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**Synthesis and Cytotoxicity evaluation of small 1,4 -
triazolic derivatives against B16 melanoma cell lines and
a methodology study on the synthesis of propargyl ethers
from their corresponding propargyl esters without
catalyst and under microwave irradiations**

Shiva Kalhor Monfared

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L'UNIVERSITE PIERRE ET MARIE CURIE

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Sujet de la thèse :

Synthesis and Cytotoxicity evaluation of small 1,4-triazolic derivatives against B16 melanoma cell lines and a methodology study on the synthesis of propargyl ethers from their corresponding propargyl esters without catalyst and under microwave irradiations

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Préparée à l'École Nationale Supérieure de Chimie de Paris

Synthesis and Cytotoxicity evaluation of small 1,4-triazolic derivatives against *B16 melanoma cell lines* and a methodology study on the synthesis of propargyl ethers from their corresponding propargyl esters without catalyst and under microwave irradiations

By
Shiva KALHOR MONFARED

Dissertation

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Table of contents

General introduction.....	17
Chapter 1: Diversity Oriented Synthesis and Click Chemistry.....	31
I. Introduction.....	33
I.1.1. Source of small molecules for use in biological screens.....	33
I.1.2. What is Diversity Oriented Synthesis.....	34
I.1.2.1. Comparing DOS, TOS, and combinatorial chemistry.....	35
I.1.2.2. Molecular diversity.....	35
I.1.2.3. Skeletal diversity.....	37
I.1.3. Screening small molecules for biological activity.....	37
I.1.4. Discovering bioactive small molecules using DOS.....	39
I.1.4.1. Protein-protein interactions (PPIs).....	39
I.1.5. Diversity Oriented Synthesis and chemical space.....	40
I.2. Click Chemistry.....	41
I.2.1. Mechanism of Cu-catalyzed azide-alkyne cycloaddition.....	43
I.2.2. Physicochemical properties of organic azides.....	45
I.2.2.1. Reactions of organic azides.....	47
I.2.2.2. Applications of azides.....	48
I.2.3. Applications of click chemical reactions.....	52
I.2.3.1. Therapeutics polymer.....	53
I.2.3.2. Drug delivery systems.....	54
I.2.3.3. Bioconjugation.....	56
I.2.3.3.1. Radiolabelling.....	57
I.2.3.3.2. Polysaccharides.....	58
I.2.3.3.3. Tagging of live organisms and proteins.....	59
I.2.3.3.4. Activity based protein profiling (ABPP).....	59
I.2.3.3.5. Labeling of DNA.....	60
I.2.4. Synthesis of lead discovery libraries.....	60
I.2.5. Limitations of Click Chemistry.....	61
I.2.6. Biologically active 1,2,3-triazoles.....	62
I.2.7. Biologically active 1,2,3-triazoles synthesized without copper catalyst.....	62
I.2.8. Click reactions and the pharmacological applications of 1,2,3-triazoles.....	63
I.2.8.1. Anticancer.....	64
I.2.8.2. <i>In vivo</i> tumor cell targeting with 'Click' nanoparticles.....	66
Chapter II: Synthesis of triazolic derivatives departing from aldehydes and by use of a solid supported catalyst (A-21.CuI) and study their biological activity.....	69
II. Solid supported catalyst.....	71
II.1. Synthesis of triazolic derivatives on a solid supported catalyst.....	72
II.2. Amberlyst copper (I)-A-21 (A-21.CuI).....	76
II.2.1. Stability of Amberlyst A-21.CuI.....	79
II.2.2. Limits of the Amberlyst A-21.CuI.....	79
II.3. Synthesis of 1,2,3-triazoles derivatives from alkynes or propargylic alcohols.....	85
II.3.1. Terminal alkynes.....	85
II.3.1.1. Seyferth-Gilbert homologation.....	86
II.3.1.2. Mechanism of the Seyferth-Gilbert homologation.....	86
II.3.1.3. Bestmann-Ohira Reagent (BOR) reaction.....	90
II.3.1.4. Mechanism of the alkynylation of an aldehyde with BOR.....	90

II.3.1.5. Some applications of Bestmann-Ohira reagent.....	91
II.3.1.6. Synthesis of alkynes.....	96
II.3.1.6.1. Synthesis of Bestmann-Ohira Reagent (BOR).....	96
II.3.1.6.2. Synthesis of some terminal alkynes.....	96
II.3.2. Propargylic alcohols.....	97
II.3.2.1. Synthesis of some propargylic alcohols.....	102
II.3.2.2. Sonogashira Cross-coupling.....	104
II.3.2.2.1. Sonogashira reaction's mechanism.....	105
II.3.2.2.2. Synthesis of internal alkynes.....	109
II.4. Azides.....	111
II.4.1. Synthesis of organic azides.....	112
II.5. Synthesis of small triazolic derivatives on a solid support catalyst (A-21.CuI).....	113
II.6. Study of anticancer property of synthesized triazoles.....	116
II.6.1. Melanoma.....	116
II.6.2. Some synthesized molecules against B16 melanoma.....	117
II.7. <i>In vitro</i> evaluation of potential anticancer activity of synthesized triazolic Derivatives.....	120
II.7.1. Synthesis of <i>Combretastatin A4</i> analogs containing a triazole core.....	120
II.7.2. Mono- and bis-1,2,3-triazole derivatives of bis-alkynes.....	122
II.7.3. Mono-1,2,3-triazoles derived from terminal alkynes and propargylic alcohols.....	124
II.8. Molecular and bioactivity properties predicted by <i>Molinspiration</i> software.....	127
II.9. Conclusion.....	134

Chapter III : Microwave reactions.....135

III. Introduction.....	137
III.1. Use of microwave in chemistry.....	137
III.2. Solvents in microwave assisted synthesis.....	141
III.3. How does microwave irradiation increase the rate of the chemical reactions ?.....	143
III.4. Different techniques of microwave assisted organic synthesis.....	144
A. Domestic household ovens- 'solvent-free' open vessel reactions.....	144
B. Reflux systems.....	144
C. Pressurized systems.....	145
D. Continuous flow systems.....	145
III.5. Preparation of tri-substituted triazoles.....	146
III.6. Microwave-assisted intra/intermolecular Huisgen cycloaddition of triazoles and alkynes.....	149
III.7. Catalyst- and solvent-free straightforward synthesis of propargylic ethers from carbonates and alcohols under microwave irradiation.....	160
III.7.1. Introduction.....	160
III.7.2. Direct propargylic substitution by Nicholas reaction.....	160
III.7.3. Palladium (0)-catalyzed substitution of propargylic acetates by different nucleophiles.....	161
III.7.4. Copper (I)-catalyzed amination of propargyl esters.....	162
III.7.5. S _N 1-type nucleophilic substitution of propargylic alcohols or acetates promoted by Lewis or Brønsted acids.....	164
III.7.6. Nucleophilic substitution of alcohols with a solid Brønsted acid.....	166
III.7.7. Metal complexes in the activation of alcohols.....	167
III.7.7.1. Ruthenium complexes.....	167
III.7.7.2. Rhenium complexes.....	168
III.7.7.3. Gold complexes.....	170
III.7.8. Direct nucleophilic substitution of alcohols in water.....	171

III.7.9. Direct nucleophilic substitution of propargylic esters under microwave irradiations.....	173
III.8. Conclusion.....	183
Experimental part.....	185

Abbreviations

A	A-21	Amberlyst-21
	A-21.CuI	Copper iodide amberlyst-21
	ABPP	Activity based protein profiling
	ADME	Absorbability, distribution, metabolism and excretion
	AIDS	Acquired immunodeficiency syndrome
	ALPO	Aluminophosphate
	AM1	Austin model 1
	APO	2-amino-3H-phenoxazin-3-one
	Ar	Aromatic
	ARC	AIDS-related complex
	ATRP	Atom transfer free radical polymerization
	AZT	3'-azido-2',3'-dideoxy-thymidine
B	BAL	Backbone amide linker
	BnAz	Benzylazide
	Boc	<i>t</i> -butoxycarbonyl
	BOR	Bestmann-Ohira reagent
	BTC	Benzene-1,3,5-tricarboxylate
	BuLi	Butyllithium
C	CA4	Carbonic anhydrase 4
	cAMP	Cyclic adenosine monophosphate
	CE code	Canadian electrical code
	cGMP	Cyclic guanosine monophosphate
	CPVM	Cowpea mosaic virus
	CuAAC	Copper catalyzed azide-alkyne cycloaddition
D	Da	Dalton
	DBU	1,8-Diazabicycloundec-7-ene
	DCM	Dichloromethane
	DFT	Density functional theory
	DIBALH	Diisobutylaluminium hydride

	DIBO	5'-Dibenzocyclooctyne
	DIPEA	N,N-Diisopropylethylamine
	DMF	Dimethylformamide
	DMSO	Dimethylsulfoxide
	DNA	Deoxyribonucleic acid
	DOS	Diversity oriented synthesis
	DOTA	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid
E	EDG	Electron donating groups
	EtOAc/EA	Ethyl acetate
	EtOH	Ethanol
	EWG	Electron withdrawing group
F	FDA	Food and drug administration
	FP	Fixed power
G	α -GalCer	α -galactosylceramide
	GHz	Giga hertz
H	HDAC	Histone deacetylase
	HDC	Huisgen 1,3-dipolar cycloaddition
	hERG	The human Ether-à-go-go related gene
	HIV	Human immunodeficiency virus
	h-NK1	Human neurokinin 1
	HPLC	High performance liquid chromatography
	HTS	High-throughput synthesis
I	IC ₅₀	Half maximal inhibitory concentration
	IFN- γ	Interferon- γ
	IL-4	Interleukin 4
	im	Imidazole
	IND	Investigation new drug application
	IR	Infrared

K	KA	Kojic acid
	KW	Kilowatt
L	LC-MS	Liquid chromatography-mass spectrometry
	LDBBA	Lithium diisobutyl- <i>t</i> -butoxyaluminium hydride
M	MCR	Multicomponent reaction
	MeCN	Acetonitrile
	MeOH	Methanol
	MHz	Mega hertz
	MIFT	Microphthalmia-associated transcription factor
	MLP	Molecular lipophilicity potential
	MLPCN	Molecular libraries probe production centers network
	MLSMR	Molecular libraries small molecules repository
	MOF	Metal organic frameworks
	mmol	Milimole
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide	
N	NDA	New drug application
	NHC	N heterocyclic carbene
	NIH	National institutes of health
	NMDA	N-methyl-D-aspartate receptor
	NME	New molecular entities
	NMR	Nuclear magnetic resonance
	NP	Nano particles
P	PCR	Polymerase chain reaction
	PEG	Poly ethylene glycol
	PEI	Poly ethylenimine
	PGE ₂	Prostaglandin E ₂
	PhAc	Phenylacetylene

	PKA	Protein kinase A
	PKG	Protein kinase G
	PMEI	Poly(N-methylethyleneimine)
	PNA	Peptidonucleic acid
	PPh ₃	Triphenyl phosphine
	PPI	Protein-protein interactions
	PSA	Molecular polar surface area
	PTP	Protein tyrosine phosphatase
	PVP	Poly(N-vinyl-2-pyrrolidone)
	Pymo	Pyrimidine
Q	QSAR	Quantitative structure-activity relationship
R	R&D	Research and development
	RES	Reticulo endothelial
S	SAR	Structure-activity relationships
	SCK	Shell cross-linked
	SLAS	Society for laboratory automation and screening
	SPAAC	Strain-promoted alkyne-azide cycloaddition
	SPOS	Solid-phase organic synthesis
T	TBTA	Tris(benzyltriazolylmethyl)amine
	TG	TentaGel
	Th2	T helper cell
	THF	Tetrahydrofuran
	TOP	Tandem oxidation processes
	TOS	Target oriented synthesis
	TPSA	Topological polar surface area
	TSAO	<i>tert</i> -butyldimethylsilyl spiroaminooxathioledioxide
U	UV	Ultra violet

V VEGF Vascular endothelial growth factor

W W Watt

General Introduction

- Medicinal Chemistry

- Cancer

Medicinal Chemistry

Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals.¹ During the early stages of medicinal chemistry development, scientists were mostly involved with the isolation of medicinal agents found in plants, but today, they are equally involved with the creation of new synthetic drug compounds, maybe based on newly discovered mechanisms. This development of new synthetic drug compounds is a consequence of the incorporation of many other disciplines, like biochemistry and molecular biology into medicinal chemistry. Medicinal chemistry is always almost adapted toward drug discovery and development.

Medicinal chemists prepare and/or select appropriate active compounds that can be served as *lead compounds* for biological evaluation. In the next step, they analyse the Structure-Activity-Relationships (SARs) of analogous compounds by considering their *in vitro* and *in vivo* efficacy and safety.²

The role of the medicinal chemist has changed drastically during the past 35 years. In the first years of drug discovery (1950 to about 1980) medicinal chemists relied on data from *in vivo* testing. In the more recent period (about 1980 to the present) a lot of changes appears in comparison with the earlier relatively simple landscape. These changes are due to the development of new technologies, such as high-throughput *in vitro* screening, large compound libraries, combinatorial technology, defined molecular targets and structure-based drug design. However these new technologies brought many opportunities to the medicinal chemist, but the multitude of the safety requirements that have arisen has also brought unexpected obstacles for the task of translating *in vitro* activity to *in vivo* activity. Despite the use of many new technologies, and the growing resources and funding for drug discovery, the number of new medicines pioneers in the form of new molecular entities (NMEs) has been generally decreasing for more than a decade.

The process of drug discovery

Inventing and developing new medicines is a long, complex costly and highly risky process. Research and development (R&D) for most of the medicines existing today needed 12-24 years for a single new medicine, from starting a project to the launch of a drug product (**Fig. 1**).² In addition, many expensive, hard and long-term research projects completely failed to produce a marketable

¹Am. Chem. Soc. Division of Medicinal Chemistry, www.acsmedchem.org. ²J. G. Lombardino, J. A. Lowe, *Nat. Rev. Drug Discovery* **2004**, *3*, 853-62.

drug. The cost for this overall process has reached to up to an estimated US \$1.4 billion for a single new drug. All of the financial supports for research in this field usually come from the income of the pharmaceutical company that sponsor the work.

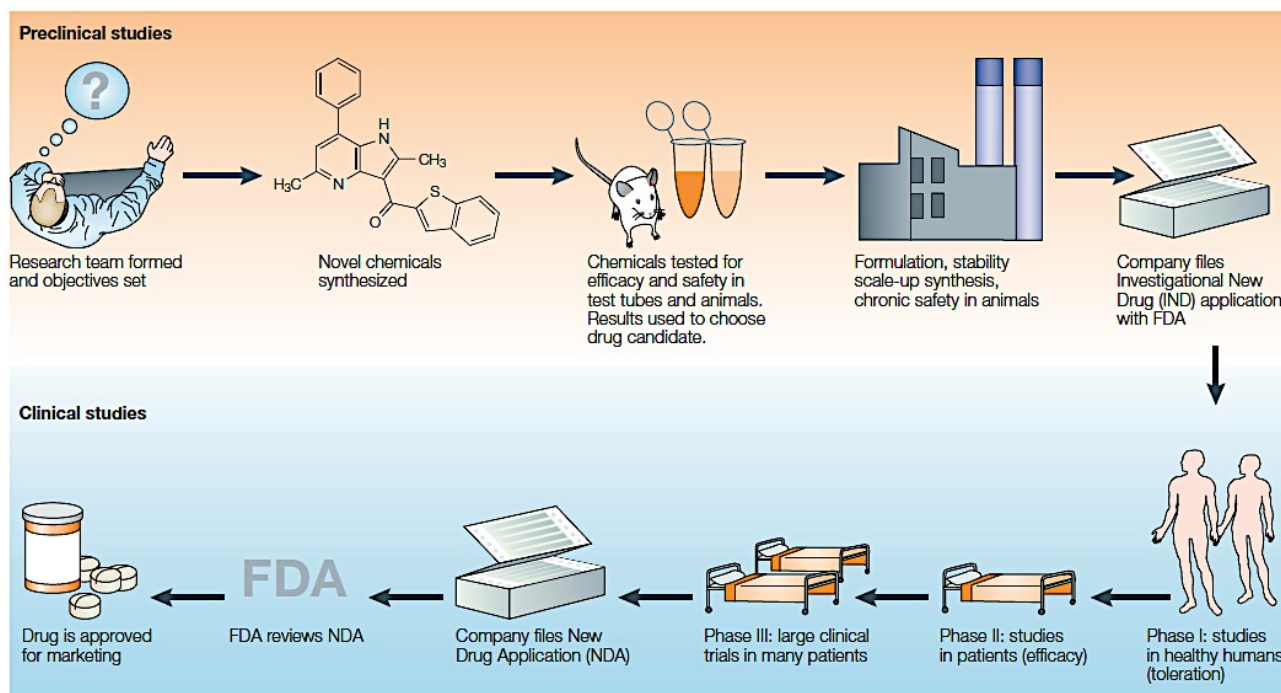


Fig. 1. Different stages in drug discovery. ²

The drug discovery process starts with the identification of a medical need, containing a judgement on the efficacy of existing therapies. From this analysis, together with an evaluation of the present knowledge about the target disease hypotheses will come about how to improve the treatment or therapy. On the basis of these hypotheses, the particular objectives will be established for the project. Then, testing selected chemicals in suitable biological tests can be started. Important following steps in the process is finding applicable biological activity (a ‘hit’) for a structurally novel compound *in vitro*, then finding an equivalent compound with *in vivo* activity in an appropriate animal model, followed by increasing this activity by preparing analogous structures, and finally selecting one compound as the drug development candidate. This drug candidate then undertakes toxicological testing in animals, as required by law. After all of these tests, all the obtained results are gathered and submitted as an Investigation New Drug Application (IND) to the Food and Drug Administration (FDA) in the United States or related agencies in other countries before clinical trials begin. In the clinic, there is subsequent evaluation in normal human volunteers of toleration (Phase I), adequacy and dose range in patients (Phase II), followed by an

extensive assays in thousands of appropriate patients to develop a vast database of efficacy and safety. For the few (4-7%) drug candidates that pass these series of development trials successfully, a New Drug Application (NDA) that includes all the assembled research data is filed for exhaustive review by the experts at the FDA. Only after their approval, these drugs can be offered to doctors and their patients for treat the disease for which it was designed.

The role of the medicinal chemist

In the early phases of drug discovery, the modern medicinal chemist has an especial critical role. The chemist, instructed to prepare new chemicals and with an obtained knowledge of the target disease and of competitive drug therapies, has an important role in shaping the hypothesis for the new drug project, which then arranges the objectives for the project. The chemist helps also to decide which existing chemicals to screen for a lead compound and which screening hits need to be resynthesized for biological evaluation. Another responsibility of a chemist is purification and complete characterization of the new chemicals. Once an *in vitro* 'hit' is identified, the chemist decides on what analogous compounds should be obtained or synthesized in order to explore the SARs for the structural family of compounds to increase the desired activity. Improving *in vivo* activity for the hit compound in a suitable animal model is also a key responsibility of a chemist that can be sometimes the most difficult steps to realize because of several factors, such as absorbability, distribution *in vivo*, rate of metabolism and rate of excretion (ADME). The aim at this stage is to maximize efficacy while minimizing side effects in an animal model.

If we want to compare the tasks of a medicinal chemist between 1950s and 1980s with a today medicinal chemist's tasks, it should be mentioned that, at that time compounds were designed and individually synthesized by the chemist in gram quantities to satisfy the need for testing in whole animals by the pharmacologist. Due to the limited known synthetic methodology, these syntheses were usually time consuming, and commercially available starting materials were also limited. In term of facilities, chemist had only a few tools such as infrared and ultraviolet spectroscopy, and column chromatography to help with compound characterization and purification. All tasks including bulk syntheses, toxicological testing and analogue synthesis were done in-house because of the lack of outsourcing. Despite of these lack of facilities, the creativity and intuition of the medicinal chemist was crucial to the success of the program. For primary screening, projects used

generally *in vivo* models, because knowledge of detailed biological mechanisms involved in most diseases was not enough. *In vitro* testing against a key enzyme or a special receptor involved in the disease process was not usually possible. It was in the 1980s and 1990s that *in vitro* receptor-based pharmacology only become common. In addition, compound collections were limited to explore biological screening, and the data obtained from the test models were assembled, analysed and presented by hand in the form of charts and graphs. For these reasons, the process of drug discovery was slower and performed from a relatively smaller knowledge base. Shortly, several factors collaborated to slow the process: lack of knowledge about diseases, fewer available compounds to screen, no computerized technology to manage information and data, a need to manually search the literature, necessity to individually prepare gram quantities of each new compound for testing, and chemists hardly received information from other disciplines about their development candidates. On the other hand, when a lead was identified in the primary *in vivo* test model, there were a lot of pharmacokinetic (ADME) problems that could be rapidly addressed.

