol) in dry THF (6 ml), TBAF (0.35 ml, 1.20 mmol) was added slowly and stirred for 12 hr. Then water (5 ml) was added and extraction was done with ethyl acetate (10 ml x 3). The organic phase was washed with brine, dried over with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **51** (0.208 g, 97%); Crystalline solid; mp 179-180 ºC; R_f = 0.58; IR: 3408 (br), 3188 (w), 2871 (w), 1726 (m), 1672 (s), 1425 (m), 1365 (m), 1245 (m), 1160 (m), 1059 (w), 954 (w), 882 (m), 765 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (dt, *J* = 10.3, Hz, 1H), 1.42 (s, 9H), 1.64 (d, *J* = 12.1 Hz, 1H), 1.95 (d, *J* = 5.9 Hz, 1H), 2.59 – 2.62 (m, 1H), 3.36 (s, 1H), 3.54 – 3.75 (m, 2H), 4.02 (s, 1H), 4.32 (s, 1H), 4.54 (s, 1H), 4.67 (s, 1H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.80 (s, 2H), 7.82 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.2, 28.7, 44.7, 50*, 52.2, 68.2, 70.8, 80.5, 121.1, 125.9, 128.6, 129.2, 130.6, 148.0, 154.8; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{19}H_{26}O_3N_4Na$: 381.1897 found 381.1896.

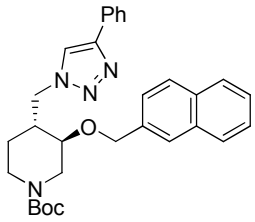
***trans-tert*-Butyl 3-hydroxy-4-((4-methoxycarbonyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (52)**



(±) **52**

Into a solution of **50** (0.568 g, 1.25 mmol) in dry THF (6 ml), TBAF (0.7 ml, 2.5 mmol) was added slowly and stirred for overnight. Then water (5 ml) was added and extraction was done with ethyl acetate (10 ml x 3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) to give **52** (0.358 g, 84%); Colorless solid; R_f = 0.14 (Hex/EtOAc, 7:3); mp 131-131.8 ºC; IR: 3390 (br), 3134 (w), 2929 (w), 2849 (w), 1727 (m), 1667 (s), 1423 (s), 1365 (s), 1209 (s), 1155 (s), 1125 (m), 1042 (s), 954 (m), 872 (m), 775 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 – 1.21 (m, 1H), 1.30 (s, 9H), 1.48 (d, *J* = 13.2 Hz, 1H), 1.78 – 1.98 (m, 1H), 2.48 (br s, 2H), 3.24 (dt, *J* = 7.5 Hz, 1H), 3.81 (br s, 3H), 3.90 (br s, 1H), 4.19 (s, 1H), 4.43 (dd, *J* = 11.1 Hz, 1H), 4.68 (dd, *J* = 8.1 Hz, 1H), 8.20 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.7, 28.2, 43*, 44.1, 50*, 52.1, 52.2, 67.6, 80.0, 128.7, 139.4, 154.4, 161.0; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{15}H_{24}N_4O_5Na$: 363.1639 found 363.1639.

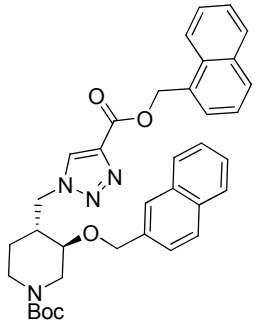
***trans-tert*-Butyl 3-(naphthalene-2-ylmethoxy)-4-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (53)**