In spite of some differences from the earlier era of drug discovery described above, medicinal chemists today experience many of the same tasks and challenges that they did 50 years ago. In a way that, the chemist still chooses the suitable structural series of compounds to follow and investigates the SARs to indicate appropriate drug candidates for evaluation to safety and clinical testing. But we cannot forget that, today's chemist has much more facilities and tools to overcome the numerous obstacles in the drug discovery process. These new tools include improvements in synthetic, analytical and purification technology, like transition-metal-catalysed carbon-carbon bond-forming reactions, high-field NMR, and preparative high-performance liquid chromatography (HPLC), as well as computer-assisted literature and data improvement and analysis. In addition, appearance of powerful technologies like combinatorial chemistry and high-throughput synthesis (HTS) was another help in drug discovery. Combinatorial chemistry helps chemists to make reasoned and focused libraries of compounds that identify SARs in a short time. By these means, they can also generate lead-compound libraries that target a key receptor or enzyme families in order to supply better quality leads that are suitable for library investigations. In the other hand, the development of HTS of large sample compounds, containing the designed libraries, has decreased required time and money needed to determine compounds that hit a special target. Finally new graphics software can facilitate the improvement and analysis of the pile of data obtained from screening compound libraries in a large board of *in vitro* tests.

Another element that has a positive influence in drug discovery process was the molecular genetics revolution,³ like the application of enzymes, receptors and transporters as molecularly defined biological targets.

Why defined molecular targets for drug discovery? In contrast to the approach used in the beginning era of drug discovery which was clinically based animal model, the desire for defined molecular targets results from several points; first the advantage of a known mechanism of action over an unknown mechanism obtained from animal-model testing that could produce unwanted toxicity during drug development; second, the use of structure-based drug design, that lets the chemist design new compounds by directly imagining the interaction of a lead compound with the target protein by X-ray crystallographic analysis that is only possible with a molecularly defined target protein.⁴

New techniques to facing pharmacokinetic problems

The importance of *in vitro* screening of compounds against molecularly determined targets, whilst fast and specific has additional results for today's medicinal chemist. Only relying on *in vivo* obtained results on animal models for the assessment of pharmacokinetic behaviour could have some disadvantages like that differences between absorption and metabolism of drugs in humans and rats which is a common test species. This can result to the development of drugs that work only in rats and not in humans. In that order, *in vitro* screens have been developed to overcome this limitation. This method can predict human pharmacokinetic performance, for example, by measuring a compound's degradation by producing human microsomes or hepatocytes or by recombinant human cytochrome P450 enzymes. P450 tests can not only evaluate metabolic stability, but also they can define if a compound is capable to prevent the metabolism of other drugs that a patient is taking in order to inhibit the P450 enzyme needed for their elimination. Another *in vitro* assay is the permeability and transporter tests that have been developed to identify drug uptake into or efflux from the target organ(s).⁵ So, today's chemist has a complex array of *in vitro* SAR models to design the production of compounds to pursue.⁶ Selected compounds need further *in vivo* testing to prove that the compound achieves levels at the target organ as well as achieving the desired biological effect that is expected to result from the *in vitro* activity. Final testing might require a disease which is closely related to the animal-model. However these data must be

³S. K. Chanda, J. S. Caldwell, *Drug Discov. Today* **2003**, 8, 168-74. ⁴S. H. Reich, S. E. Webber, *Drug Discov. Design* **1993**, 1, 371-90. ⁵J. H. Lin, M. Yamazaki, *Clin. Pharmacokinet.* **2003**, 42, 59-98. ⁶J. Lin, D. C. Sahakian, S. M. F. Morais, J. J. Xu, R. J. Polzer, S. M. Winter, *Curr. Top. Med. Chem.* **2003**, 3, 1125-54.

surveyed attentively due to some limitations. For example, many diseases, such as stroke, atherosclerosis and Alzheimer's disease, do not have clinically effective drugs that can validate a disease-progression-relevant animal model. In addition, former models are based on drugs working by specific mechanisms. So, the disease-relevant animal-model is only one of many tests used to assess new compounds and that comes later in the testing sequence with less effect on decision made by today's chemist.

Synthesis of 'drug-like' compounds: is another way to diminish pharmacokinetic problems. Highly lipophilic, high-molecular-mass compounds can have more effect *in vitro* binding activity, in order to eliminate water from the enzyme or receptor surface and so improving additional hydrophobic interactions. But the synthesized compounds are usually not drug-like because of their poor water solubility, and they generally fail in further development because of poor pharmacokinetics and oral bioavailability.

Employment of in vitro toxicity screens to reduce attrition: another method that help to select the next compound to synthesize in addition of *in vitro* screens is the toxicity tests that eliminate compounds predicted to fail for safety reasons. Among the ancient used *in vitro* tests for mutagenicity and carcinogenicity can mention the Ames test that has a long history, but recent addition to these tests is the hERG channel, a cardiac potassium ion channel involved in cardiac repolarization following ventricle contraction during the heartbeat.⁷ Drugs that bind to this channel and inhibit it can cause prolongation of the QT interval of the electrocardiogram, and result the loss of a synchronous heartbeat and eventually ventricular fibrillation, and even death. An example is the allergic rhinitis drug astemizole (Hismanal; Janssen) that was taken by patients and caused their deaths because of inhibition of the hERG channel, which led to its immediate withdrawal from the market.⁸ Due to this and other happenings of deadly complications from hERG blocking drugs, the FDA is making guidelines to overcome the problem. In that order, most pharmaceutical companies now have hERG screening in place to provide chemists a hint of the therapeutic index of their compounds for this end point.⁹ Different factors that today's chemist must follow to develop a successful drug candidate have been summarized in box 1.

⁷G. N. Tseng, *J. Mol. Cell. Cardiol.* **2001**, 33, 835-49. ⁸M. Tagliatela, P. Castaldo, A. Pannaccione, G. Giorgio, A. Genovese, G. Marone, L. Annunziato, *Clin. Exp. Allergy* **1999**, 29, 182-9. ⁹W. S. Redfern, L. Carlsson, A. S. Davis, W. G. Lynch, I. Mackenzie, S. Palethorpe, P. K. S. Siegl, I. Strang, A. T. Sullivan, R. Wallis, *Cardiovasc. Res.* **2003**, 58, 32-45.

BOX 1. ²*In vitro* tests; ‘now’ and ‘then’

The following is a typical battery of tests for a modern drug discovery program ‘today’; those marked with an asterisk were also in use ‘then’.

In vitro target

- Primary
- Whole cell
- Functional
- Selectivity assays

In vitro absorption, distribution, metabolism and elimination (ADME)

- Microsomal stability
- Hepatocyte stability
- P450 substrate
- P450 inhibitor
- Permeability
- Transporter efflux (for example, P-glycoprotein)
- Protein binding

BOX 1. ²*In vitro* tests; ‘now’ and ‘then’

Physical properties

- Rule of five (explained in the last second chapter of this dissertation)
- *In silico* ADME

In vivo

- Functional
- *Secondary (behavioural, chronic)

Toxicity

- *Ames test
- Micronucleous test
- hERG half-maximal inhibitory (IC₅₀)
- P450 induction
- Broad screening
- *Others (depending on project)

By having backgrounds in our research group, we also work on medicinal chemistry and synthesis of biologically active small molecules. Our objective for this Ph.D. project was synthesis of a bank highly diversified small molecules following by study their activity against cancer cells like B16 melanoma cell line that we will speak in detail about them in the second chapter.

Here is worth to explain a little about cancer and its causes.

Cancer

Cancer is a term used for diseases in which abnormal cells divide without any control and are able to attack other tissues.¹⁰ Cancer is not just one disease but a group of more than 200 different diseases. The name of a cancer comes mostly from the organ or type of cell in which they start, for example, cancer that begins in the colon is named colon cancer or cancer that begins in melanocytes of the skin is called melanoma.

The main categories of cancer include:

- **Carcinoma;** which refers to the type cancer that starts in the skin or in tissues that cover internal organs. There are a number of subclasses of carcinoma, such as adenocarcinoma, basal cell carcinoma, squamous cell carcinoma, and transitional cell carcinoma.
- **Sarcoma;** cancer that starts in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue.
- **Leukemia;** cancer that begins in blood-forming tissue such as the bone marrow and causes large numbers of abnormal blood cells to be produced and enter the blood.
- **Lymphoma and myeloma;** cancers that begin in the cells of the immune system.
- **Central nervous system cancers;** that begin in the tissue of the brain and spinal cord.

Origins of cancer

All cancers start in cells that is the body's basic unit of life. To understand cancer, one should know how normal cells become cancer cells.

The body is made up of different kinds of cells which grow and divide in a controlled manner to produce more cells as they are needed to keep the body healthy. When cells become old or damaged, they die and are replaced by new ones. But, sometimes this well ordered process goes wrong. The genetic material (DNA) of a cell can become damaged or changed, and producing mutations that can have an effect on normal cell growth and division (**Fig. 2**). Once this takes place, cells do not die when they should and new cells form when the body does not need them. These extra cells then may form a mass of tissue called a tumor.

¹⁰What is cancer? –National Cancer Institute; www.cancer.gov/cancertopics/cancerlibrary/what-is-cancer

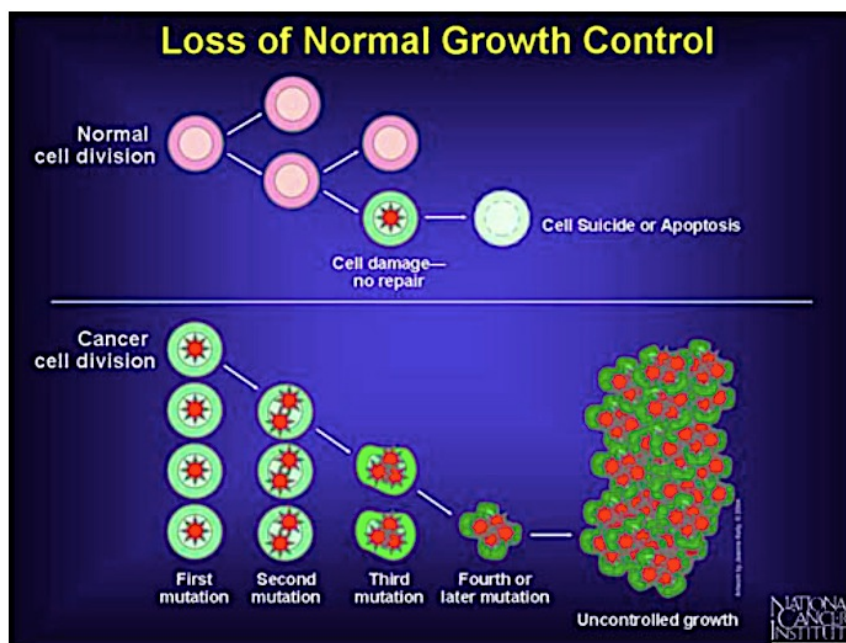


Fig. 2. Process through which a normal cell converts to a cancer one.¹⁰

But it should be mentioned that, all the tumors are not cancerous. Tumors can be either benign or malignant.

- **Benign tumors** are not cancerous. They can often be removed, and in most cases, they won't come back.
- **Malignant tumors** are the class cancerous tumors. In this case, cells can attack nearby tissues and spread to other parts of the body. The spread of cancer from one part of the body to another is called metastasis. But all of the cancers do not form tumors, like leukemia.

Some causes of cancers

Different factors can cause cancer depending on the type of the cancer. Some cancers are more common than others, and chances for survival differ among different types. Most cancers do not have known causes from a chemical, environmental, genetic, immunologic, or viral origin. They can be resulted from the unexplained causes. The causes of cancer are very complicated, containing both the cell and factors in the environment.¹¹ Possible causes of cancer include:

Chemicals and other substances. Substances such as certain chemicals, metals, or pesticides are toxic and being exposed to them can increase the risk of cancer. Chemicals that known to cause a cancer are called carcinogen. Asbestos, nickel, cadmium, uranium, radon, vinyl chloride, benzidine,

¹¹Agency for Toxic Substances and Disease Registry (ATSDR)-Community Matters-Cancer Fact Sheet.

and benzene are examples of well-known carcinogens. These chemicals can act alone or in company with another carcinogen, like cigarette smoke, to increase the risk of cancer. For example, inhaling asbestos fibers increases the risk of lung diseases, including cancer, and this risk is especially higher for asbestos workers who smoke.

Tobacco. The most common carcinogens in today's society are those present in cigarette smoke. It is known that tobacco smoke contains at least 60 carcinogens and 6 developmental toxicants. It is not only responsible for 80 to 90 percent of lung cancers, but is also associated with cancers of mouth, pharynx, larynx, esophagus, pancreas, kidney, and bladder. So preventing tobacco products is one way decrease a person's risk of cancer.

Ionizing radiation. Some kinds of radiation, such as x-rays, rays from radioactive substances, and ultraviolet rays from exposure to the sun, can produce damage to the DNA of cells, which might lead to cancer.

Heredity. Some types of cancer occur more frequently in some families than in others, showing some inherited liability to the development of cancer. Even in these cases, environment plays a part in the development of cancer.

How cancer develops

Cancer can develop in people of all ages, but it is more common in people over 60 years old. It is estimated that, one out of every three people will develop cancer at some point in their lives. People are now living longer, the risk of developing cancer is increasing. The development of cancer is a long process that is usually starts with genetic changes in the cells, and continues in the growth of these cells over time. The time from genetic change to development of cancer is called the latency period. This period can be as long as 30 years or more. This means that some identified today can be due to genetic changes that happened in the cells a long time ago. Theoretically, the body develops cancer cells continuously, but the immune system recognizes them as foreign cells and destroys them. The body's ability to protect itself from cancer can be diminished by some drugs and viral infections.

Environmental toxicants

This type of toxicants are classified by the National Toxicology Program as both known human carcinogens and rationally considered to be human carcinogens to discriminate the level of evidence

available to support the carcinogenicity of a possible toxicant. Carcinogens include a wide variety of synthetic and naturally occurring substances, containing hormones, immunosuppressants, organic and inorganic chemicals, and cytotoxins. It is difficult to study populations that live near a risky waste site and ascertain if there is a relation between their cancer and exposures. A key problem for those studying these populations is the lack of knowledge of the exact level of individual exposure to a carcinogenic agent. In addition, waste sites contain normally more than one chemical, which makes it difficult to associate health outcomes to a single exposure. Because of the long latency period of cancer development and the type of behavioral risk factors associated with cancers (such as tobacco use, alcohol consumption, and diet), it is difficult to collect information about environmental exposures that occurred years ago.

Cancer statistics worldwide¹²

The highest cancer rate for men and women together was found in Denmark with 338 people per 100,000 being diagnosed in 2012. The age-standardised rate was at least 300 per 100,000 for nine countries (Denmark, France, Australia, Belgium, Norway, United States of America, Ireland, Republic of Korea and The Netherlands). The countries in the top ten come from Europe, Oceania, Northern America and Asia.

- There were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer (within 5 years of diagnosis) in 2012 worldwide. 57% (8 million) of new cancer cases, 65% (5.3 million) of the cancer deaths and 48% (15.6 million) of the 5-year prevalent cancer cases occurred in the less developed regions.¹²
- The types of cancer that are or will be on the rise vary by a country's development status. In the U.S., for example, rates of obesity-related cancers such as breast cancer and colon cancer are projected to rise. The U.S. is also still facing the lingering-effects of smoking-related cancers. In poorly developed countries such as sub-Saharan Africa, rates of cancers that are related to infection are high. These include cervical cancer, liver cancer, and stomach cancer.

So the urgent need to discover new drugs toward treatment of different cancer cells, forces chemists to find new facile synthetic methodologies in order to prepare biologically active diverse molecules

¹²J. Ferlay, I. Soerjomataram, M. Ervik, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D. M. Parkin, D. Forman, F. Bray, *Globocan 2012, v 1.0*, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: <http://globocan.iarc.fr>, accessed on 13/12/2013.

in a short time.

As is already mentioned, in our chemists group, we are also focused on the synthesis of molecules with interesting biological activity. In that order, for this project, we decided to prepare a bank of small molecules based on terminal alkynes and propargylic alcohols. These alkynes were then subjected into a 1,2,3-dipolar Huisgen cycloaddition reaction which is a part of what is known as *Click Chemistry* to find triazolic derivatives. The choice of triazolic derivatives results from our previous results and synthesized triazolic core structures for which we could find biological activities against cancer cells notably B16 melanoma cell line.

These studies will be explained through the next chapters.

Chapter I

Diversity Oriented Synthesis and Click Chemistry

I. INTRODUCTION

Small molecules usually refer to orally bioavailable compounds that have a molecular weight of less than 1500 Da¹³ and they are dissimilar from naturally occurring biological molecules like DNA, RNA and proteins.¹⁴ This fact that small molecules interact with biological macromolecules and proteins and exert special effects in a selective and dose dependent manner make them considered as a powerful tools to study and manipulate biological systems.¹⁵ The application of small molecules to manipulate biological function deliberately and selectively construct the fields of medicinal chemistry in the way that molecules are used to treat a disease, and also chemical genetics where small molecules are used as a probe to study biological systems.^{13,16,17} So finding small molecules with these characteristics is a real challenge. When the biological target is known and understood, the design of ligand is possible, especially when the structure of the native ligand or its single protein target is known,^{15b} but for less known disease states or when a novel mode of binding or biological target is researched, it is impossible. In this case High-Throughput Screening (HTS) of small-molecule libraries can provide an effective solution.¹⁸ This method has been used traditionally in pharmaceutical industries in order to find bioactive small molecules.¹⁹ Chemical genetics also screens large compound collections in phenotypic analysis to determine compounds with biological effect.^{16,17} HTS of functionally diverse compound collections is becoming a powerful method for finding chemical probes of biological function and also lead compounds for drug development.^{19a, 20} Making libraries of functionally diverse compound has become an important field in organic chemistry, which is known as ‘Diversity Oriented Synthesis’ (DOS) that used to synthesize, structurally complex small molecules in an efficient manner.^{15b, 21}

I. 1.1. Source of small molecules for use in biological screens:

- **Natural products.** Traditionally, this class of products has been used as a valuable source of leads in drug development, especially in the field of cancer therapeutics and anti-infective agents.²²⁻²³ However natural products represent a vast pool of structural diversity, but there are some difficulties with them, such as access and supply, purification, identification, chemical

¹³B. R. Stockwell, *Nat. Rev. Genet.* **2000**, *1*, 116-125. ¹⁴S. L. Schreiber, *Nat. Chem. Biol.* **2005**, *1*, 64-66. ^{15a}M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58. b) D. S. Tan, *Nat. Chem. Biol.* **2005**, *1*, 74-84. c) W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Chem. Commun.* **2009**, 2446-62. ¹⁶D. R. Spring, *Chem. Soc. Rev.* **2005**, *34*, 472-482. ¹⁷C. J. O’Connor, L. Laraia, D. R. Spring, *Chem. Soc. Rev.* **2011**, *40*, 4332-45. ¹⁸W. P. Walters, M. Namchuk, *Nat. Rev. Drug Discov.* **2003**, *2*, 259-266. ^{19a}R. Macarron, M. N. Banks, D. Bojanic, D. J. Burns, D. A. Cirovic, T. Garyantes, D. V. S. Green, R. P. Hertzberg, W. P. Janzen, J. W. Paslay, V. Schopfer, G. S. Sittampalam *et al.*, *Nat. Rev. Drug Discov.* **2011**, *10*, 188-195 b) J. A. Frearson, I. T. Collie, *Drug Discov. Today* **2009**, *14*, 1150-58. ²⁰M. Ricardo, *Drug Discov. Today* **2006**, *11*, 277-79. ²¹S. L. Schreiber, *Science* **2000**, *287*, 1964-69. ^{22a}D. J. Newman, G. M. Cragg, *J. Nat. Prod.* **2007**, *70*, 461-77. b) J. W. –H. Li, J. C. Vederas, *Science* **2009**, *325*, 161-5. ²³A. L. Harvey, *Drug Discovery Today* **2008**, *13*, 894-901.

modification of these often extremely complex structures.^{22b, 23}

- **Commercial compound collections.** Another sources for small molecules are commercially available libraries and pharmaceutical compound collections. This class of compounds has been highly used towards traditional drug targets like GPCRs, ion channels and kinases areas²⁰ but they are less successful in screening against non-traditional targets such as PPIs (Protein-Protein Interactions). The scaffold diversity of small molecules prepared by combinatorial chemistry program showed that 83% of the core ring scaffolds found in natural products are absent between commercially available compounds.²⁴ Another problem with commercially available libraries is the low stereochemical complexity, containing few stereogenic centers and a high proportion of sp²-hybridized carbon atoms.²⁵ Because of these mentioned limitations, commercially available small molecules are not a good source for undruggable targets; in that order another class of small molecules prepared by “Diversity Oriented Synthesis” have been applied.

I.1.2. What is Diversity Oriented Synthesis?

In the year 2000, Stuart Schreiber introduced for the first time the term Diversity Oriented Synthesis (DOS) in a paper.²¹ This article was focused on drug discovery where the term was used to differentiate between compound libraries (or single compounds), which were synthesized to interact with preselected protein targets [called Target-Oriented Synthesis (TOS)] and (or) those libraries to identify at the same time therapeutic protein targets and their small molecule regulators.²¹ As Schreiber said, DOS library should contain high levels of structural diversity in the compound collection, however for TOS compounds, as the preselected target is known only some degree of rational design being applies. Another definition for DOS, which was introduced later by D. R. Spring was that “ Diversity-Oriented Synthesis involves the deliberate, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem”.²⁶ These two definitions demonstrate that by use of DOS large areas of chemical space including both known and original regions of bioactive chemical space can be explored. Another characteristic of DOS libraries is that complex molecules are usually prepared in no more than 5 synthetic steps in an efficient and modular way.

²⁴J. Hert, J. J. Irwin, C. Laggner, M. J. Keiser, B. K. Shoichet, *Nat. Chem. Biol.* **2009**, *5*, 479-83. ²⁵P. A. Clemons, N. E. Bodycombe, H. A. Carrinski, J. A. Wilson, A. F. Shamji, B. K. Wagner, A. N. Koehler, S. L. Schreiber, *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 18787-92. ²⁶D. R. Spring, *Org. Biomol. Chem.* **2003**, *1*, 3867-70.

I.1.2.1. Comparing DOS, TOS, and combinatorial Chemistry

Fundamental aim in DOS is achieving a collection of small molecules with high skeletal diversity, which can interrogate large areas of chemical space, however in TOS (of natural and unnatural products) and focused library synthesis (combinatorial chemistry), from the beginning a target structure(s) is in mind, then these structures are broken down into simpler starting materials and building blocks through a retrosynthetic analysis, but a DOS pathway is analysed in the *forward* sense, in a way that, a simple starting material is converted into a collection of structurally diverse small molecules, usually in no more than five synthetic steps. DOS libraries are usually smaller in size compared with commercially available (combinatorial) libraries, but molecules are structurally more complex and have a greater diversity of core scaffolds that lead to a greater overall coverage of chemical space (**Fig. 3**).²⁷

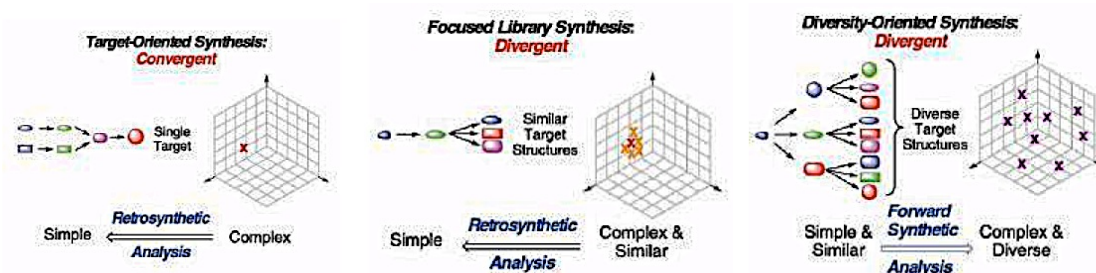


Fig. 3. Planning strategies and end goals involved in target-oriented synthesis, focused library synthesis (combinatorial synthesis), and diversity-oriented synthesis. The first two approaches use retrosynthetic analysis to design the synthesis of target compounds. DOS uses forward synthetic analysis to produce libraries that occupy diffuse regions of chemical space.²⁸

I.1.2.2. Molecular Diversity

There are four kinds of molecular diversity that have been emphasized in the literature:

- 1) Appendage or building block diversity: in which variation exists around a common skeleton or variation of R groups around a single skeleton.
- 2) Functional group diversity: variation of the existing functional groups in a molecule or at specific sites in the gross structures, which increase interactions with different polar, apolar, or charged groups existing in biological macromolecules.
- 3) Stereochemical diversity: variation in the orientation of functional groups and potential

²⁷a) W. R. J. D. Galloway, D. R. Spring, *Exp. Opin. Drug Discov.* **2009**, *4*, 467-72. b) S. Borman, *Chem. Eng. News: Sci. Technol.* **2004**, *82*, 32-40.

²⁸K. M. O'Connell, W. R. J. D. Galloway, D. R. Spring, *Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, drug Discovery, and Chemical Biology*, 1st Edition. Ed. A. Trabocchi: © 2013 John Wiley and Sons, Inc. Published 2013 by John Wiley and Sons, Inc.

macromolecule-interacting elements. As nature is a three-dimensional environment, this characteristic is so important.

4) Skeletal (scaffold) diversity: variation in ring structures and other rigidifying elements, in an other word, variation in the overall molecular framework, which results in molecules with specific scaffolds and clear (definite) molecular shapes.

It is worth highlighting that the most fundamental factor of a small molecule, which control its biological effects is the overall shape of a small molecule. As it's mentioned before, nature sees molecules as three-dimensional (3D) surfaces of chemical information, therefore, a biological macromolecule will interact only with those small molecules that have a complementary 3D binding surface.²⁹ For that, it is a given biological macromolecule that imposes a shape selection for binding partners, so it is expected that molecules possessing shape similarities cause similar pharmacological responses,³⁰ therefore the most fundamental indicator of general functional diversity is the *molecular shape diversity* of a small-molecule library. Compounds in libraries with different molecular skeletons will demonstrate chemical information differently in 3D space, which lead to a high possible biological binding partners.^{29b}

To provide a basically and interpretable comparison of the relative molecular diversity existing in different compound collections, Spandl *et al.* proposed to consider molecular diversity as a spectrum.³¹ At one extreme the synthesis of a single compound that occupy a single point in chemical space, and at the other extreme, where all of the possible chemical space coverage is achieved (**Fig. 4**). Upon this spectrum, the goal of DOS is to synthesize quantitatively small molecule libraries toward the right-hand side of the spectrum. What can be understood from this presentation of molecular diversity in a sliding scale is that, DOS libraries should be notably more diverse than their traditional combinatorial collections.

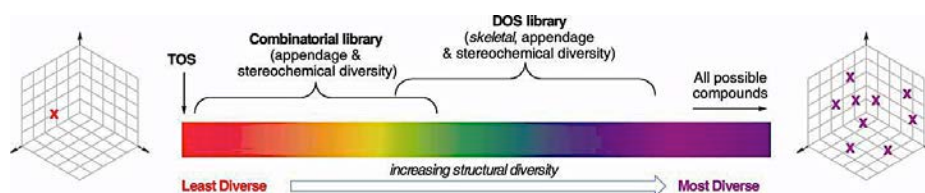


Fig 4. The 'molecular diversity spectrum'. In qualitative terms, diversity can be viewed as a spectrum ranging from a TOS to the synthesis of all possible molecular entities. Traditional combinatorial chemistry, where diversity primarily arises from building block variation, and DOS, where skeletal diversity is also incorporated, produce compound collections between these two extremes.³¹

²⁹a) M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58. b) W. R. J. D. Galloway, A. Bender, M. Welch, D. R. Spring, *Chem. Commun.* **2009**, 2446-62. c) M. D. Burke, E. M. Berger, S. L. Schreiber, *Science* **2003**, *302*, 613-18. ³⁰J. A. Haigh, B. T. Pickup, J. A. Grant, A. Nichols, *J. Chem. Inform. Model.* **2005**, *45*, 673-84. ³¹R. J. Spandl, A. Bender, D. R. Spring, *Org. Biomol. Chem.* **2008**, *6*, 1149-58.

I.1.2.3. Skeletal Diversity

Two possible ways to achieve skeletal diversity are: 1) departing from a common starting material and using different reagents. This ‘reagent-based approach’ is also known as a branching pathway. 2) Another pathway is ‘substrate-based approach’, where different starting materials containing a convenient pre-encoded skeletal information are used in the presence of a common set of conditions, which lead to different skeletal outcomes (**Fig. 5**).³²

Successful DOS processes were suggested in a review by utilizing these two approaches in different ways: 1) the use of a variant functionality, in this way the same part of a molecule is subjected to different transformations caused by different reagents; 2) the use of a densely *functionalized molecule*, where different functionalities in the same molecule are transformed by different reagents (*i.e.* pairing different parts of the same densely functionalized molecule); or, (3) the use of a *folding process*, where different structurally encoding elements (σ), contained in different substrates, are subjected to the same reaction conditions (*i.e.* pairing same parts of different densely functionalized molecules).

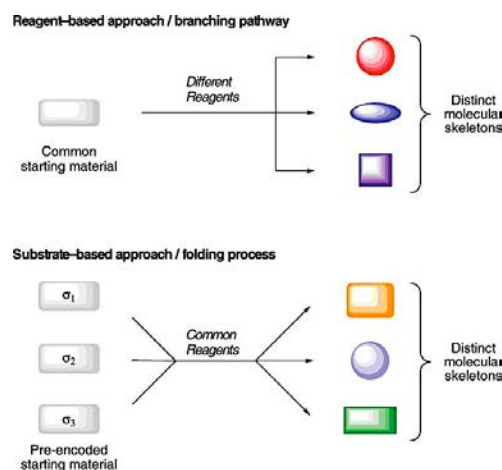


Fig. 5. Generalized methods for achieving skeletal diversity.³¹

I.1.3. Screening Small Molecules For Biological Activity

In recent years, DOS has developed the construction of diverse compound libraries; however making a library containing diverse small molecules covering total chemical space remains still

³²M. D. Burke, E. M. Berger, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 14095-14104.

idealistic. Additionally, in order to appraise biological activity of these libraries, academic labs limited their synthesis around a limited structure, so there are only a small number of biological targets, which have been tested to find high bioactive diversity and their full potential remains underexplored; in that order, national and international compound banks and screening campaigns try to find a solution for these both problems. A large number of drug discovery and chemical genetics programs can be screened by organizing diverse collections, which lead to a large compound collection of high bioactivity diversity.

HTS in drug discovery has been employed by pharmaceutical industry and biological companies for decades.^{29, 33} Nowadays, a large number of academic labs has the possibility to perform medium- to high-throughput screening programs and this can be due to the availability of commercial compound collections and advancement in automated instrumentation and concerning system software.^{19b}

85 academic screening facilities were been listed by the Society for laboratory Automation and Screening (SLAS) (**Fig. 6**). Over half of these facilities are located in US (<http://www.slas.org>). Many of these listed facilities working together in screening networks in order to increase their screening capabilities by pooling resources. As an example, the US National Institutes of Health (NIH) built the Molecular Libraries Small Molecules Repository (MLSMR) that collected 400,000 compounds from different sources, including academic groups (<http://mlsmr.glp.gov>). This compound collection is the main source for a full-scale screening program administered by the Molecular Libraries probe Production Centers Network (MLPCN). This network is composed of nine US institutions and each of them has different screening capabilities (<http://mli.nih.gov/mli/mlpcn/mlpcn>). In Europe networks also exist with screening facilities and support services such as ChemBioNet (<http://www.chembionet.info/>) and the UK Drug Discovery Consortium (<http://www.ukddc.org/>). These networks were been designed to support chemical biology programs for the development of bioactive small molecules. The EU-OPENSREEN campaign is another network (a pan-European network) connecting high-throughput screening centers, chemical libraries, medicinal chemistry facilities for hit optimization, informatics support and a central database (<http://www.eu-openscreen.eu/>).

³³J. T. Heeres and P. J. Hergenrother, *Chem. Soc. Rev.* **2011**, *40*, 4398-4410.

Success of these networks in constructing new leads for drug discovery will increase diversification of the compound collections and also variety and robustness of biological assays available for screening, against the increase in academic screening networks.³⁴

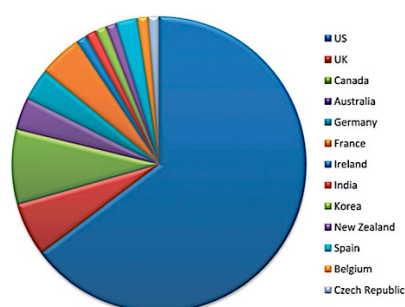


Fig. 6. Geographical distribution of academic screening centres.

I.1.4. Discovering bioactive small molecules using DOS

Both academic and industrial drug discovery initiatives depend on screening large compound collections for activity against biological targets. However, there is a huge advancement in genomics and proteomics, but only 500 genes in a total of 20,000 genes are disposed to small molecule modulation.³⁵ Identification of small molecule modulators which are known challenging therapeutic targets will be increased by developments in library construction and assay improvement. In that way, druggable molecules can be reidentified. Examples like PPIs better show the ability of DOS as a tool for discovering active biomolecules.³⁴

I.1.4.1 Protein-protein interactions (PPIs)

Protein-protein Interactions are one of the fundamental biological interactions, which supervise profound cellular functions including DNA replication and repair, intracellular communication and programmed cell death (apoptosis). If PPIs don't act as well, it can cause plenitude of diseases, and because of that they are interesting targets for therapeutic interference.³⁶ However, some difficulties with PPIs as a drug target exist, but several methods have been used to find highly strong molecule modulators.^{36,37} By screening DOS libraries some examples of small molecule

³⁴C. J. O'Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 4444-56. ³⁵K. -H. Altmann, J. Buchner, H. Kessler, F. Diederich, B. Krautler, S. Lippard, R. Liskamp, M. K. E. M. Nolan, B. Samori, G. Schneider, S. L. Schreiber, H. Schwalbe, C. Toniolo, C. A. A. Van Boeckel, H. Waldmann, C. T. Walsh, *Chem. Bio. Chem.* **2009**, *10*, 16-29. ³⁶M. R. Arkin, J. A. Wells, *Nat. Rev. Drug Discov.* **2004**, *3*, 301-17. ³⁷a) J. A. Wells, C. L. McClendon, *Nature* **2007**, *450*, 1001-9. b) G. Zinzalla, D. E. Thurston, *Future Med. Chem.* **2009**, *1*, 65-93. c) A. K. Franz, J. T. Shaw, Y. Tang, in *Protein Surface Recognition: Approaches for Drug Discovery*, Ed. E. Giralt, M. W. Pecuh and X. Salvatella, Wiley, Chichester, **2011**, p. 1938.

modulators have been found such as inhibition of the sonic hedgehog signaling pathway, inhibiting members of Bcl-2 family, DNA damage checkpoint inhibitors, antibiotics, histone deacetylase (HDAC) inhibitors (**Fig. 7**).

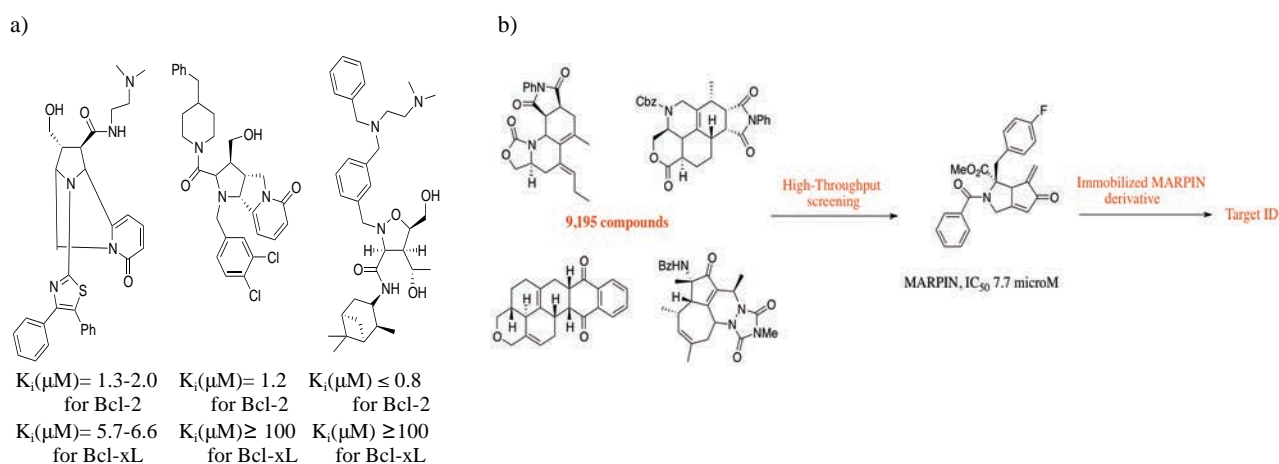


Fig. 7. a) Small molecule modulators of Bcl-2 family proteins.³⁸ b) Screening of DOS library identified a novel DNA checkpoint inhibitor, MARPIN.³⁹

I.1.5. Diversity Oriented Synthesis and Chemical space

As it is already mentioned in previous pages, DOS collections cover larger areas of chemical space in comparison with traditional combinatorial chemistry. Despite of TOS where the aim is to populate a specific area of interest that lead to a focused library, with DOS we try to expand chemical area in a diverse and non-focused manner.

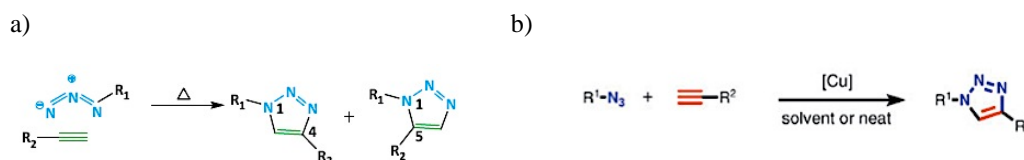
By keeping the concept of DOS in mind, for this thesis project, in order to diversify our organic molecules and study their biological activities, we applied 1,3 dipolar cycloaddition of an organic azide and a terminal alkyne, which is known as 'Click Chemistry'. In the following section, this reaction and its mechanism will be discussed completely. Some applications of Click Chemistry in Drug Discovery will also be detailed.

³⁸a) L. A. Marcaurelle, C. Johannes, D. Yohannes, B. P. Tillotson, D. Mann, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2500-3. b) United States Pat. 7851637, **2010**. ³⁹D. M. Huryh, J. L. Brodsky, K. M. Brummond, P. G. Chambers, B. Eyer, A. W. Ireland, M. Kawasumi, M. G. LaPorte, K. Llyod, B. Manteau, P. Ngheim, B. Quade, S. P. Seguin, P. Wipf *et al.*, *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 6757-62.

I.2. Click Chemistry

By looking at natural product's structures, one can observe a preference of carbon-heteroatom bonds over carbon-carbon bonds, such as proteins, nucleic acids, and polysaccharides. Among the chemical reactions, 1,3-dipolar cycloaddition reaction of 1,3-dipole with a dipolarophile has been taken as the most convenient way to obtain different (simple, fused or strained) five membered heterocyclic skeleton containing molecules of great chemotherapeutic value.

Synthesis of 1,2,3-triazoles by 1,3-dipolar cycloaddition was the first heteroatomic cycloaddition reaction, which was discovered by Michael at the end of the 19th century. This reaction was then improved by Huisgen in the 1960s by using an organic azide and a terminal alkyne.⁴⁰ Huisgen proposed a thermal condition, which affords a mixture of two regioisomers 1,4- and 1,5-disubstituted 1,2,3-triazole (**Scheme 1**, a). Finally in 2001, this initiative study of Huisgen has been completed by two independent research groups of Meldal^{41a} and Sharpless^{41b} where they proposed a catalytic version of this reaction in the presence of copper (I), so the reaction could be performed at room temperature (**Scheme 1**, b).



Scheme 1. ^{a)} Huisgen's proposed Thermal 1,3-dipolar cycloaddition reaction of organic azides and terminal alkynes. ^{b)} Copper catalyzed azide-alkyne cycloaddition (CuAAC).

The term 'Click' was attributed for the first time by K. B. Sharpless in 1999 before the discovery of Cu(I)-catalyzed azide-alkyne cycloaddition reaction, which describes those reactions that are highly efficient, high yielding, regioselective, modular, wide in scope, easy to be done, resulting no or inoffensive by-products, involving readily available starting materials, and can be performed in easily removable or benign solvents.⁴² In another word, reactions that show following characteristics could be considered as click reaction:

- 1- Should be modular. The reactants in the form of blocks could be joined to form the desired product.
- 2- Must be wide in scope, which means the reaction should have variety of applications.
- 3- Products must be obtained in high yields.

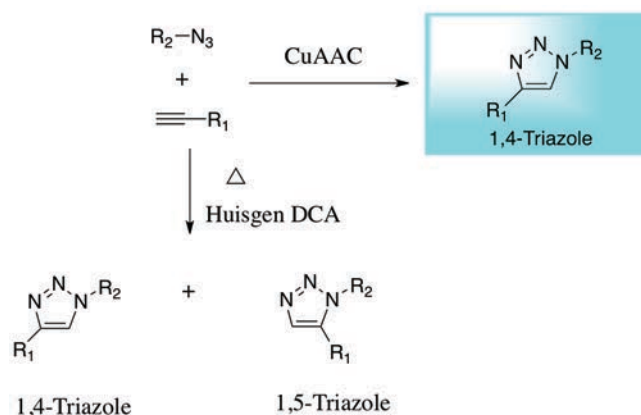
⁴⁰a) R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, 2, 565-98. b) R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, 2, 633-96. ⁴¹a) C. W. Meldal, C. Tornøe, M. Meldal, *J. Org. Chem.* **2002**, 67, 3057-62. b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, 41, 2596-99.

⁴²H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, 40, 2004-21.

- 4- At the end of the reaction, only inoffensive by-products should be formed that can be removed by non-chromatographic methods such as crystallization or distillation.
- 5- The reaction should be stereospecific (but not necessarily enantioselective).
- 6- A reaction with enough thermodynamic force to achieve completion. (no need for extra energy to complete the reaction).
- 7- Reactions with no sensitivity to oxygen or water, so the reaction condition should be simple.
- 8- Availability of the starting materials and the reagents.
- 9- The reaction must be done without any solvent or by use of benign solvents like water or which can be removed easily.
- 10- Isolation of the final product in a click reaction must be easy.
- 11- At the end, the product must be stable under physiological conditions.