(±) **53**

A solution of **51** (0.101 g, 0.28 mmol) in DMF (2 ml) was added to a stirred suspension of NaH (22 mg, 0.92 mmol) in DMF (1 ml) and stirred for 30 min. Tetrabutylammonium iodide (10 mg, 0.03 mmol) and 2-bromomethylnaphthalene (0.124 g, 0.56 mmol) in DMF (2 ml) were added and the reaction mixture stirred for 12 hr. The reaction mixture was diluted with EtOAc (10 ml) and poured into water (5 ml). The solution was washed with 10% aq. HCl (3 ml), saturated aq. $NaHCO_3$ (3 ml), and water (3 ml), dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 8:2) gave **53** (0.128 g, 93%); Powdery solid; mp 130-130.7 ºC; R_f = 0.10 (Hex/EtOAc, 8:2); IR: 3433 (br), 2973 (w), 2860 (w), 1682 (s), 1463 (m), 1421 (m), 1364 (m), 1241 (s), 1154 (s), 1076 (s), 952 (m), 855 (m), 816 (m), 762 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 – 1.32 (m, 2H), 1.44 (s, 9H), 2.04 (s, 1H), 2.50 – 2.60 (m, 2H), 3.20 (td, *J* = 7.3 Hz, 1H), 4.01 (s, 1H), 4.37 (dd, *J* = 10.4 Hz, 1H), 4.52 – 4.71 (m, 2H), 4.78 – 4.95 (m, 2H), 7.27 – 7.38 (m, 3H), 7.43 – 7.56 (m, 4H), 7.64 (s, 2H), 7.84 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.8, 28.4, 43.1, 43.2, 51.5, 65.1, 71.3, 74.8, 80.1, 120.3, 125.5, 126.1, 126.3, 126.4, 127.1, 127.8, 128.1, 128.6, 128.8, 130.5, 133.2, 135.2, 147.6, 154.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{30}H_{34}O_3N_4Na$: 521.2523 found 521.2527.

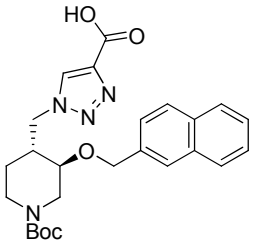
***trans-tert*-Butyl 4-((4-((naphthalen-1-ylmethoxy)carbonyl)-1*H*-1,2,3-triazol-1-yl)methyl)-3-(naphthalen-2-ylmethoxy)piperidine-1-carboxylate (54)**



(±) **54**

A solution of **52** (0.174 g, 0.51 mmol) in DMF (2 ml) was added to a stirred suspension of NaH (40 mg, 1.68 mmol) in DMF (2 ml) and stirred for 30 min. Tetrabutylammonium iodide (18 mg, 0.05 mmol) and 2-bromomethylnaphthalene (0.225 g, 1.02 mmol) in DMF (2 ml) were added and the reaction mixture stirred for 12 hr. The reaction mixture was diluted with EtOAc (10 ml) and poured into water (10 ml). The solution was washed with 10% aq. HCl (3 ml), saturated aq. $NaHCO_3$ (3 ml), and water (3 ml), dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **54** (0.145 g, 47%) and **55** (0.110 g, 47%); For **54**; thick oil; R_f = 0.50 (Hex/EtOAc, 7:3); IR: 3054 (w), 2973 (w), 2928 (w), 2860 (w), 1731 (w), 1683 (s), 1539 (w), 1422 (m), 1364 (m), 1261 (m), 1155 (s), 1039 (m), 952 (w), 815 (s), 727 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 – 1.31 (m, 1H), 1.43 (s, 9H), 1.52 (d, *J* = 12.9 Hz, 1H), 2.02 – 2.09 (m, 1H), 2.51 – 2.60 (m, 2H), 3.16 (dt, *J* = 7.2 Hz, 1H), 4.01 (br s, 1H), 4.30 – 4.36 (m, 1H), 4.64 (d, *J* = 11.0 Hz, 3H), 4.87 (d, *J* = 9.1 Hz, 1H), 5.51 (s, 2H), 7.60 – 7.41 (m, 6H), 7.86 – 7.75 (m, 7H), 7.90 (s, 1H), 7.97 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 27.9, 28.4, 43.2, 46.4, 52.2, 67.1, 71.6, 75.2, 80.3, 125.9, 126.2, 126.3, 126.4, 126.5, 127.0, 127.7, 127.8, 127.9, 128.0, 128.1, 128.4, 128.5, 128.6, 132.9, 133.1, 133.2, 133.3, 135.1, 139.9, 154.5, 160.6; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{36}H_{38}O_5N_4Na$: 629.2734 found 629.2741.