Several reactions have been recognized to satisfy these necessities, and called as click reactions, like (i) nucleophilic ring-opening of electrophilic heterocycles such as aziridines, epoxides, cyclic sulfates, aziridinium ions, episulfonium ions; (ii) non-aldol type reaction of carbonyl compounds, like formation of hydrazones, oxime, amides, and heterocycles; (iii) additions to carbon-carbon multiple bonds such as epoxidations, aziridinations, dihydroxylations, sulfonyl halide additions, nitrosyl halide additions, and certain Michael additions; (iv) and another cycloaddition reactions mainly 1,3-dipolar cycloadditions and Diels-Alder cycloadditions.^{41b}

These examples show the variety of the click reactions, but among them, Cu (I) catalyzed azide-alkyne cycloaddition (CuAAC) remains as the first example of click reaction that has several applications in different field of science. In comparison with the uncatalyzed thermal Huisgen reaction, CuAAC follows a completely different pathway, which is 10^7 times faster than thermal reaction and shows a remarkable level of regioselectivity that gives exclusively 1,4-disubstituted 1,2,3-triazole (**Scheme 2**).



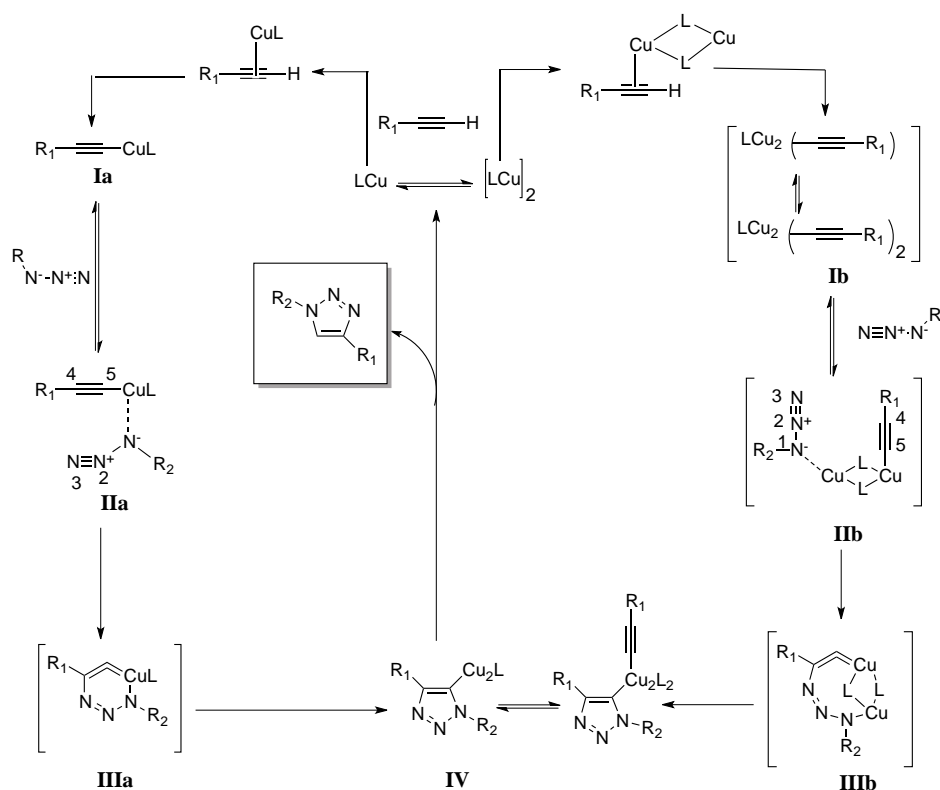
Scheme 2. Regioselectivity in alkyne-azide 1,3-dipolar Cycloaddition Reaction.

I.2.1. Mechanism of Cu-catalyzed azide-alkyne cycloaddition

It was found that copper assisted cycloaddition has a stepwise mechanism, according to the DFT calculations and kinetic analysis, this reaction has an activation energy of 11 Kcal/mol lower than the uncatalyzed version.⁴³ Although Cu-catalyzed cycloaddition has a simple look, but its mechanism is complex, which is due to presence of the copper in the reaction medium. Also, coordination of copper (I) with various additives of reaction such as solvents, ligands, reactants, and final products etc. made this catalytic process even more complicated, because this coordination leads to different dynamic equilibria in reaction medium like disproportionation of Cu(I) to Cu(0) and Cu(II) in polar medium.

Two possible pathways have been suggested upon the available experimental evidences (**Scheme 3**). Based on DFT calculation, path 1 suppose participation of single CuL metal center into reaction,⁴⁴ however kinetic evidences propose participation of dimeric copper species in transition state.^{43b,45} However recent researches show that more than one or two Cu species in transition state are possible to construct the triazolic product.⁴⁶

⁴³a) V. D. Bock, H. Hiemstra, J. H. V. Marseveen, *Eur. J. Org. Chem.* **2006**, 51-68. b) V. O. Rodionov, V. V. Fokin, M. G. Finn, *Angew. Chem. Int. Ed.* **2005**, *44*, 2210-15. ⁴⁴F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless, V. V. Fokin, *J. Am. Chem. Soc.* **2005**, *127*, 210-16. ⁴⁵B. F. Straub, *Chem. Commun.* **2007**, 3868-70. ⁴⁶Q. Wang, T. R. Chan, R. Hilgraf, V. V. Fokin, K. B. Sharpless, M. G. Finn, *J. Am. Chem. Soc.* **2003**, *125*, 3192-93.



Scheme 3. Mechanism of Cu(I)-catalyzed azide-alkyne cycloaddition reaction.

Mechanism begins by complexation of CuL metal on the terminal alkyne to give π -coordinated complex,⁴⁵ this complex then gets deprotonated in a protic medium and result copper acetylide **Ia** and **Ib** in the first step. In the next step, azide and CuL metal center form a complex which increase nucleophilicity of terminal N-3, now this nucleophile N attacks on C-4 by forming a metallacycle **IIIa** or **IIIb**.^{42, 44, 47}

In a recent research performed by Micouin *et al.*, it was showed that the high regioselectivity existing in CuAAC for 1,4-disubstituted product is due to development of [3+2] cycloaddition during a concerted pericyclic type mechanism that takes place via a six membered transition state **IIIa**.⁴⁸

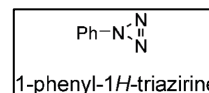
Through the next step, lone pair of N-1 attacks at C-5 position and construct intermediate species **IV** by simple ring contraction of metallacycle. Isolation of CuL triazolide using N heterocyclic carbene (NHC) ligand proved existence of this Cu intermediate.⁴⁹ At the end, 1,4-disubstituted 1,2,3-triazole product has been released by protonation of **IV** with solvent or base, following the

⁴⁷M. Ahlquist, V. V. Fokin, *Organomet.* **2007**, *26*, 4389-4439. ⁴⁸Y. Zhou, T. Lecourt, L. Micouin, *Angew. Chem. Int. Ed.* **2010**, *49*, 2607-10. ⁴⁹C. Nolte, P. Mayer, B. F. Straub, *Angew. Chem. Int. Ed.* **2007**, *46*, 2101-3.

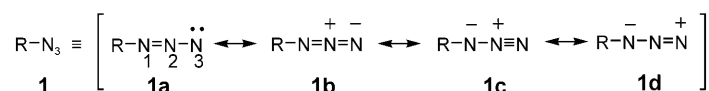
dissociation of labile copper complex that could conduct second catalytic cycle (**Scheme 3**).

I.2.2. Physicochemical Properties of Organic Azides

Azide's structure derived from a cyclic 1H-triazirine structure was proposed for the first time by Curtius and Hantzsch,⁵⁰ however the linear structure was later favoured over this one.



Physicochemical properties of azides influence its chemical diversity. Thought of polar mesomeric structure of azide can explain some of its physico-chemical properties.⁵¹ Conjugation with aromatic systems can stabilize the aromatic azides. Pauling proposed a dipolar structure of azide **1c, d**,⁵² which explain easily decomposition of azide into the corresponding nitrene and nitrogen as well as the reactivity as a 1,3-dipole.



The mesomeric structure of **1d** describes the regioselectivity of the reaction of azides with electrophiles and nucleophiles, in fact nucleophiles attack on N^3 and electrophiles are attacked by N^1 . The angles $R-N^1-N^2-N^3$ and $RN^1-N^2-N^3$ are respectively 115.28° and 172.58° . (calculated for methylazide, $R = CH_3$).⁵³ The bond lengths in methyl azide were calculated as $d(R-N^1) = 1.472$, $d(N^1-N^2) = 1.244$, and $d(N^2-N^3) = 1.162 \text{ \AA}$, and with aromatic azides they could find a little shorter bond lengths for N^2-N^3 , so an almost linear azide structure is present, with sp^2 hybridization at N^1 and a bond order of ≈ 2.5 between N^3 and N^2 and ≈ 1.5 between N^2 and N^1 . Figure 8 presents an example of the molecular structure of an aromatic azide.

⁵⁰a) T. Curtius, *Ber. Dtsch. Chem. Ges.* **1890**, 23, 3023-33; b) T. Curtius, *J. Prakt. Chem.* **1894**, 50, 275; c) A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **1933**, 66, 1349-54. ⁵¹a) E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, 88, 297-368; b) G. L'abbé, *Chem. Rev.* **1969**, 69, 345-63. ⁵²a) L. Pauling, L. O. Brockway, *J. Am. Chem. Soc.* **1937**, 59, 13-20; b) L. O. Brockway, L. Paulin, *Proc. Natl. Acad. Sci. USA* **1933**, 19, 860-67. ⁵³M. T. Nguyen, D. Sengupta, T. -K. Ha, *J. Phys. Chem.* **1996**, 100, 6499-6503.

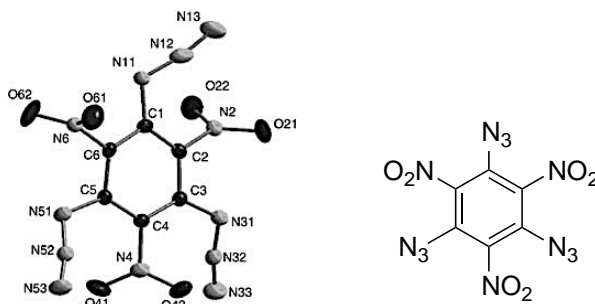
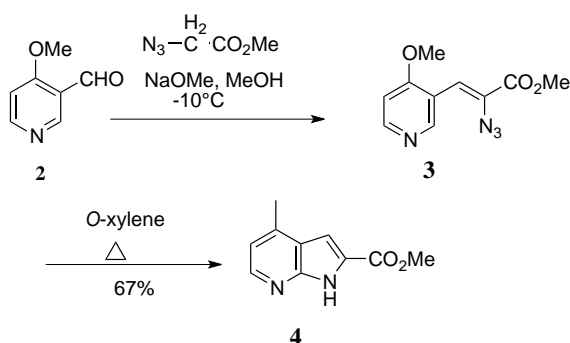


Fig. 8. ORTEP representation of 1,3,5-triazido-2,4,6-trinitrobenzene with the ellipsoids of the C, N, and O atoms drawn at the 50% probability level.⁵⁴

The polar resonance structures of **1 b, c** reveals some facts like strong IR absorption at $\approx 2114 \text{ cm}^{-1}$ (for phenyl azide),⁵⁵ the UV absorption (287 nm and 216 nm for alkyl azides), the weak dipole moment (1.44 D for phenyl azide), and the acidity of aliphatic azides (*e.g.* **Scheme 4**).⁵⁶



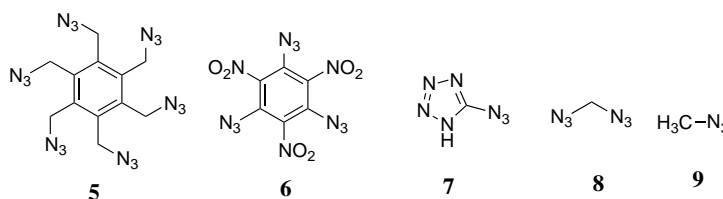
Scheme 4. Synthetic steps in the synthesis of the alkaloid varioline (**45**) and its analogues according to Molina *et al.*⁵⁷

The azide ion is considered as a pseudohalide⁵⁸ and because of that the organic azides are somehow similar to organic halogen compounds. For arenes with azide groups in the *meta* and *para* positions, the Hammett parameters are respectively 0.35 and 0.1 that are similar to those of fluoroarenes. In another reactions such as aromatic substitution reactions, the azide group represents an *ortho*- and *para*-directing substituent.

Since ionic azides like sodium azide are fairly stable, heavy metal and covalently bound azides are thermally decomposable and they can be considered as explosive categories of compounds.

⁵⁴D. Adam, PhD Thesis, Ludwigs-Maximilians-Universität München (Germany), **2001**.⁵⁵Further vibrations exist at $1340\text{--}1180 \text{ cm}^{-1}$ and 680 cm^{-1} .
⁵⁶A. Breuning, R. Vicik, T. Schirmeister, *Tetrahedron: Asymm.* **2003**, *14*, 3301-12. ⁵⁷P. Molina, P. M. Fresneda, S. Delgado, *J. Org. Chem.* **2003**, *68*, 489-99. ⁵⁸Mulliken electronegativities: Cl (8.3 eV), Br (7.5 eV), N₃ (7.7 eV). I. C. Tornieporth, T. M. Klapötke, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 511-20.

For organic azides considered as non-explosive and manipulable, they should respect a rule, which is the number of nitrogen atoms that should not be more than the number of carbon ($N_C + N_O$)/ $N_N \geq 3$, here N represents the number of atoms.⁵⁹ Among synthesized azides there are some, which are potentially explosive like compounds containing hexakis(azidomethyl)benzene (**2**),⁵⁴ triazidotrinitrobenzene (**3**),⁶⁰ azidotetrazole (**4**) (88 % nitrogen !),⁶¹ and azidomethane (**6**).



There are some other unexplained situations in which even proved nonreactive low-molecular-weight azides can be decomposed, so their manipulation should be done with some precautions.

I.2.2.1. Reactions of organic azides

As is mentioned above, azides can behave very differently under different reaction conditions. As a main reaction of azides, we can mention reaction with electron-deficient compounds at N¹ and also electron-rich compounds (nucleophiles) through N³ (**Fig. 9**).

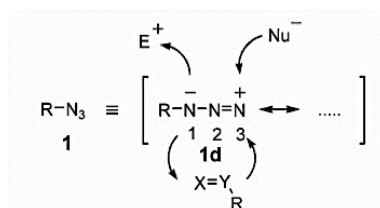


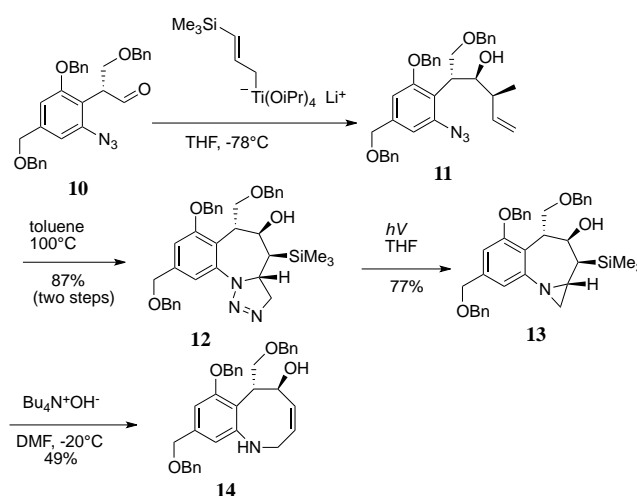
Fig. 9. Reactivity of organic azides⁵¹

In the reaction of azides, retention of the azide unit can be observed, but cleavage of the nitrogen-nitrogen single bond is also possible, like in the case of nitrene chemistry. Cycloaddition of azides is the simplest mechanistically case in which azides can be used extensively.

⁵⁹a) P. A. S. Smith, *Open-Chain Nitrogen Compounds*, vol. 2, Benjamin, New York, **1966**, 211-56; b) J. H. Boyer, R. Moriarty, B. de Darwent, P. A. S. Smith, *Chem. Eng. News* **1964**, 42, 6. ⁶⁰D. Adam, K. Karaghiosoff, T. M. Klapötke, G. Holl, M. Kaiser, *Propellants Explos. Pyrotech.* **2003**, 27, 7-11. ⁶¹A. Hammerl, T. M. Klapötke, H. Nöth, M. Warchhold, G. Holl, *Propellants Explos. Pyrotech.* **2003**, 28, 165-73.

I.2.2.2. Applications of azides

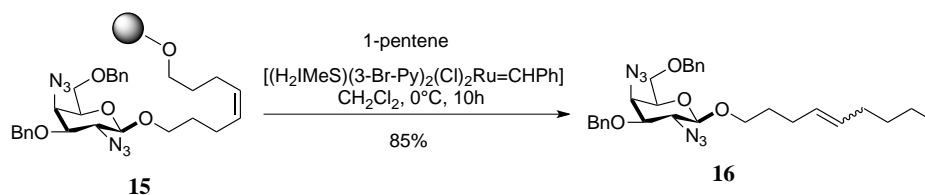
A) As protecting group: To protect coordinating primary amines, the azide function proved a good possibility especially in substrates like oligosaccharides, aminoglycoside antibiotics, ⁶² glycosyloaminoglycans such as heparin ^{63a,b} and peptidonucleic acids (PNA) ^{63c} that are sensitive substrates. In addition, another property of azide as protecting group is that this function is stable in osmium- ^{64a} and ruthenium- ^{64b} induced dihydroxylations or alkylations (**Scheme 5**).



Scheme 5. Part of the total synthesis of FR66979 according to Ciufolini and co-workers. ^{64c} Bn = benzyl.

Another example in the context of the stability of azides around organometallic catalysts was given by Seeberger and co-workers where the utility of the azide group in cleavage from a polymeric support by an alkene metathesis of saccharides was possible (**Scheme 6**).⁶⁵

⁶²a) W. A. Greenberg, E. S. Priestley, P. S. Sears, P. B. Alper, C. Rosenbohm, M. Hendrix, S.-C. Hung, C.-H. Wong, *J. Am. Chem. Soc.* **1999**, *121*, 6527-41; b) D. Maclean, J. R. Schullek, M. M. Murphy, Z. J. Ni, E. M. Gordon, M. A. Gallop, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 2805-10. ⁶³a) C. A. A. van Boeckel, M. Petitou, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1671-90; b) H. A. Orgueira, A. Bartolozzi, P. Schell, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2002**, *41*, 2128-31; c) F. Debaene, N. Winssinger, *Org. Lett.* **2003**, *5*, 4445-47. ⁶⁴a) T. Ainai, Y.-G. Wang, Y. Tokoro, Y. Kobayashi, *J. Org. Chem.* **2004**, *69*, 655-59; b) B. Plietker, M. Niggeman, *Org. Lett.* **2003**, *5*, 3353-56; c) R. Ducray, M. A. Ciufolini, *Angew. Chem. Int. Ed.* **2002**, *41*, 4688-91. ⁶⁵T. Kanemitsu, P. H. Seeberger, *Org. Lett.* **2003**, *5*, 4541-44.

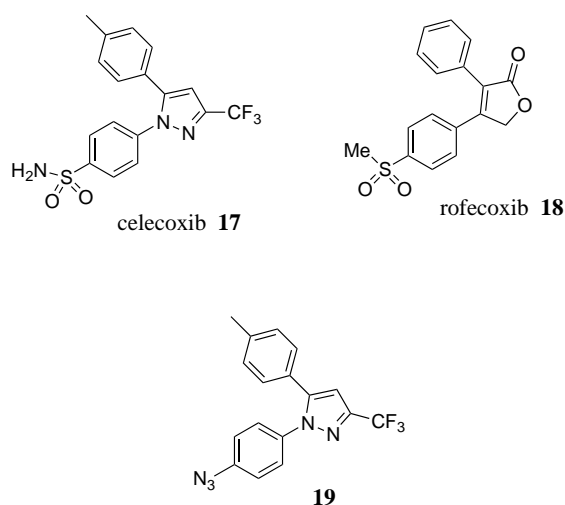


Scheme 6. Cleavage metathesis of organoazides.

The azide group can be used not only as a protecting group but also it proved a compatibility in the aza-wittig reaction.

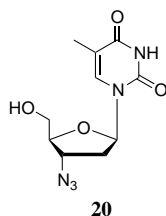
B) Azides as Biologically Active Compounds and in Natural Products Synthesis :

Azides functionality in natural products doesn't exist, but some compounds with this functionality could be found as potential active compounds. Comparison between azide groups and aminosulfonyl and methylsulfonyl groups showed that relatively smaller size of azide function cause more lipophilic properties than these two other groups and because of that it can, as an example, interact better with arginine units than sulfonyl functions. There are also azide compounds stronger than the corresponding sulfone derivatives such as **19** of the COX-2 inhibitors celecoxib (**17**) and rofecoxib (**18**).⁶⁶



⁶⁶A. G. Habeeb, P. N. P. Rao, E. E. Knaus, *J. Med. Chem.* **2001**, *44*, 3039-42.

A similar behaviour was also found by a comparison between a 1,1-dichloroethyl group (as in chloramphenicol) and the azidomethyl group, as a well-known example we can mention the anti-HIV medication AZT (**20**; 3'-azido-2',3'-dideoxy-thymidine).⁶⁷



C) Photoaffinity labeling: Another application of azide group is that they can be used in the labeling of receptor compounds and ligands used in photoaffinity labeling.⁶⁸ For this purpose, the ligand is provided with this nitrene precursor in a way that does not influence its affinity for the receptor, but keeps it close enough to its target protein. The azide group is especially appropriate for this labeling, because after photolysis, the organoazide can be entered into many carbon, nitrogen, oxygen, or sulfur compounds by the formation of nitrenes. In order to identify the ligand-protein complex an additional radioactive label can also be applied (**Fig. 10**).