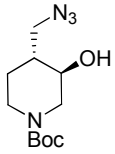
***trans*-1-(*tert*-Butoxycarbonyl)-3-(naphthalen-2-ylmethoxy)piperidin-4-yl)methyl)-1*H*-1,2,3-triazole-4-carboxylic acid (55)**



(±) **55**

See description of synthesis of **54** for experimental details. For **55**; White solid; mp 120-120.5 ºC; R_f = 0.10 (Hex/EtOAc, 7:3); IR: 3378 (br), 3101 (w), 2931 (w), 2867 (w), 1728 (s), 1681 (s), 1426 (s), 1364 (s), 1245 (m), 1199 (s), 1175 (s), 1127 (s), 1055 (s), 1033 (m), 956 (m), 888 (m), 782 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11– 1.18 (m, 1H), 1.39 (s, 9H), 1.45 – 1.59 (m, 1H), 1.82 – 1.87 (m, 1H), 2.48 – 2.54 (m, 2H), 3.24 – 3.29 (m, 1H), 3.99 – 4.11 (m, 1H), 4.28 (br s, 1H), 4.43 (dd, *J* = 10.3 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 5.52 (s, 2H), 7.46 – 7.52 (m, 3H), 7.78 – 7.84 (m, 3H), 7.89 (s, 1H), 8.11 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.1, 28.6, 43.7, 44.5, 50.1, 52.4, 67.4, 67.9, 80.5, 126.4, 126.6, 126.7, 127.9, 128.2, 128.3, 128.7, 128.9, 133.1, 133.4, 133.5, 139.9, 154.8, 160.8; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{25}H_{30}O_5N_4Na$: 489.2108 found 489.2106.

***trans-tert*-Butyl 4-(azidomethyl)-3-hydroxypiperidine-1-carboxylate (56)**

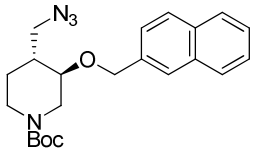


(±) **56**

Into a solution of *trans*-**48** (0.160 g, 0.43 mmol) in dry THF (4 ml), TBAF (0.12 ml, 0.86 mmol) was added slowly and stirred for 24 hr. Then water (5 ml) was added and

extraction was done with ethyl acetate (10 ml x 3). The organic phase was washed with brine, dried over with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **56** (90 mg, 81%); Clear oil; R_f = 0.45; IR: 3400 (br), 2976 (w), 2927 (w), 2095 (s), 1662 (s), 1426 (s), 1366 (s), 1244 (m), 1162 (s), 1131 (s), 1056 (m), 956 (m), 881 (w), 832 (s), 768 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 – 1.39 (m, 2H), 1.44 (s, 9H), 1.57– 1.62 (m, 1H), 1.67 – 1.74 (m, 1H), 2.51 (s, 1H), 2.67 (br s, 1H), 3.44 (dt, *J* = 7.0 Hz, 2H), 3.54 (s, 1H), 4.10 (s, 1H), 4.23 (s, 1H); ^{13}C NMR (101, MHz, $CDCl_3$) δ 27.9, 28.5, 43.5, 44*, 50.0, 53.9, 68*, 80.2, 154.7; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{11}H_{20}N_4O_3Na$: 279.1428 found 279.1431.