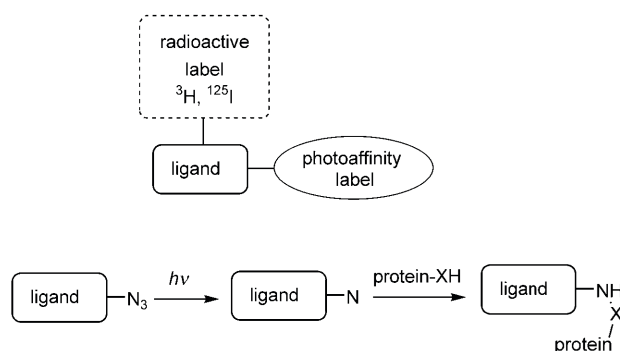


Fig. 10. The principle of photoaffinity labeling.

An example of use of this principle is synthesis of combrestatin analogues as molecular probes for tubulin polymerization (**Fig. 11**). In addition some other applications in medicinal chemistry have been reported.⁶⁹

⁶⁷a) S. Piantadosi, C. J. Marasco, E. J. Modest, *J. Med. Chem.* **1991**, *34*, 1408-14; b) T. Pathak, *Chem. Rev.* **2002**, *102*, 1623-67. ⁶⁸a) C. A. Gartner, *Curr. Med. Chem.* **2003**, *10*, 671-89; b) S. A. Fleming, *Tetrahedron* **1995**, *51*, 12479-520; c) E. Okada, Y. Komazawa, M. Kuriwara, H. Inoue, N. Miyata, H. Okada, T. Tsuchiya, Y. Yamakochi, *Tetrahedron Lett.* **2004**, *45*, 527-29. ⁶⁹a) K. G. Pinney, M. P. Mejia, V. M. Villalobos, B. E. Rosenquist, G. R. Pettit, P. Verdier-Pinard, E. Hamel, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2417-25; b) K. A. H. Chehade, K. Kiegiel, R. J. Issacs, J. S. Pickett, K. E. Bowers, C. A. Fierke, D. A. Andres, H. P. Spielmann, *J. Am. Chem. Soc.* **2002**, *124*, 8206-19; c) F. Mesange, M. Sebban, J. Capdevielle, J. -C. Guillemot, P. Ferrera, F. Bayard, M. Poirrot, J.-C. Faye, *Bioconjugate Chem.* **2002**, *13*, 766-72.

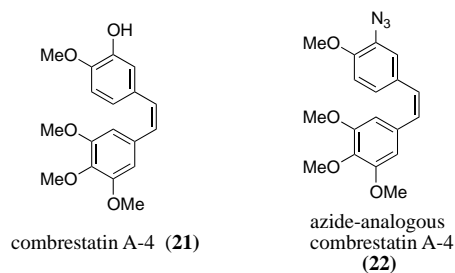


Fig. 11. Aryl azides as molecular probes according to Pinney et al.^{69a}

Interaction of small molecules⁷⁰ with proteins is not the only category that can be explored with organoazides but also protein-protein^{71a,b} and protein-nucleic acids interactions^{71c} are another class that can be investigated by photolabeling. The photolabeling with organoazide can also be performed in an intramolecular manner that results in crosslinking. The covalent bonding of RNA duplex strand with an internally attached aryl azide (**24**) by photolysis is an example that can be carried out in this fashion. It was important that a hydroxyl group exist on 3-position of aryl azide **24**, which help the nucleophilic attack by the antisense strand on a ketene imine or a corresponding sequential product as active species that cause crosslinking (**Fig. 12**).⁷²

⁷⁰a) E. Mappus, C. Chambon, B. Fenet, M. Rolland de Ravel, C. Grenot, C. Y. Cuillero, *Steroids* **2000**, *65*, 459-81; b) J. J. Chambers, H. Gouda, D. M. Young, I. D. Kuntz, P. M. England, *J. Am. Chem. Soc.* **2004**, *126*, 13886-87. ⁷¹a) F. Teixeira-Clerc, S. Michalet, A. Menez, P. Kessler, *Bioconj. Chem.* **2003**, *14*, 554-62; b) S. C. Alley, F. T. Ishmael, A. D. Jones, S. J. Benkovic, *J. Am. Chem. Soc.* **2000**, *122*, 6126-27; c) D. Hu, M. Crist, X. Duan, F. A. Quicho, F. S. Gimble, *J. Biol. Chem.* **2000**, *275*, 2705-12. ⁷²K. L. Buchmueller, B. T. Hill, M. S. Platz, K. M. Weeks, *J. Am. Chem. Soc.* **2003**, *125*, 10850-61.

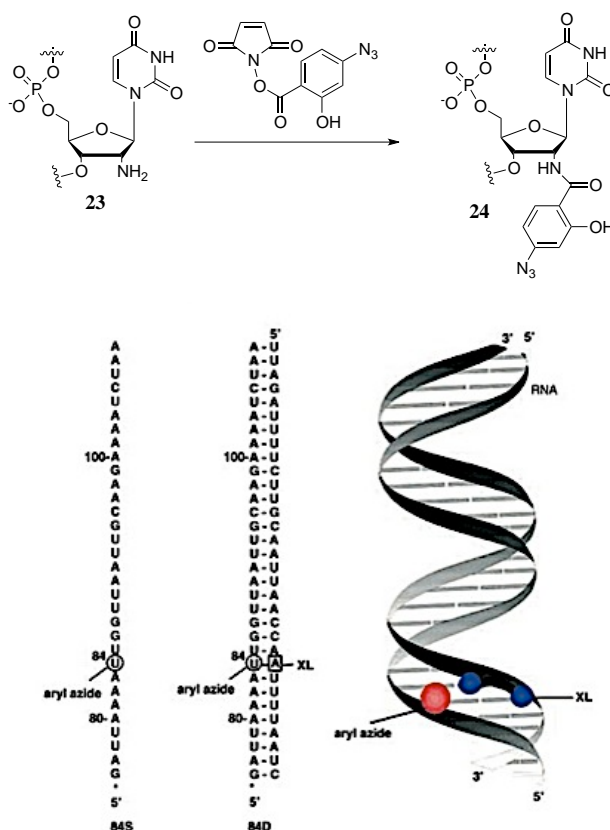


Fig. 12. 3-Hydroxyaryl azides as crosslinkers according to Platz, Weeks et al.⁷² *: Position of a radioactive ³²P label, XL = crosslinking

I.2.3. Applications of Click chemical reactions

As is already mentioned, Click Chemistry is a flexible synthetic approach towards construction of new molecular units. The large application area of this reaction is showed by its use in different fields of life and material sciences like drug discovery,⁷³ bioconjugation,⁷⁴ polymer and materials science,⁷⁵ and related areas^{43a,76} such as supramolecular chemistry,⁷⁷ DNA labeling,⁷⁸ and oligonucleotide synthesis,⁷⁹ assembly of glycoclusters⁸⁰ and glycodendrimers,⁸¹ preparation of stationary phases for HPLC column,⁸² improvement of microcontact printing,⁸³ conjugation of

⁷³a) K. B. Sharpless, R. Manetsch, *Expert Opin. Drug Discov.* **2006**, *1*, 525-38. b) G. C. Tron, T. Pirali, R. A. Billington, P. L. Canonico, G. Sorba, A. A. Genazzani, *Med. Res. Rev.* **2008**, *28*, 278-308. ⁷⁴a) J. F. Lutz, *Angew. Chem. Int. Ed.* **2008**, *47*, 2182-84; b) J. F. Lutz, H. G. Börner, *Prog. Polym. Sci.* **2008**, *33*, 1-39. ⁷⁵a) W. H. Binder, C. Kluger, *Curr. Org. Chem.* **2006**, *10*, 1791-1815; b) H. Nandivada, X. W. Jiang, J. Lahann, *Adv. Mater.* **2007**, *19*, 2197-2208; c) D. Fournier, R. Hoogenboom, U. S. Schubert, *Chem. Soc. Rev.* **2007**, *36*, 1369-80; d) P. L. Golas, K. Matyjaszewski, *QSAR Comb. Sci.* **2007**, *26*, 1116-34. ⁷⁶a) F. Santoyo-Gonzalez, F. Hernandez-Mateo, *Top. Heterocycl. Chem.* **2007**, *7*, 133-177; b) J. F. Lutz, H. Schlaad, *Polymer* **2008**, *49*, 817-24. ⁷⁷a) W. B. Zhang, Y. Tu, R. Ranjan, R. M. VanHorn, S. Leng, J. Wang, M. J. Polce, C. Wesdemiotis, R. P. Quirk, G. R. Newkome, S. Z. D. Cheng, *Macromol.* **2008**, *41*, 515-17; b) J. S. Marois, K. Cantin, A. Desmarais, J. F. Morin, *Org. Lett.* **2008**, *10*, 33-36. ⁷⁸J. Gierlich, G. A. Burley, P. M. E. Gramlich, D. M. Hammond, T. Carell, *Org. Lett.* **2006**, *8*, 3639-42. ⁷⁹A. Nuzzi, A. Massi, A. Dondoni, *QSAR Comb. Sci.* **2007**, *26*, 1191-99. ⁸⁰A. Dondoni, A. Marra, *J. Org. Chem.* **2006**, *71*, 7546-57. ⁸¹a) J. A. F. Joosten, N. T. H. Tholen, F. Ait El Maate, A. J. Brouwer, G. W. vanEsse, D. T. S. Rijkers, R. M. J. Liskamp, R. J. Pieters, *Eur. J. Org. Chem.* **2005**, 3182-85; b) E. Fernandez-Megia, J. Correa, I. Rodriguez-Meizoso, R. Riguera, *Macromol.* **2006**, *39*, 2113-20. ⁸²Z. Guo, A. Lei, X. Liang, Q. Xu, *Chem. Commun.* **2006**, 4512-14. ⁸³D. I. Rozkiewicz, D. Janczewski, W. Verboom, B. J. Ravoo, D. N. Reinhoudt, *Angew. Chem. Int. Ed.* **2006**, *45*, 5292-96.

molecular clusters to the headgroup of phospholipids⁸⁴ and building bolaamphiphilic structures⁸⁵ are some examples of the application of CuAAC. Here some of these examples will be explained in details.

I.2.3.1. Therapeutics Polymers, which includes polymer-protein conjugates, drug polymer conjugates, polymeric drug delivery systems and polymeric micelles to which the drug is covalently bound.⁸⁶ Click Chemistry is widely used in these areas of polymer therapeutics.

Synthesis of block copolymers, involves two or more homopolymer subunits which associated by covalent bonds, and have important pharmaceutical properties. Many methods have been used to synthesize block copolymers like Click Chemistry that is one of the most efficient methods to bind two substances. By efficiently use of CC block copolymers were formed by linking homopolymers. For example, amphiphilic copolymers were synthesized by use of Cu (I)-catalyzed Huisgen 1,3-dipolar cycloaddition (HDC) reaction and combination of atom transfer free radical polymerization (ATRP). The two polymers were synthesized by ATRP and were linked one with alkyne functionality and the other with azide functionality [*e.g.* poly (1-ethoxy ethyl acrylate) and poly (acrylic acid)], that they were clicked together to construct copolymer (**Fig. 13**).⁸⁷

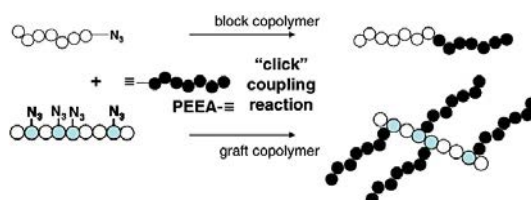


Fig. 13. Schematic depiction of the synthesis of block and graft copolymers using “click” chemistry.⁸⁷

Polymeric micelles, which have important applications in the fields like drug delivery, drug targeting, drug solubilisation and controlled drug release. One of the use of Click Chemistry in this field is its application in the formation of the cross-links within the shell of polymer micelles that provide stability to the nanostructured buildings, which increase weak interactions that facilitate polymer micelle existence (**Fig. 14**).⁸⁸

⁸⁴a) H. J. Musiol, S. Dong, M. Kaiser, R. Bausinger, A. Zumbusch, U. Bertsch, L. Moroder, *Chem. Bio. Chem.* **2005**, *6*, 625-8; b) S. Cavalli, A. R. Tipton, M. Overhand, A. Kros, *Chem. Commun.* **2006**, 3193-95; c) F. S. Hassane, B. Frisch, F. Schuber, *BioConj. Chem.* **2006**, *17*, 849-54. ⁸⁵B. D. Smith, *Org. Lett.* **2007**, *9*, 199-202. ⁸⁶a) R. Haag, F. Kratz, *Angew. Chem. Int. Ed. Engl.* **2006**, *45* (8), 1198-215; b) CD Hein, XM Liu, D. Wang, *Pharm. Res.* **2008**, *25* (10), 2216-30. ⁸⁷WV Camp, V Germonpre, L Mespouille, P Dubois, EJ Goethals, FE Du Prez, *React. Funct. Polym.* **2007**, *67*, 1168-80. ⁸⁸KB Thurmond, H Huang, CG Jr Clark, T Kowalewski, KL Wooley, *Biointerfaces* **1999**, *16*,45-54.

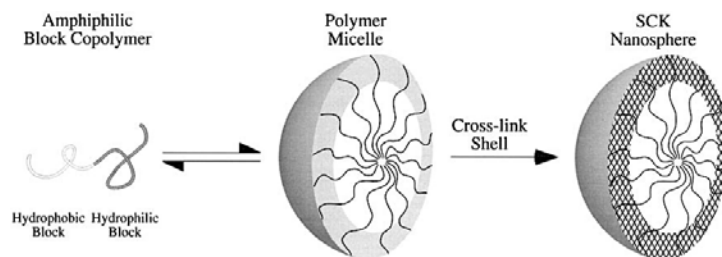


Fig. 14. The general method for Shell Cross-Linked (SCK) nanosphere construction includes the self assembly of block copolymers in a solvent system that is selective for one of the copolymer blocks, followed by covalent bond formation between the chain segments that compose the polymer micelle shell.⁸⁸

Polymeric drug delivery systems, Liu *et al.*⁸⁹ prepared linear multifunctional poly ethylene glycol (PEG) by using click chemistry, which can be used as polymeric drug carrier. In their paper, a short acetylene-terminated PEG was linked to 2,2-bis(azidomethyl)propane-1,3-diol through HDC reaction in water and at room temperature. Another polymer, which was synthesized by using this method was a prototype bone-targeting polymeric drug delivery system (**Fig. 15**).⁸⁹

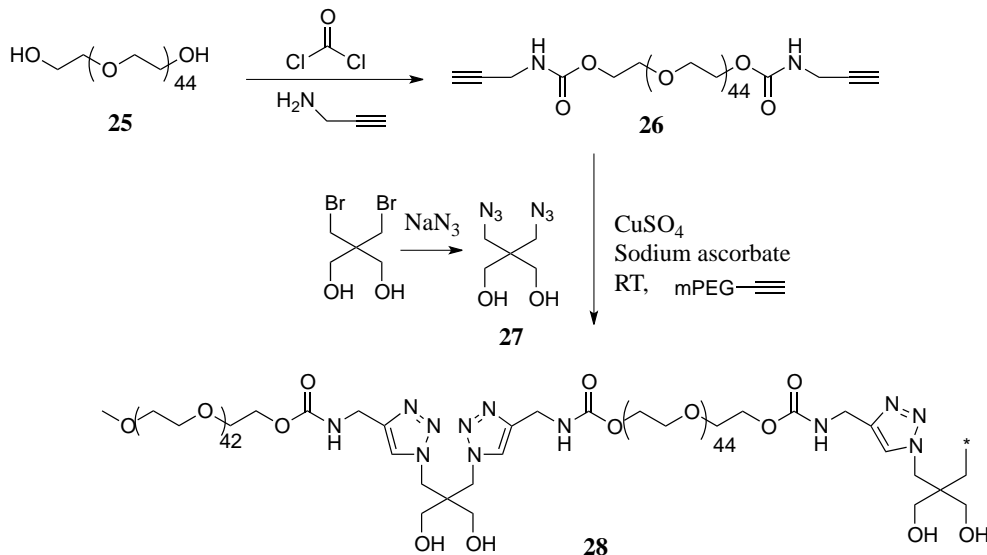


Fig. 15. Synthesis of Linear Multifunctional PEG via Cu(I)-Catalyzed Huisgen 1,3-Dipolar Cycloaddition

1.2.3.2. Drug Delivery Systems

Liposomes that can be used as drug carrier in drug delivery systems. In this system, the drug that should be delivered is attached to liposome through different sites available on it. In this way,

⁸⁹X. M. Liu, A. Thakur, D. Wang, *Biomacromol.* **2007**, 8(9), 2653-58.

delivery of agents to the reticuloendothelial system (RES) is easily obtained as most of the liposomes are caught by the RES. This fusion of drug or ligand to the surface of liposomes can be done by using HDC reaction, *e.g.* conjugation of mannose ligands to the surface of liposomes, for this ligation, they functionalized a lipid anchor with alkyne moiety and this was then introduced into the liposomes.^{84c} In the next step mannosyl residue, which was functionalized with azide group was linked to the surface of liposomes through HDC reaction (**Fig. 16**). This reaction gave mannosylated liposomes that can be used as vehicles to target specific cells such as human dendritic cells.⁹⁰

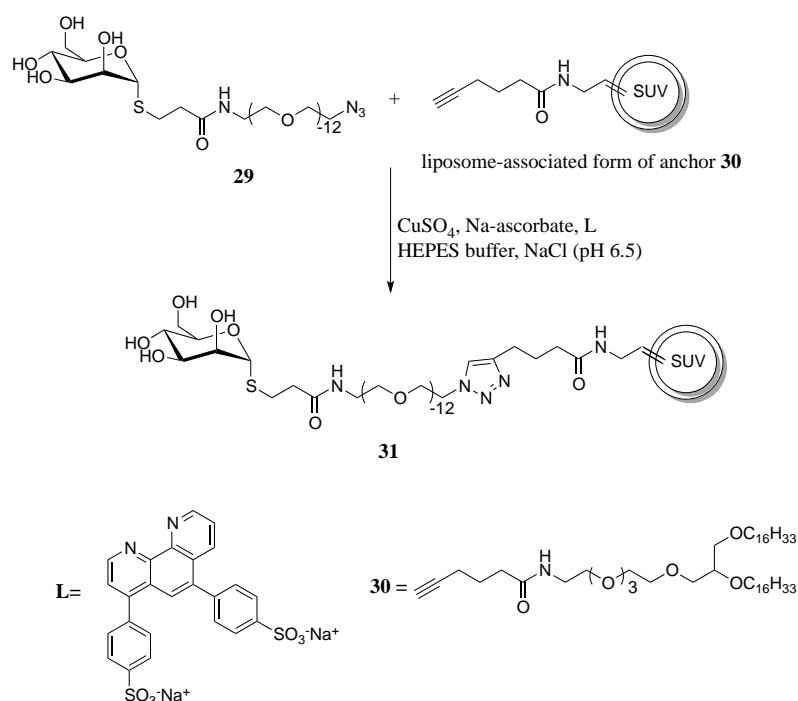


Fig. 16. Coupling of the Ligand **29** to preformed liposomes that incorporate the alkyne functionalized anchor **30** by Click Chemistry in the presence of the Cu(I) ligand bathophenanthrolinedisulfonate.^{84c}

Dendrimers, have great applications in drug delivery, gene delivery, etc. as they are multivalent, highly branched and globular macromolecules.⁹¹ Here, Click reaction can be used to synthesize dendrimers. In this field, copper catalysed HDC has been applied for designing and functionalizing dendrimers (**Fig. 17**).⁹²

⁹⁰MJ Copland, MA Baird, T Rades, JL Mckenzie, B Becker, F Reck, PC Tayler, NM. Davies, *Vaccine* **2003**, *21*, 883-90. ⁹¹E. R. Gillies, J. M. J. Fréchet, *Drug Discov. Today* **2005**, *10*, 35-43. ⁹²G. Franc, A. Kakkar, *Chem. Commun.* **2008**, *42*, 5267-76.

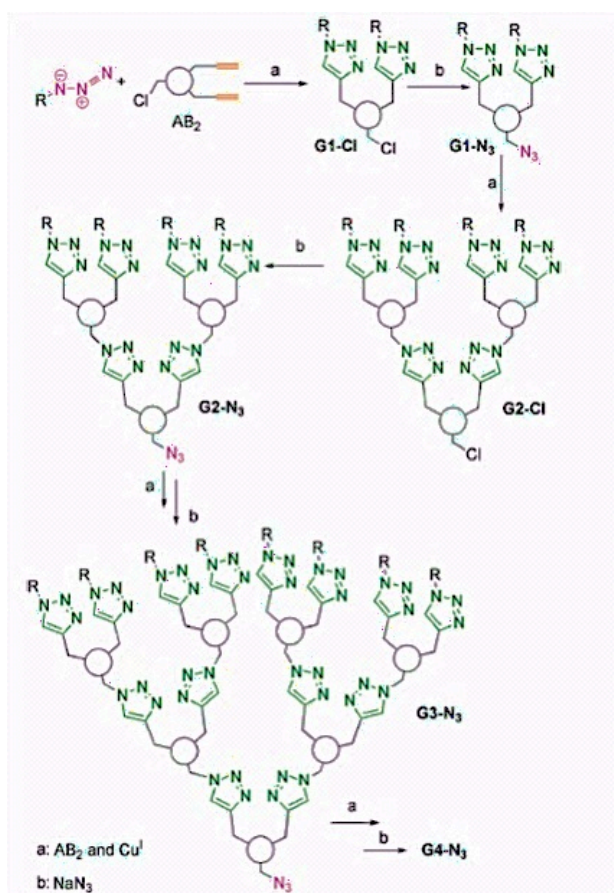


Fig. 17. First examples of triazole dendrimers synthesized using a convergent methodology.⁹²

I.2.3.3. Bioconjugation

Copper catalysed HDC reaction is highly recommended in both *in-vivo* and *in-vitro* bioconjugation:

Bioconjugation to gold and magnetic nanoparticles

Due to their interesting properties, gold nanoparticles have shown some applications in therapeutic domain⁹³ like cancer cell diagnostics,⁹⁴ in drug delivery systems,⁹⁵ labeling antibodies⁹⁶ and other areas. These methods need attachment of biological molecules to the nanoparticle and this bioconjugation to the gold nanoparticle through a covalent bond can be reached by HDC reaction. Magnetic nanoparticles have also applications in medicine because of their biocompatibility and their high accumulation in target tissues under a local magnetic field.⁹⁷ With HDC reaction, a lot of organic molecules containing 2,4-dinitrophenol, flag peptides, biotin and maltose binding protein have been linked to magnetic nanoparticles in this way that magnetic nanoparticles were functionalized by azide moiety and the molecule, which is going to be attached, was functionalized

⁹³J. L. West, N. J. Halas, *Annu. Rev. Biomed. Eng.* **2003**, *5*, 285-92. ⁹⁴X. Huang, P. K. Jain, I. H. El-Sayed, M. A. El-Sayed, *Nanomed.* **2007**, *2*, 681-93. ⁹⁵G. Han, P. Ghosh, M. De, V. M. Rotello, *Nanobiotech.* **2007**, *3*, 40-45. ⁹⁶P. W. Faulk, M. G. Taylor, *Immunochem.* **1971**, *8*, 1081-83. ⁹⁷A. Ito, M. Shinkai, H. Honda, T. Kobayashi, *J. Biosci. Bioeng.* **2005**, *100*, 1-11.

with a terminal alkyne moiety and then they were clicked together (**Fig. 18**).⁹⁸

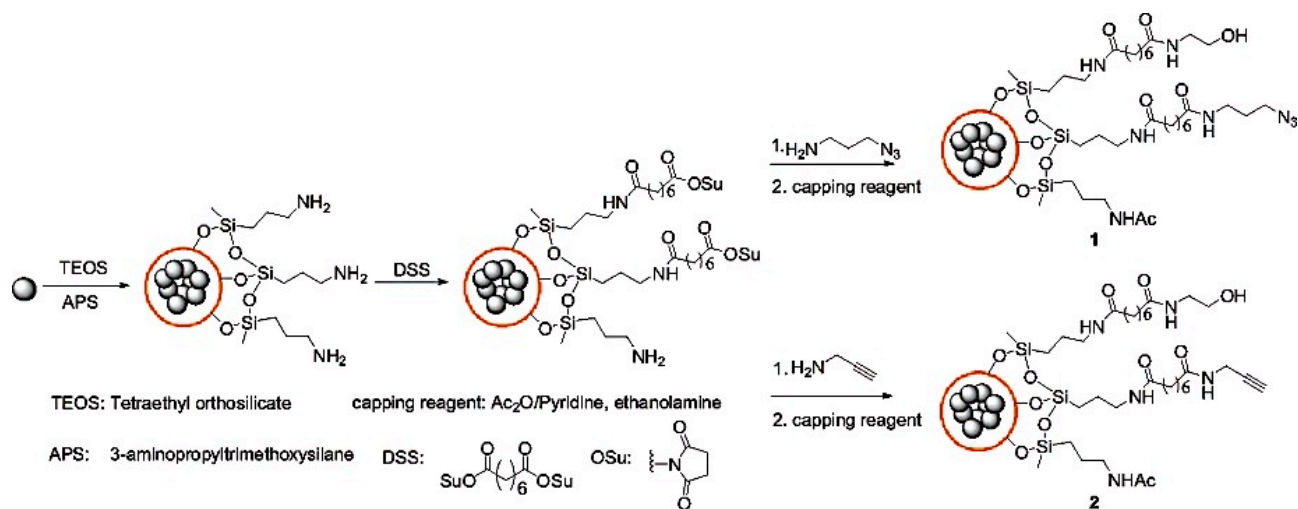
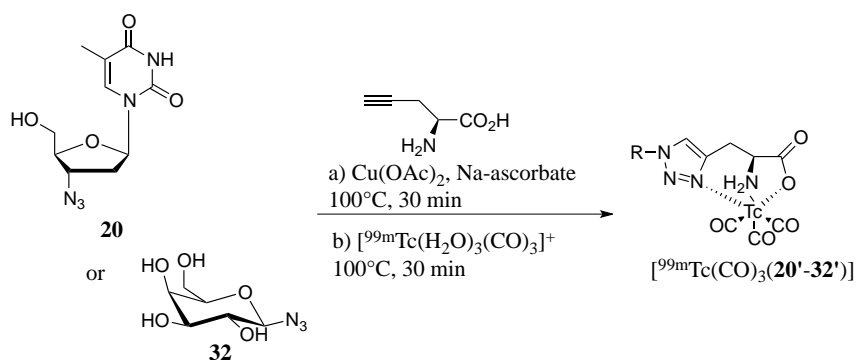


Fig. 18. Fabrication of azido- and alkynyl-MNPs (Magnetic NanoParticles).⁹⁸

1.2.3.3.1. Radiolabelling

In this method, the drug has been attached to the radionucleotide that allow to follow its distribution inside the body and its metabolic pathway.⁹⁹ One of the common used radioisotope is technetium-99m. Different Click reactions have been reported to link this radioisotope to various organic molecules (**Scheme 7**).¹⁰⁰



Scheme 7. One-pot procedure to yield radiolabeled conjugates directly.¹⁰⁰

⁹⁸P. C. Lin, S. H. Ueng, S. C. Yu, M. D. Jan, A. K. Adak, C. C. Yu, C. C. Lin, *Org. Lett.* **2007**, 9, 2131-34. ⁹⁹R. B. Silverman, *The Organic Chemistry of Drug Design and Drug Action*, 2nd edition, Elsevier Scientific, San Diego, CA **2004**. ¹⁰⁰T. L. Mindt, H. Struthers, L. Brans, T. Anguelov, C. Schweinsberg, V. Maes, D. Tourwe, R. Schibli, *J. Am. Chem. Soc.* **2006**, 128, 15096-97.

1.2.3.3.2. Polysaccharides

Another application of Click reactions is modifications of polysaccharides in order to develop their pharmacological properties. An example of this application was mentioned in a paper by Libert *et al.*¹⁰¹ where they modified the surface of cellulose through click reactions. For this work, they tosylated the primary alcohol group of the glucose units followed by azidation with sodium azide, which enabled azide functional groups to be introduced into cellulose. In the next step, they mixed three alkyne with low molecular weight (methylpropiolate, 2-ethynylaniline and 3-ethynylthiophene) with three different strands of cellulose functionalized with azide. They performed this reaction in the presence of copper as catalyst and sodium ascorbate (**Fig. 19**).¹⁰¹

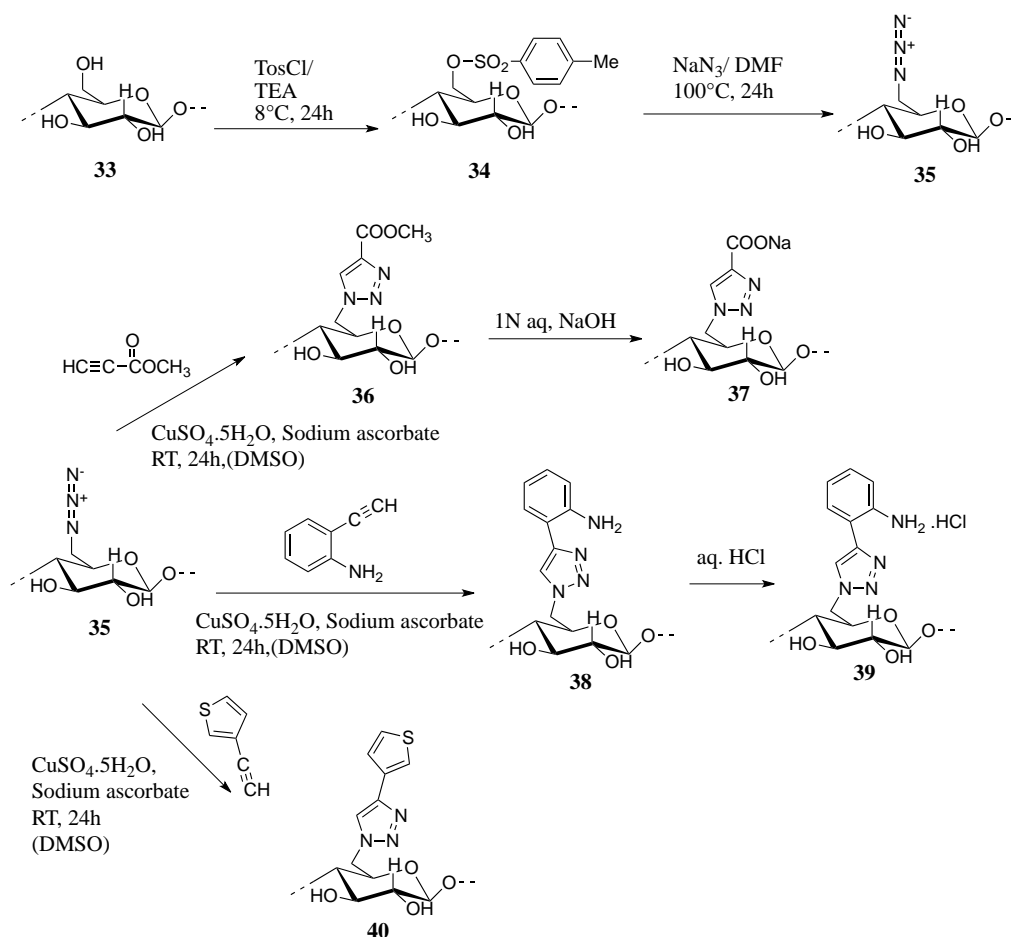
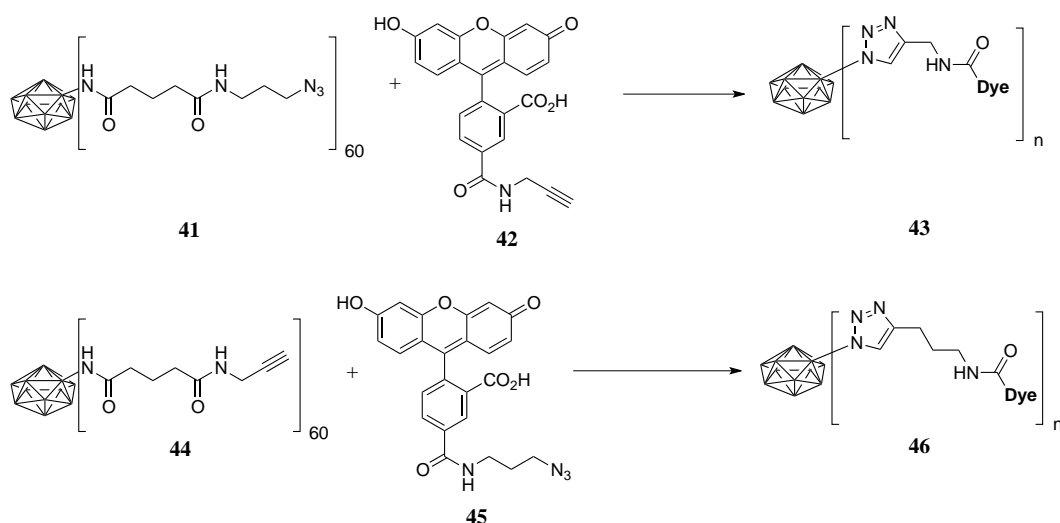


Fig. 19. Reaction scheme for preparation of 6-azido-6-deoxy cellulose (**35**) and subsequent copper(I)-catalyzed Huisgen reaction of 1,4-disubstituted 1,2,3-triazoles used as linker for the modification of cellulose with methylcarboxylate (**36**), 2-aniline (**38**), and 3-thiophene (**40**) moieties.

¹⁰¹T. Liebert, C Hänsch, T Heinze, *Rapid Commun.* **2006**, *27*, 208-13.

I.2.3.3.3. Tagging of live organisms and proteins

Live organisms and proteins can also be tagged by click reactions. As an example, Cowpea mosaic virus (CPVM) that its capsid is made up of 60 copies of an asymmetric two protein units containing RNA genome has been tagged by use of bioconjugation methods using 60 azides per virus particles. Interestingly, it was found that all the 60 azide groups reacted to form triazoles with >95% yield that was helpful for labeling the virus with fluorescein derivatives (**Scheme 8**).⁴⁶



Scheme 8. [3 + 2] Cycloaddition reactions of virus-azides/alkynes **41**, **44** with Dye-Alkyne **42** and dye-azide **45**

I.2.3.3.4. Activity based protein profiling (ABPP)

ABPP is a method to analyse the function of enzymes in biological systems.¹⁰² This method needs two conditions: a) A site directed reactive group which binds covalently and labels a specific family of enzymes; b) Reporter tag (fluorescein/ biotin) for detection and quantification of labeled enzymes. Because of the bulky nature of reporter tags (**Fig. 20**),¹⁰² the ABPP probes have less cell permeability, so to resolve this problem, the reporter tag is replaced by small chemical groups like alkyne or azide which allow the probes to be entered into the cells without any problems. With the help of Cu catalyzed HDC reaction, this orthogonal reporter tag is then attached to the probe.

¹⁰²N. Jassani, B. F. Cravatt, *Curr. Opin. Chem. Biol.* **2004**, 8, 54-59.

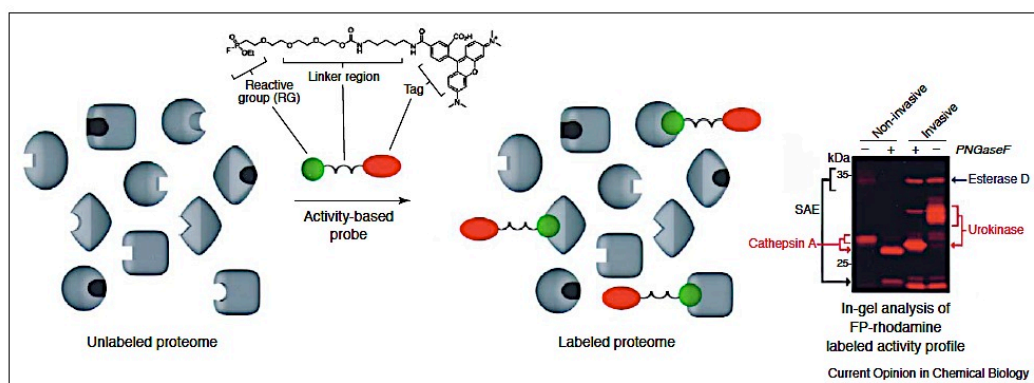


Fig. 20. Comparative ABPP of human cancer cells ¹⁰²

I.2.3.3.5. Labeling of DNA

Click chemistry plays also an important role in oligonucleotide labeling with fluorescent dyes. As DNA can be cleaved in the presence of copper, free metal click chemistry must be used for labeling DNA. In that order, a method has been applied in which 5'-dibenzocyclooctyne (DIBO)-modified oligonucleotides were used that was prepared from a new DIBO phosphoramidite, then this react with azide through copper-free, strain-promoted alkyne-azide cycloaddition (SPAAC) introduced by Bertozzi *et al.*,¹⁰³ see their publications. After performing polymerase chain reaction (PCR) DIBO-modified primers produced “clickable” amplicons, which could be tagged with azide-modified fluorophores (**Fig. 21**).¹⁰⁴

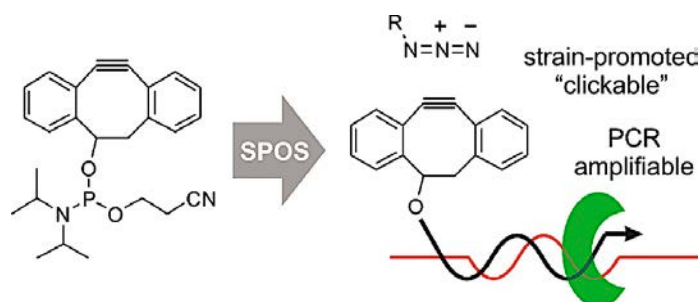


Fig. 21. solid-phase synthesis and characterization of 5'-dibenzocyclooctyne (DIBO)-modified oligonucleotides, using a new DIBO phosphoramidite, which react with azides via copper-free, strain-promoted alkyne-azide cycloaddition (SPAAC).

I.2.4. Synthesis of Lead Discovery Libraries

These libraries include lead compounds with biological activities and their chemical structure can

¹⁰³N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.* **2005**, *127*, 11196. ¹⁰⁴I. S. Marks, J. S. Kang, B. T. Jones, K. J. Landmark, A. J. Cleland, T. A. Taton, *BioConj. Chem.* **2011**, *22*, 1259-63.

be used as a starting hint for chemical modifications, which increase their physicochemical properties. This ‘lead discover libraries’ can be prepared by use of click reactions, and each library compound can be constructed in few steps, for example, the Cu catalyzed formation of 1,2,3-triazoles has recently been used to prepare functionalized resins for solid phase synthesis of a library of dopaminergic arylcarbamides (**Fig. 22**).¹⁰⁵

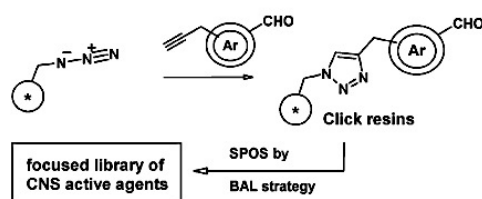


Fig. 22. First series of click linkers in the presence of aldehyde functionality for the traceless attachment of the substrate by use of BAL (*Backbone Amide Linker*) strategy with an application for a solid phase supported construction of a focus library of biologically active compounds.¹⁰⁵

I.2.5. Limitations of Click Chemistry

However HDC reaction showed a vast application in pharmaceutical area, but there are some limitations that can be seen using this synthetic method:

- 1. Alkyne homocoupling;** In this reaction, sometimes alkyne unifies with another alkyne molecule instead of azide, which yields a different product^{41a} (**Fig. 23**), however using a bulky base in this reaction enables us to decrease the homocoupling reaction.

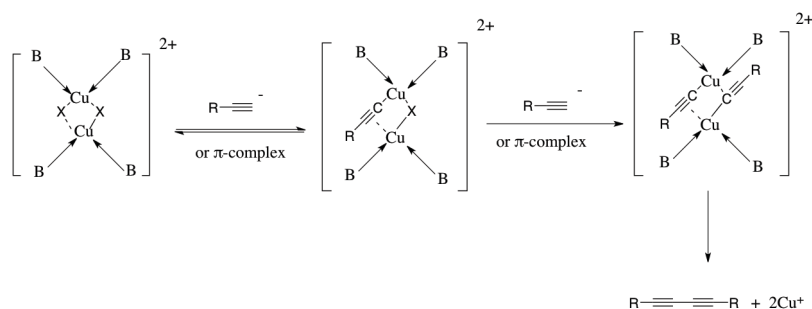


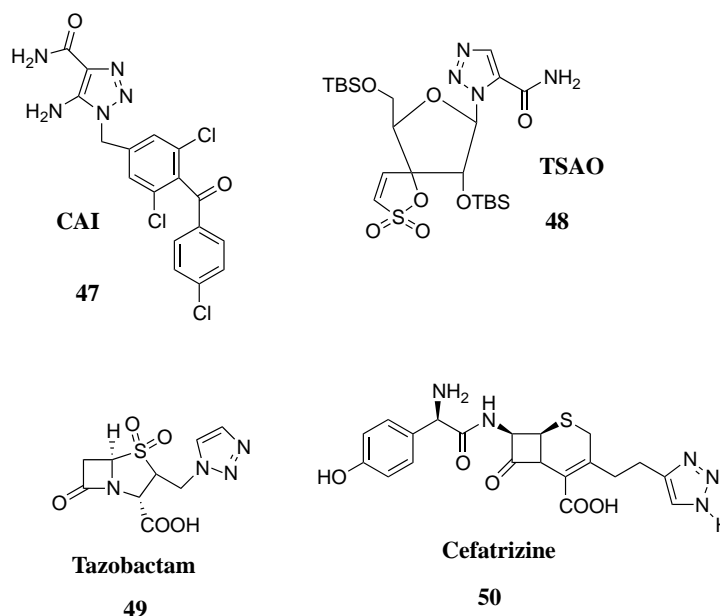
Fig. 23. Mechanism of acetylene homocoupling catalyzed by Cu^{2+}

¹⁰⁵S Loeber, P Rodriguez-Loaiza, P. Gmeiner, *Org. Lett.* **2003**, *5*, 1753-55.