***trans-tert*-Butyl 4-(azidomethyl)-3-(naphthalene-2-ylmethoxy)piperidine-1-carboxylate (57)**

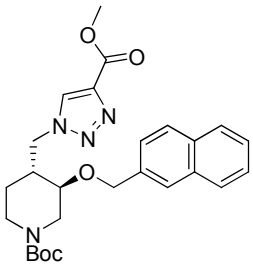


(±) **57**

A solution of **56** (84 mg, 0.33 mmol) in DMF (2 ml) was added to a stirred suspension of NaH (26 mg, 1.09 mmol) in DMF (1 ml) and stirred for 30 min. Tetrabutylammonium iodide (12 mg, 0.03 mmol) and 2-bromomethylnaphthalene (0.145 g, 0.66 mmol) in DMF (2 ml) were added and the reaction mixture stirred for overnight. The reaction mixture was diluted with EtOAc (10 ml) and poured into water (10 ml). The solution was washed with 10% aq. HCl (3 ml), saturated aq. $NaHCO_3$ (3 ml), and water (3 ml), dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 8:2) gave **57** (0.129 g, 99%); Thick paste; R_f = 0.90; IR: 2922 (w), 2856 (w), 2095 (s), 1689 (s), 1421 (s), 1365 (s), 1272 (w), 1244 (m), 1163 (s), 1141 (s), 1080 (m), 953 (w), 888 (w), 855 (w), 817 (m), 751 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$)

δ 1.21 – 1.34 (m, 2H), 1.47 (s, 9H), 1.68 – 1.77 (m, 1H), 2.48 – 2.63 (m, 1H), 2.68 (br s, 1H), 3.25 (s, 1H), 3.41 (dd, *J* = 9.0 Hz, 1H), 3.57 (dd, *J* = 7.0 Hz, 1H), 4.07 – 4.16 (m, 1H), 4.66 (d, *J* = 11.0 Hz, 1H), 4.78 (br s, 1H), 4.85 (s, 1H), 7.44 – 7.54 (m, 3H), 7.79 (s, 1H), 7.86 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.9, 28.4, 42.5, 44*, 53.1, 71.7, 72.2, 74.8, 79.9, 125.9, 126.2, 126.6, 126.8, 127.7, 127.9, 128.3, 133.0, 133.2, 135.4, 154.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{22}H_{28}N_4O_3Na$: 419.2054 found 419.2057.

***trans-tert*-Butyl 4-((4-(methoxycarbonyl)-1*H*-1,2,3-triazol-1-yl)methyl)-3-(naphthalen-2-ylmethoxy)piperidine-1-carboxylate (58)**

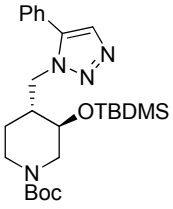


(±) **58**

A mixture of azide **57** (0.129 g, 0.33 mmol), methyl propiolate (42 mg, 0.50 mmol), $CuSO_4 \cdot 5H_2O$ (3 mg, 0.01 mmol) and Na-ascorbate (7 mg, 0.03 mmol) in dioxane/water (4 ml, 3:1) was stirred for 18 hr at 65 ºC. The extraction was done with ethyl acetate (5 ml x 3). The combined organics were washed with brine, dried over anhydrous $MgSO_4$ and concentrated. Purification of the crude product with flash column chromatography using (hexanes-EtOAc, 7:3) gave **58** (0.138 g, 88%); Yellow oil; R_f = 0.17; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.0 Hz, 2H), 1.42 (s, 9H), 2.05 – 2.10 (m, 1H), 2.45 – 2.70 (m, 2H), 3.16 (dt, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.94 – 4.20 (m, 2H), 4.35 (dd, *J* = 10.0 Hz, 1H), 4.65 (d, *J* = 10.4 Hz, 2H), 4.86 (s, 1H), 7.39 – 7.57 (m, 3H), 7.77 – 7.82 (m, 4H), 7.95 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.3, 28.1, 28.6, 43.4, 46*, 52.4, 60.7, 71.7, 75.4, 80.4, 126.2, 126.5, 126.6, 127.2,

128.1, 128.2, 128.5, 128.8, 133.4, 133.5, 135.3, 140.1, 154.6, 161.3; HRMS (ESI): *m/z* $[M+H]^+$ cald for $C_{26}H_{33}O_5N_4$: 461.2450 found 461.2448.