2. Presence of copper as catalyst; as copper is cytotoxic, so its use can be a disadvantage in medicinal domain, because copper can cause diseases like hepatitis, Alzheimer, neurological disorders etc..¹⁰⁶

I.2.6. Biologically active 1,2,3-triazoles

There are not a lot of 1,2,3-triazolic derivatives, which are in the last stage of clinical examinations or are on the market. Among them, we can mention anticancer compound carboxyamidotriazole (CAI, **47**),¹⁰⁷ the nucleoside derivative non-nucleoside reverse transcriptase inhibitor *tert*-butyldimethylsilylspiroaminoxathioledioxide (known as TSAO, **48**),¹⁰⁸ β -lactam antibiotic Tazobactam (**49**), the cephalosporine Cefatrizine (**50**), etc. (Scheme 9).



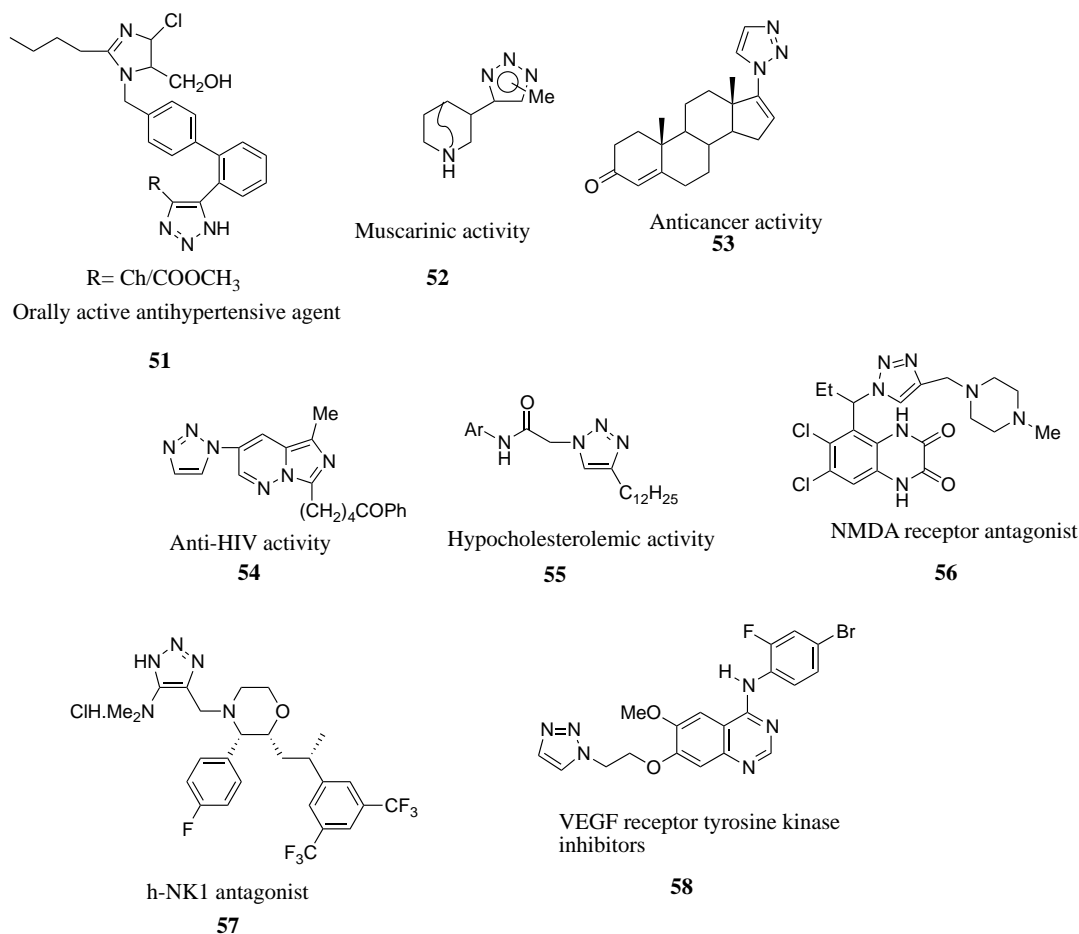
Scheme 9. Potential pharmaceuticals based on 1,2,3-triazoles.¹⁰⁹

I.2.7. Biologically active 1,2,3-triazoles synthesized without copper catalyst

As there is a high request in pharmaceutical domain to find out molecules with high selectivity and medicinal and pharmacokinetic properties, chemists are trying hard to explore potential pharmaceutical molecules, which can be prepared in a shorter time and contain all the required conditions for a medicinal agent.¹¹⁰ In this effort, some molecules with 1,2,3-triazole moiety were found that show interesting pharmaceutical applications. These molecules have been synthesized

¹⁰⁶T. Wang, Z. Guo, *Curr. Med. Chem.* **2006**, *13*, 525-53. ¹⁰⁷M. J. Soltis, H. J. Yeh, K. A. Cole, N. Whittaker, R. P. Wersto, E. C. Kohn, *Drug Metab. Dispos.* **1996**, *24*, 799-806. ¹⁰⁸C. Sheng, W. Zhang, *Curr. Med. Chem.* **2011**, *18*, 733-766. ¹⁰⁹S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696-2718. ¹¹⁰R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. De Clercq, C.-F. Perno, A. Karlsson, J. Balzarini, M. J. Camarasa, *J. Med. Chem.* **1994**, *37*, 4185-94.

before development of click chemistry and so without use of copper catalyst (**Scheme 10**). Some examples are shown in the following scheme. These molecules were synthesized by use of different methods.



Scheme 10. 1,2,3-Triazole-containing molecules with different biological activities.¹⁰⁹

I.2.8. Click reactions and the pharmacological applications of 1,2,3-triazoles

After appearance of the click chemistry term, this reaction was used widely to prepare triazolic derivatives by use of terminal alkynes and azides, which are stable under different conditions and they are inert to most biological and organic conditions, molecular oxygen, water, and the majority of common reaction conditions in organic synthesis.¹¹¹ Since 1,2,3-triazole moieties are stable to metabolic degradation and they can form hydrogen bonding that is favourable in the binding of biological targets and make better their solubility, they are attractive connecting units. Although 1,2,3-triazole moiety doesn't form in nature, but the synthetic molecules containing this unit

¹¹¹J. M. Baskin, C. R. Bertozzi, *QSAR Comb. Sci.* **2007**, 26, 1211-19.

showed interesting biological properties. Due to the poor basicity, the triazolic ring is not protonated at physiological pH, against other azaheterocycles. Another point is that, the nonprotonated sp^2 -hybridized nitrogen atoms of 1,2,3-triazoles could better imitate the partial positive charge at the anomeric carbon in the transition state of the glucosidase-catalyzed reaction in comparison with corresponding nitrogen atoms of iminosugars.¹¹² In a review paper, Meldal and Tornøe summarized some enzyme inhibitors and receptor ligands containing triazole moiety. They also mentioned some 1,2,3-triazole-modified natural products (**Fig. 24**).¹¹³

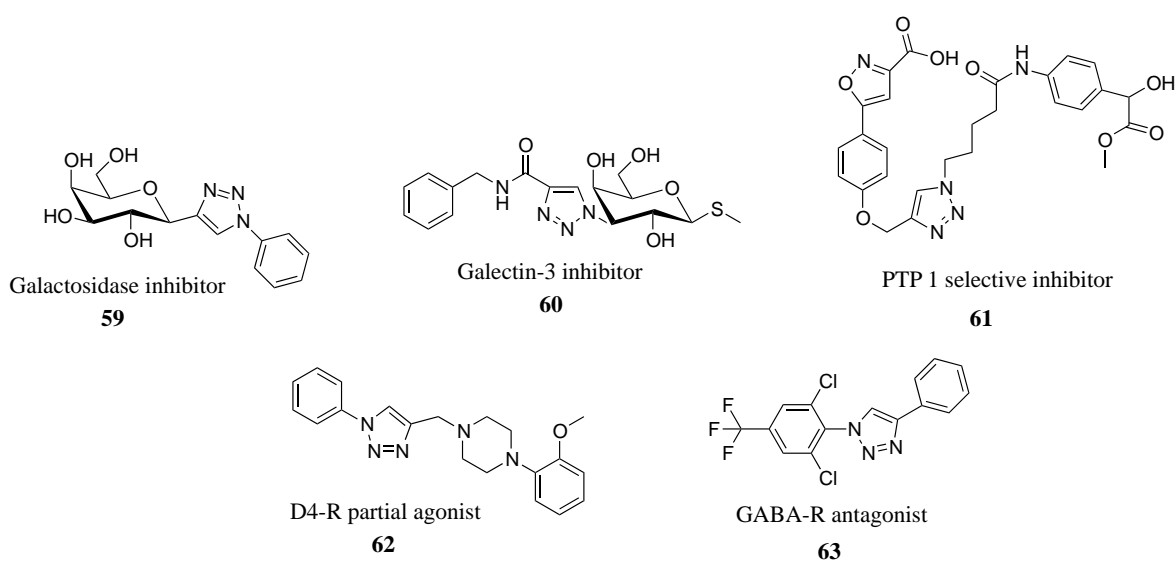


Fig. 24. Some examples of inhibitors containing triazolic moiety¹¹³

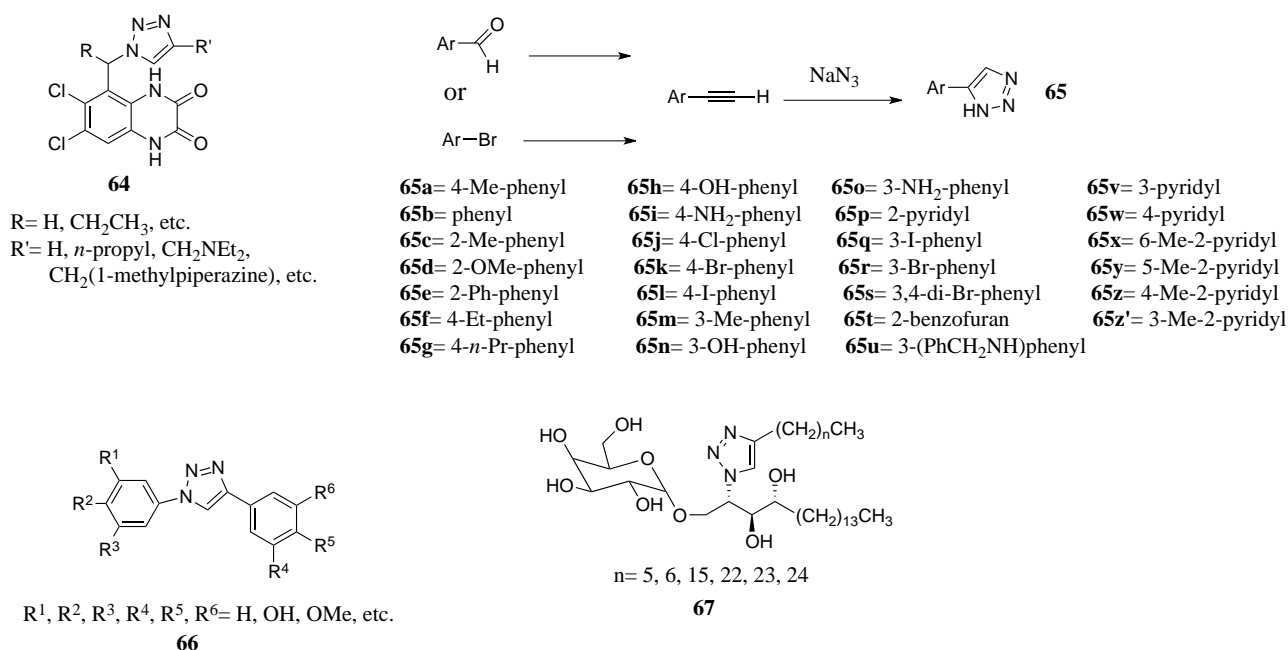
1.2.8.1. Anticancer

As the aim of our project in the synthesis of triazolic derivatives is mainly their application as anticancer agents, here we focused more on this property of 1,2,3-triazole containing molecules, however their application, as mentioned in above is not only limited to this area.

Nowadays, cancer is a main health problem in both developed and developing countries. Some anticancer agents containing taxol, vinblastine, vincristine, camptothecin derivatives, topotecan and irinotecan, and etoposide prepared from epipodophyllotoxin are in clinical use all over the world. There are also some potential agents such as flavopiridol, roscovitine, combretastatin A-4, betulinic acid, and silvestrol, which are in clinical or preclinical evolution. Despite of the existence of these pharmaceutical compounds, there is still a need to research and find new molecules with better

¹¹²M. I. Garcia-Moreno, D. Rodriguez-Lucena, C. O. Mellet, J. M. G. Fernandez, *J. Org. Chem.* **2004**, *69*, 3578-81. ¹¹³M. Meldal, C. W. Tornøe, *Chem. Rev.* **2008**, *108*, 2952-3015.

modes of action, and also a research on finding new analogues of the existing clinical agents is necessary. A series of 6,7-dichloro-1,4-dihydro-(1H,4H)-quinoxaline-2,3-diones were reported by M. J. Fray *et al.*, in which the 5-position substituent was a heterocyclylmethyl or 1-(heterocyclyl)-1-propyl group (**Scheme 11, 64**).¹¹⁴ Most of these reported compounds include a 1,2,3-triazole ring as a heterocyclic ring. Between these reported compounds, 6,7-dichloro-5-[1-(1,2,4-triazol-4-yl)propyl]-1,4-dihydro-(1H,4H)-quinoxaline-2,3-dione was the most important compound in the serie. Its brain penetration extent was also reported.



Scheme 11. Structures 1–4 and the synthesis of the 1,2,3-triazoles.¹⁰⁹

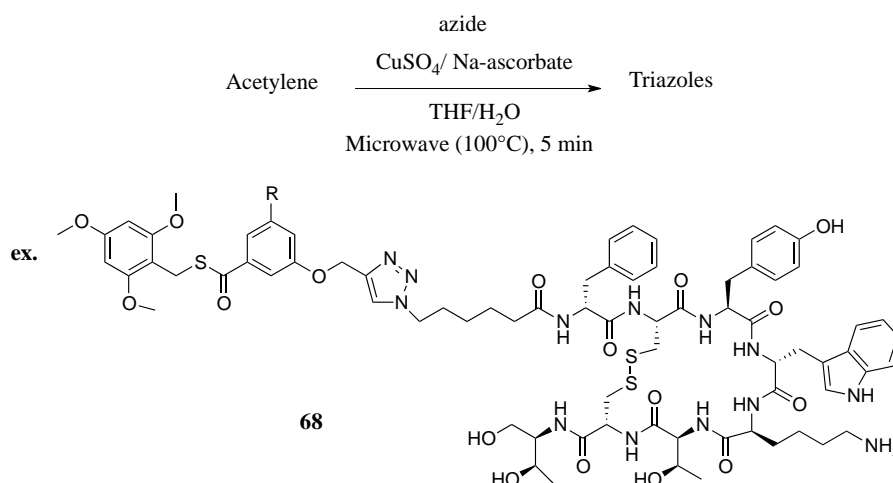
Another class of compound, which is used as inhibitors of human methionine aminopeptidase type 2 (hMetAP2) is 4-aryl-1,2,3-triazoles (**Scheme 11, 65**) that has been reported by Kallander *et al.* These compounds can be used as anticancer agents.¹¹⁵ In another paper, Pagliai *et al.* reported other anticancer agents, which were a large number of triazole derivatives of resveratrol. These compounds were prepared by a parallel combinatorial approach that used a typical click reaction (**Scheme 11, 66**).¹¹⁶ A few of these reported compounds showed antiproliferative activity.

As it is shown in scheme 11, derivatives **67** are a series of 1,2,3-triazole-containing α -GalCer analogues that are the most powerful agonist antigen of a natural killer T-cell receptor. These

¹¹⁴M. J. Fray, D. J. Bull, C. L. Carr, E. C. L. Gautier, C. E. Mowbray, A. Stobie, *J. Med. Chem.* **2001**, *44*, 1951-62. ¹¹⁵L. S. Kallander, Q. Lu, W. Chen, T. Tomaszek, G. Yang, D. Tew, T. D. Meek, G. A. Hofmann, C. K. Schulz-Pritchard, W. W. Smith, C. A. Janson, M. D. Ryan, G.-F. Zhang, K. O. Johanson, R. B. Kirkpatrick, T. F. Ho, P. W. Fisher, M. R. Mattern, R. K. Johnson, M. J. Hansbury, J. D. Winkler, K. W. Ward, D. F. Veber, S. K. Thompson, *J. Med. Chem.* **2005**, *48*, 5644-47. ¹¹⁶F. Pagliai, T. Pirali, E. D. Grosso, R. D. Brisco, G. C. Tron, G. Sorba, A. A. Genazzani, *J. Med. Chem.* **2006**, *49*, 467-70.

compounds were reported by Lee *et al.*, in which the lipid chain lengths were increasingly varied.¹¹⁷ By replacing the amide moiety of α -GalCer with a triazole they could increase the IL-4 versus IFN- γ bias of released cytokines. By increasing the length of the attached chain, they could also find a stronger Th2 cytokine response.

At the following of anticancer agents, Yim *et al.* explained the synthesis of a series of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-conjugated monomeric, dimeric, and tetrameric [Tyr³]octreotide-based analogues that were used as a tool for tumor imaging and/or radionuclide therapy (**Scheme 12**).¹¹⁸ These molecules were prepared in a CuI-catalyzed 1,3-dipolar cycloaddition condition, which was run between peptide azides and dendrimer-derived alkynes following of a metal-free introduction of DOTA by use of thio-acid/sulfonyl azide amidation (“sulfo-click” reaction, for this reaction see reference 118).



Scheme 12. Synthesis of Tetrameric [Tyr³]Octreotide Triazoles.¹¹⁸

I.2.8.2. *In-vivo* tumor cell targeting with ‘Click’ nanoparticles

As nanomaterials showed efficiency in *in-vivo* experiments, scientists try to improve library screening methods to find targeting ligands for different *in-vivo* sites. This aim needs ligand attachment chemistries, which are universal, effective, covalent, orthogonal to different biochemical libraries, useful under aqueous conditions, and stable in biologic environments. Among chemical reactions, copper (I)-catalyzed Huisgen 1,3-dipolar cycloaddition in another word ‘click’ reaction

¹¹⁷T. Lee, M. Cho, S.-Y. Ko, H.-J. Youn, D. J. Baek, W.-J. Cho, C.-Y. Kang, S. Kim, *J. Med. Chem.* **2007**, *50*, 585-89. ¹¹⁸C.-B. Yim, I. Dijkgraaf, R. Merckx, C. Versluis, A. Eek, G. E. Mulder, D. T. S. Rijckers, O. C. Boerman, R. M. J. Liskamp, *J. Med. Chem.* **2010**, *53*, 3944-53.

proved these characteristics that can be used for developing targeted nanomaterials *in vitro*. In a paper in 2011, Chaturvedi *et al.*, reported the use of “click” chemistry for the *in vivo* targeting of inorganic nanoparticles to tumors. In this research, they found that cyclic Lyp-1 targeting peptides could be linked to azido-nanoparticles in a specific way by “click” reaction. This linkage conducts them to bind to p32-expressing tumor cells *in vitro*. In addition, “click” nanoparticles circulate durable for hours *in vivo* through intravenous direction (>5h circulation time), and get into tumors and penetrate the tumor interstitium to bind specifically p32-expressing cells in tumors (**Fig. 25**).¹¹⁹

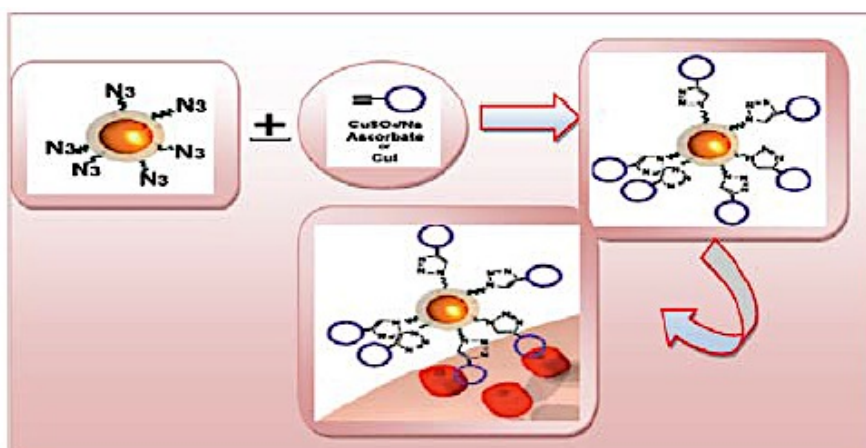


Fig. 25. Design of a nanoparticle that targets Tumor Cells *in-vivo* and *in-vitro*.

From these vast applications of Click Chemistry in different field, for this project in our laboratory, we decided to focus on the synthesis of highly diversified small-molecules based on triazole derivatives and study their biological activity especially as anti-cancer agents. In the next chapter we will focus on the synthesis of these small-molecules.

¹¹⁹P. Chaturvedi, N. Chaturvedi, S. Gupta, A. Mishra, M. Singh, T. Siddhartha, *Intl. J. Pharm. Sci. Rev. Res.* **2011**, *10*, 111-17.