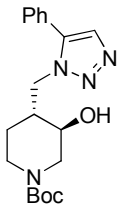
***trans-tert*-Butyl 3-(*tert*-butyldimethylsilyloxy)-4-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (59)**



(±) **59**

A mixture of *trans*-**48** (0.233 g, 0.63 mmol), phenyl acetylene (96 mg, 0.95 mmol) and $Cp^*RuCl(PPh_3)_2$ (5 mg) in C_6H_6 (6 ml) was refluxed for 4 hr under N_2. Then the solvent was removed under reduced pressure. Purification of the crude product with flash column chromatography using (hexane-EtOAc Purification with flash column (Hex/EtOAc, 8:2) gave **59** (0.263 g, 89%); Reddish brown oil; R_f = 0.20; IR: 2953 (w), 2928 (w), 2856 (w), 1690 (s), 1461 (w), 1417 (m), 1364 (m), 1245 (s), 1154 (s), 1111 (m), 1083 (s), 959 (m), 830 (s), 768 (s), 698 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (d, 6H), 0.84 (s, 9H), 1.07 (m, 1H), 1.23 (s, 1H), 1.40 (s, 9H), 1.80-2.01 (m, 1H), 2.35-2.52 (m, 2H), 3.25-3.33 (m, 1H), 3.93 (br s, 1H), 4.08 (dd, *J* = 12.0 Hz, 2H), 4.77 (d, *J* = 12.7 Hz, 1H), 7.32 – 7.42 (m, 2H), 7.51 – 7.42 (m, 3H), 7.68 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ -4.0, 17.9, 25.8, 27.6, 28.4, 42*, 44.9, 50.2, 51*, 70.1, 79.9, 127.1, 128.8, 129.3, 129.6, 133.2, 138.2, 154.4; HRMS (ESI): *m/z* $[M+H]^+$ cald for $C_{25}H_{41}O_3N_4Si$: 473.2947 found 473.2927.

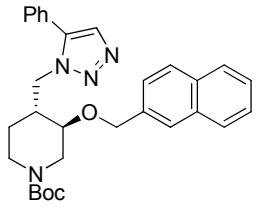
***trans-tert*-Butyl 3-hydroxy-4-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (60)**



(±) **60**

Into a solution of **59** (0.250 g, 0.53 mmol) in dry THF (5 ml), TBAF (0.31 ml, 1.06 mmol) was added slowly and stirred for 24 hr. Then water (5 ml) was added and extraction was done with ethyl acetate (10 ml x 3). The organic phase was washed with brine, dried over with anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) to give **60** (0.170 g, 89%); Red brown oil; R_f = 0.10; IR: 3450 (w), 2974 (w), 2917 (w), 1681 (s), 1419 (s), 1365 (m), 1237 (m), 1153 (w), 1056 (m), 954 (w), 768 (m), 729 (m), 697 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (s, 1H), 1.22 (s, 1H), 1.37 (s, 9H), 1.87 – 2.07 (m, 1H), 2.49 (br s, 2H), 3.30 – 3.35 (m, 1H), 3.91 (br s, 2H), 4.22 – 4.30 (m, 2H), 4.77 (br s, 1H), 7.44 (m, 5H), 7.65 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.8, 28.4, 44.3, 50.1, 51*, 68.6, 79.9, 126.9, 129.0, 129.2, 129.6, 132.9, 138.7, 154.5; HRMS (ESI): *m/z* $[M+H]^+$ cald for $C_{19}H_{27}O_3N_4$: 359.2083 found 359.2068.

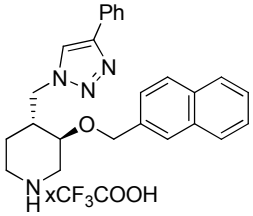
***trans-tert*-Butyl 3-(naphthalene-2-ylmethoxy)-4-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine-1-carboxylate (61)**



(±) **61**

A solution of **60** (0.160 g, 0.45 mmol) in DMF (2 ml) was added to a stirred suspension of NaH (36 mg, 1.49 mmol) in DMF (1 ml) and stirred for 30 min. Tetrabutylammonium iodide (17 mg, 0.04 mmol) and 2-bromomethylnaphthalene (0.199 g, 0.90 mmol) in DMF (2 ml) were added and the reaction mixture was stirred for overnight. The reaction mixture was diluted with EtOAc (5 ml) and poured into water (5 ml). The solution was washed with 10% aq. HCl (3 ml), saturated aq. $NaHCO_3$ (3 ml), and water (3 ml), dried over anhydrous $MgSO_4$ and concentrated. . Purification of the crude product with flash column chromatography using (hexane-EtOAc, 7:3) gave **61** (0.200 g, 89%); Thick yellow oil; $R_f = 0.35$; IR: 2973 (w), 2919 (w), 2860 (w), 1687 (s), 1422 (m), 1365 (m), 1245 (m), 1154 (s), 1086 (m), 769 (w), 698 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 – 1.10 (s, 1H), 1.25 (s, 1H), 1.42 (s, 9H), 1.53 (br s, 1H), 2.09 – 2.14 (m, 1H), 2.54 – 2.67 (m, 2H), 3.23 (dt, J = 7.2 Hz, 1H), 3.94 (br s, 1H), 4.15 (br s, 1H), 4.59 (br s, 1H), 4.78 – 4.85 (m, 2H), 7.30 – 7.41 (m, 5H), 7.54 – 7.47 (m, 2H), 7.68 (s, 1H), 7.71 (s, 1H), 7.81 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 27.8, 28.4, 43.0, 49.7, 71.4, 75.5, 80.1, 125.9, 126.1, 126.3, 126.7, 127.0, 127.8, 127.9, 128.3, 128.9, 129.2, 129.5, 133.1, 133.3, 135.5, 138.4, 154.6; HRMS (ESI): *m/z* $[M+H]^+$ cald for $C_{30}H_{35}O_3N_4$: 499.2709 found 499.2704.

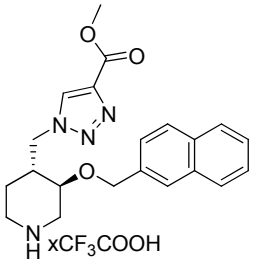
***trans*-3-(Naphthalen-2-ylmethoxy)-4-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)piperidine (62)**



(±) **62**

The solution of **53** (0.144 g, 0.29 mmol) in 2 ml of CH_2Cl_2/TFA (1:1) was stirred for 30 min. The solvent was removed under reduced pressure. The toluene (5 ml x 2), acetonitril (5 ml x 2) and CH_2Cl_2 (5 ml x 2) were added and removed under reduced pressure. Purification using semi-preparative HPLC gave **62** (49 mg, 34%) after lyophilization. ^{1}H NMR (400 MHz, MeOD) δ 1.28 – 1.35 (m, 1H), 1.40 – 1.52 (m, 1H), 1.80 – 2.05 (m, 1H), 2.30 – 2.37 (m, 1H), 2.79 – 3.02 (m, 2H), 3.58 – 3.65 (m, 2H), 4.54 (dd, *J* = 14.1, 6.9 Hz, 1H), 4.69 – 4.81 (m, 3H), 7.29 – 7.40 (m, 3H), 7.43 – 7.57 (m, 3H), 7.65 (d, *J* = 7.0 Hz, 2H), 7.73 – 7.90 (m, 5H), 8.09 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.5, 40.6, 42.7, 45.8, 50.9, 71.6, 72.7, 121.9, 125.5, 126.1, 126.2, 126.3, 127.1, 127.6, 127.9, 128.2, 128.3, 128.8, 130.3, 133.5, 133.6, 135.3, 147.7; HRMS (ESI): *m/z* $[M+H]^+$ cald for $C_{25}H_{27}ON_4$: 399.2179 found 399.2181.

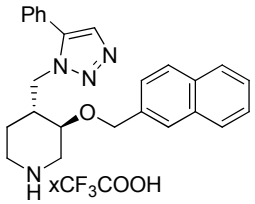
***trans*-Methyl-3-(naphthalen-2-ylmethoxy)piperidin-4-yl)methyl)-1*H*-1,2,3-triazole-4-carboxylate (63)**



(±) **63**

The solution of **58** (0.126 g, 0.26 mmol) in 2 ml of CH_2Cl_2/TFA (1:1) was stirred for 30 min. The solvent was removed under reduced pressure. The toluene (5 ml x 2), acetonitril (5 ml x 2) and CH_2Cl_2 (5 ml x 2) were added and removed under reduced pressure. Purification using semi-preparative HPLC gave **63** (72 mg, 58%) after lyophilization. ^{1}H NMR (400 MHz, MeOD) δ 1.45 – 1.52 (m, 1H), 1.96 (dd, *J* = 9.2 Hz, 1H), 2.40 – 2.52 (m, 1H), 2.87 – 3.07 (m, 2H), 3.52 – 3.86 (m, 2H), 3.80 (s, 3H), 4.50 – 4.58 (m, 1H), 4.72 (dd, *J* = 9.2 Hz, 2H), 4.78 – 4.82 (m, 2H), 7.42 – 7.52 (m, 3H), 7.77 (s, 1H), 7.84 (m, 3H), 8.44 (s, 1H); ^{13}C NMR (101 MHz, MeOD) δ 24.8, 41.1, 43.4, 46.3, 52.1, 52.5, 72.9, 73.4, 127.1, 127.3, 127.4, 128.1, 128.8, 128.9, 129.4, 130.4, 134.6, 134.7, 136.1, 140.5, 162.2; HRMS (ESI): *m/z* $[M+H]^+$ cald for for $C_{21}H_{25}O_3N_4$: 381.1921 found 381.1920.

trans-3-(naphthalen-2-ylmethoxy)-4-((5-phenyl-1_H_-1,2,3-triazol-1-yl)methyl)piperidine (62)



(±) **64**

The solution of **61** (0.187 g, 0.38 mmol) in 2 ml of CH_2Cl_2/TFA (1:1) was stirred for 30 min. The solvent was removed under reduced pressure. The toluene (5 ml x 2), acetonitril (5 ml x 2) and CH_2Cl_2 (5 ml x 2) were added and removed under reduced pressure. Purification using preparative HPLC gave **64** (80 mg, 42%) after lyophilization. ^{1}H NMR (400 MHz, MeOD) δ 1.31 – 1.48 (m, 1H), 1.77 – 1.96 (m, 1H), 2.14 – 2.22 (m, 1H), 2.82 – 2.92 (m, 2H), 3.15 – 3.21 (m, 1H), 3.52 (dd, *J* = 9.0, 4.5 Hz, 2H), 4.34 (dd, *J* = 14.3, 8.4 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.71 – 4.84 (m, 2H), 7.30 – 7.40 (m, 6H), 7.44 – 7.61 (m, 2H), 7.72 (s, 2H), 7.75 – 7.93 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.6, 39.7, 41.9, 44.8, 49*, 71.6, 71.7, 125.8, 126.1,

126.2, 126.9, 127.5, 127.7, 128.2, 128.8, 129.1, 129.6, 132.6, 133.4, 134.9, 138.9; HRMS (ESI): *m/z* $[M+H]^+$ cald for $C_{25}H_{27}ON_4$: 399.2179 found 399.2182.

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