Chapter II

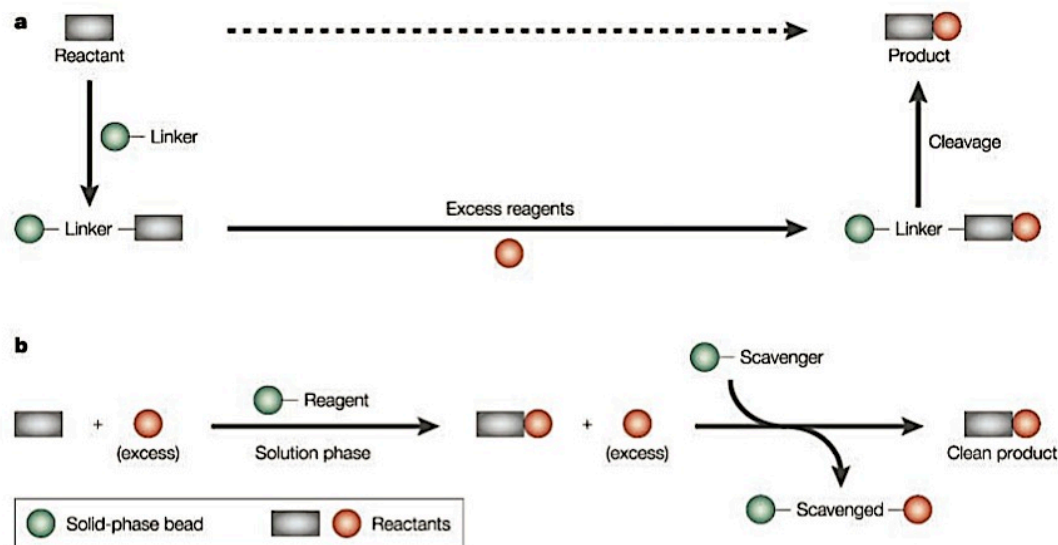
Synthesis of triazolic derivatives departing from aldehydes and by use of a solid supported catalyst (A-21.CuI) and study their biological activity

II- Solid Supported catalyst

The concept of solid-phase organic synthesis (SPOS) was presented for the first time in mid 1940's and Merrifield developed solid-phase peptide synthesis in the 1960s.¹²⁰ During the last two decades there was a huge interest in developing SPOS¹²¹ that can be due to the need to find more environmentally friendly and rational routes to various materials. This effort is justified by the growth of green chemistry.¹²² Application of environmentally friendly surface catalysts like a solid catalyst is an important aspect of clean technology that can be easily recovered once the reaction is complete.¹²³ On the other hand, one of the most important advantages of using polymer supports in organic synthesis is the clean isolation of the products by simple filtration, and because of that this method has become a valuable tool in combinatorial chemistry and high-throughput chemistry, an integral part of drug discovery and research.¹²⁴

There exist two sub-classifications for supported reagents: organic and inorganic supports¹²⁵ that the former are polymeric, such as cross-linked polystyrenes, and are numerous, covering ion-exchange resins through to those based on quite complex surface architectures. Among inorganic supports that are suitable for conversion into supported reagents can mention silicas, aluminas, carbons (notably charcoals), montmorillonites, zeolites and other aluminosilicates, as well as more complex materials such as partially substituted aluminosilicates (*e.g.* aluminophosphates or ALPOs) and more complex materials such as hetero- polyacids. There are some important points for choosing a suitable polymer or a solid phase in order to have successful and efficient solid-phase synthetic protocol such as suitable linkers with polymers, the nature of binding with the substrate/reagent (covalent or noncovalent), stability and recyclability (**Scheme 13**).¹²⁶

¹²⁰R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149-54. ¹²¹a) G. H. Posner, *Angew. Chem. Int. Ed.* **1978**, *17*, 487-96; b) A. Mckillop, K. W. Young, *Synthesis* **1979**, 401-22; c) A. Cornelis, P. Laszlo, *Synthesis* **1985**, 909-18; d) J. H. Clark, *Catalysis of Organic Reactions by Supported Inorganic Reagents*, VCH, New York, NY, USA **1994**; e) R. L. Lestinger, V. Mahadevan, *J. Am. Chem. Soc.* **1965**, *87*, 3526-27; f) J. M. Fraile, J. A. Mayoral, A. J. Royo, R. V. Salvador, B. Altava, S. V. Luis, M. I. Burguete, *Tetrahedron* **1996**, *52*, 9853-62. ¹²²a) A. P. T. Anastas, J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford Science Publications, New York, NY, USA, **1998**; b) P. T. Anastas, T. Williamson, *Green Chemistry: Frontiers in Benign Chemical Synthesis and Procedures*, Oxford Science Publications, New York, NY, USA, **1998**; c) J. H. Clark, *Green Chem.* **1999**, *1*, 1-8; d) M. Lancaster, *Green Chemistry: An Introductory Text*, Royal Society of Chemistry, Cambridge, Mass, USA, **2002**. ¹²³G. W. V. Cave, C. L. Raston, J. L. Scott, *Chem. Commun.* **2001**, *21*, 2159-69. ¹²⁴a) M. Lebel, *Biopol.* **1998**, *47*, 397-404; b) N. J. Maeji, R. M. Valerio, A. M. Bray, R. A. Campbell, H. M. Geysen, *React. Pol.* **1994**, *22* (3), 203-12; c) N. Hird, I. Hughes, D. Hunter, M. G. J. T. Morrison, D. C. Sherrington, L. Stevenson, *Tetrahedron* **1999**, *55*, 9575-84. ¹²⁵a) D. C. Sherrington, "Polymer-Supported Synthesis", in *Chemistry of Waste Minimisation*, J. H. Clark, Ed., chapter 6, Blackie Academic, London, UK, **1995**; b) J. H. Clark, A. P. Kybett, D. J. Macquarrie, *Supported Reagents: Preparation, Analysis and Applications*, VCH, New York, NY, USA, **1992**; c) D. J. Gravert, K. D. Janda, *Chem. Rev.* **1997**, *97*, 489-509. ¹²⁶S. V. Ley, I. R. Baxendale, *Nat. Rev.* **2002**, *1*, 573-586.



Scheme 13. Polymer supports in organic synthesis. a | Conventional solid-supported chemistry as used in combinatorial chemistry programmes. The initial substrate is immobilized on a polymeric resin and taken through a synthetic sequence, with the product being recovered at the end by cleavage back into solution. Reactions can be driven to completion with excess reagents. **b** | Solid-supported reagents in clean synthesis. Here, the reaction between substrates takes place in solution, with the reagent being associated with a support material. Excess or spent reagent can be easily removed by filtration, and impurities or unreacted substrates can be removed from solution using a scavenger that is immobilized on a support.¹²⁶

II. 1. Synthesis of triazolic derivatives on a solid-supported catalyst

As it was mentioned in the previous chapter, 1,2,3-triazole heterocycles have some interesting characteristics such as having high dipoles, stability toward different conditions like oxidizing and reducing agents, the ability of making hydrogen bonds and also ability of interacting with a variety of molecules such as biological targets. Against these advantages of triazole derivatives, their synthesis was limited until recently because of the absence of a reliable method to synthesize these kind of molecules. In that order, studies to find a better reaction condition were performed. In this context, Fokin *et al.*¹²⁷ developed stable and simple catalysts based on polymer-bound copper (I) catalyst (TG-TBTA-CuPF₆), which performs well in a range of solvents. This catalyst fulfils simplified workup protocol by preventing the leaching of the copper catalyst that results the product contamination. The usefulness of polymer-bound reagents and catalysts are well known today.¹²⁸ These reagents permit isolation of final product by only a simple filtration or evaporation.

¹²⁷T. R. Chan, V. V. Fokin, *QSAR Comb. Sci.* **2007**, 26, 1274-79. ¹²⁸a) S. Brase, F. Lauterwasser, R.E. Ziegert, *Adv. Synth. Catal.* **2003**, 345, 869-929; b) N. Leadbeater, M. Marco, *Chem. Rev.* **2002**, 102, 3217-73.

In this proposed resin (TG-TBTA-CuPF₆) by Fokin, which is a TentaGel[®]-immobilized TBTA(Tris(Benzyltriazolylmethyl)Amine)(**Fig. 26**) proved acceleration of the reaction by protecting and stabilizing the copper (I) from oxidation, and so improved the efficiency of the CuAAC. TBTA has also extensive applications in biological domain¹²⁹ as well as in the synthetic processes.¹³⁰

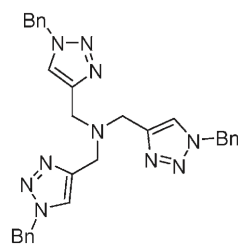
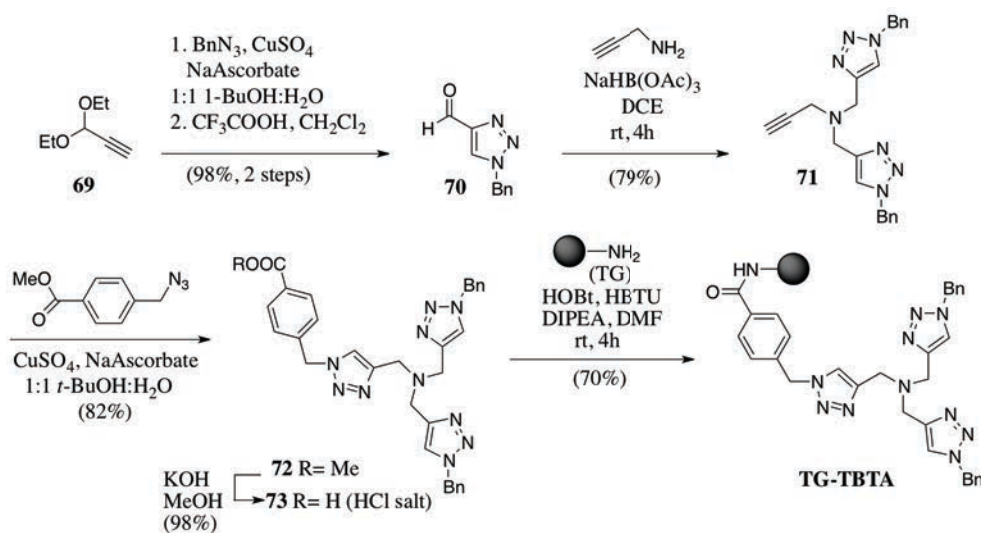


Fig. 26. TBTA's structure

Fokin and his co-workers observed that immobilization of a polytriazole ligand on a solid support could make easy the set-up and purification protocols of the reaction for use in large parallel synthetic collections. The synthesis of the resin TentaGel[®]-immobilized TBTA can be performed in several steps, as is shown in Scheme 14.



Scheme 14. Synthesis of the TentaGel-supported TBTA ligand.

In the last step, immobilization was done with the standard peptide bond forming conditions that is performed in the presence of a carboxy functionalized TBTA, which was attached to NovaSyn[®]

¹²⁹a) E. K. Beatty, F. Xie, Q. Wang, D. A. Tirrell, *J. Am. Chem. Soc.* **2005**, *127*, 14150-1; b) A. J. Link, D. A. Tirrell, *J. Am. Chem. Soc.* **2003**, *125*, 11164-5. ¹³⁰M. Cassidy, J. Raushel, V. V. Fokin, *Angew. Chem. Int. Ed.* **2006**, *45*, 3154-7.

TG amino resin. Here, TG resin, which is a polystyrene-PEG graft polymer, is selected due to its excellent swelling properties in a variety of solvents. The choice of a Merrifield resin to reach to catalytic activities was not successful because of its poor swelling properties of the support and incapable linker lengths. In this procedure, the resin TG-TBTA was loaded with 0.19 mmol/g that was determined by elemental analysis, and copper (I) was preloaded onto the resin by a simple washing of the TG-TBTA with an appropriate copper (I) solution (*e.g.* 10% solution of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ in acetonitrile/dichloromethane).¹²⁷

Another organic polymeric solid support for Huisgen 1,3-dipolar cycloaddition reaction was proposed by Du Prez group¹³¹ that was based on a cross-linked poly(*N*-methylethylenimine) (PMEI). This polymer can be easily prepared from readily available branched PEI (Fig. 27).

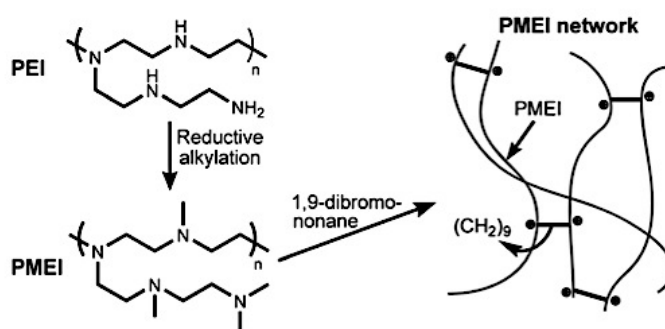
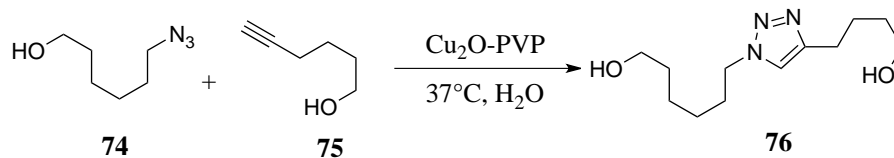


Fig. 27. Synthesis of a PMEI network as a solid support for Cu(I).¹³¹

However a lower amount of copper can be loaded on the support, but still quantitative yields could be obtained within 40 min for the click reaction of phenylacetylene (PhAc) and benzylazide (BnAz) (2.2 eq.) at room temperature. By the use of this polymer high molecular weight compounds could also be successfully clicked, despite a reduced reaction rate.

Poly(*N*-vinyl-2-pyrrolidone) (PVP) has also been used as a stabilizer for the copper catalyst in heterogeneous azide-alkyne click chemistry (Scheme 15).¹³²

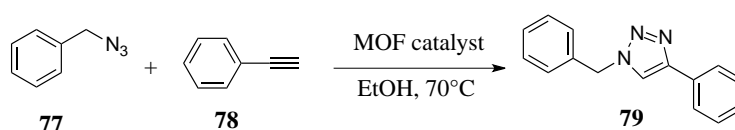
¹³¹B. Dervaux, F. E. Du Prez, *Chem. Sci.* **2012**, 3, 959-66. ¹³²Z. F. Zhang, C. M. Dong, C. H. Yang, D. Hu, J. Long, L. Wang, H. Li, Y. Chen, D. L. Kong, *Adv. Synth. Catal.* **2010**, 352, 1600-4.



Scheme 15. Huisgen 1,3-dipolar cycloaddition reaction in the presence of Cu_2O -NPs as a solid-support catalyst.¹³²

This PVP-coated Cu_2O nanoparticles system was a better catalyst in comparison with other catalytic systems because of its biocompatibility. Because of a high surface area, an increased catalytic activity was expected, but long reaction times were still obtained for the model click reaction. In addition, another problem with this catalytic system was impossibility or hard method for recycling.

A recyclable heterogeneous catalyst that was proposed for the Huisgen 1,3-dipolar cycloaddition reaction was based on metal organic frameworks (MOFs).¹³³ MOFs are crystalline and porous materials that contain an extended network of copper ions that are readily and strongly interacting with organic ligands. Some of MOFs proposed by Corma's group¹³³ are Copper hydroxypyrimidinolate, $[\text{Cu}(2\text{-pymo})_2]$, copper imidazolate, $[\text{Cu}(\text{im})_2]$, copper trimesate, $[\text{Cu}_3(\text{BTC})_2]$, and copper terephthalate, $[\text{Cu}(\text{BDC})]$ (**Scheme 16**).¹³⁴



Scheme 16. The 1,3-dipolar cycloaddition reaction catalyzed by various copper-containing MOF catalysts.¹³³

However this catalytic system required high reaction temperatures, but it showed an activity comparable to that of homogeneous catalysts. In addition, no leaching of the copper catalyst was observed.

¹³³I. Luz, F. X. Llabrés i Xamena, A. Corma, *J. Catal.* **2010**, 276, 134-40. ¹³⁴a) L. C. Tabares, J. A. R. Navarro, J. M. Salas, *J. Am. Chem. Soc.* **2001**, 123, 383-7; b) N. Masciocchi, S. Bruni, E. Cariati, F. Cariati, S. Galli, A. Sironi, *Inorg. Chem.* **2001**, 40, 5897-5905; c) S. S. Y. Chui, S. M. F. Lo, J. P. H. Charmant, A. G. Orpen, I. D. Williams, *Science* **1999**, 283, 1148-50; d) C. G. Carson, K. Hardcastle, J. Schartz, X. Liu, C. Hoffmann, R. A. Gerhardt, R. Tannenbaum, *Eur. J. Inorg. Chem.* **2009**, (16), 2338-43.

II.2. Amberlyst copper (I)-A-21 (A-21.CuI)

Another organic polymer-supported catalyst which was the first proposed by our group was a heterogeneous catalytic system based on copper (I) iodide chelated on Amberlyst[®] A-21 resin that was used widely in the synthesis of 1,4-disubstituted 1,2,3-triazoles from organic azides and terminal alkynes.¹³⁵ This Amberlyst A-21 polymer is a dimethylaminomethyl-grafted polystyrene with an amine group (**Fig. 28**), which acts both as a base and a chelant, so the copper can be chelated on this resin.

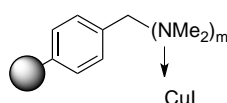
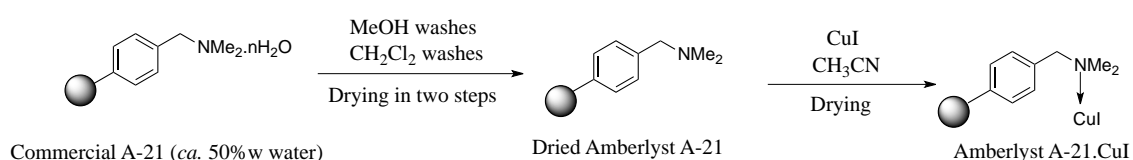


Fig. 28. Structure of Amberlyst A-21.CuI

The advantage of this catalytic system is its ease of preparation, fast and simple isolation of the final product by filtration and in addition the catalyst could be recycled and reused several times. In order to prepare Amberlyst A-21.CuI, first we need to dry A-21 because commercially available A-21 is wet (**Scheme 17**). In that order, only a simple washing of A-21 beads with MeOH and DCM is necessary and then it was kept in Büchi over night at 50°C.



Scheme 17. Amberlyst A-21.CuI catalyst preparation.

After this first step we examined the fixation and activity of copper (I) salts on Amberlyst A-21, because this catalytic system can be prepared by a simple incubation of Amberlyst A-21 and CuI in a suitable organic solvent, and for this reason, the solubility of copper (I) halides in different organic solvents was tested (**Table 1**). Cuprous chloride is completely insoluble in usual solvents, but by using the corresponding bromide a better solubility was obtained in solvents such as EtOH, MeOH, DMSO, and DMF and cuprous iodide showed a unique solubility in acetonitrile, so acetonitrile was selected as the best solvent. The choice of solvent to fix copper salt onto the polymer depends on the compatibility of the used solvent with hydrophobic polystyrene network and also the ease of removal of the solvent at the end of the doping process of polymer with copper.

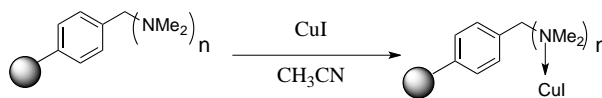
¹³⁵C. Girard, E. Onen, M. Aufort, S. Beauvière, E. Samson, J. Herscovici, *Org. Lett.*, **2006**, 8, 1689-92.

Table 1. Solubility tests of copper (I) halides in organic solvents¹³⁵

Salt	EtOH	MeOH	DMSO	DMF	THF	AcOEt	CH ₃ CN	CH ₂ Cl ₂
CuCl	I	I	I	I	I	I	I	I
CuBr	S	S	S	S	I	I	I	I
CuI	I	I	I	I	I	I	S	I

I= instable or partially stable ; S= stable.

In the second step, fixation of CuI on A-21 was examined by using different ratios of each of these components in the same volume of acetonitrile. The results are summarized in Table 2. As is shown in Table 2, the longer we keep the CuI solution in contact with resin, the more is the amount of the fixed CuI on resin (Table 2, entries 2 and 3), so for the other tests incubation was performed overnight for better fixation of CuI and finally a better fixation was obtained by use of 2.4 mmol of amine/0.5 mmol of CuI and when we increased mmol of CuI to 1.0 mmol for 2.4 and 4.8 mmol of amine (Table 2, entries 4 and 6) again better fixation was observed. Finally from all of these results we chose a ratio of 2.4 mmol of amine/1.0 mmol of CuI that conducted a polymer with a final composition of 1.23 mmol of CuI/g of resin.

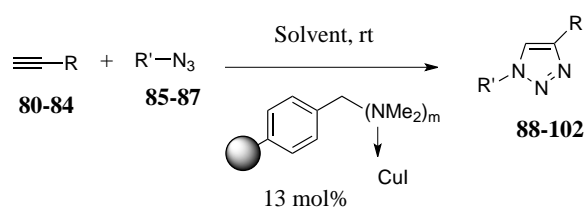
Table 2. Fixation tests of Cuprous Iodide on Amberlyst A-21 in Acetonitrile at Room Temperature^a

Entry	A-21 ^b mg (mmol)	CuI mg (mmol)	time h	CuI fixed ^c mmol (mg)	Catalyst mmol CuI/g
1	250 (1.2)	95 (0.5)	24	0.221 (42)	0.76
2	500 (2.4)	95 (0.5)	24	0.368 (70)	0.65
3	500 (2.4)	95 (0.5)	1	0.195 (37)	0.36
4	1 000 (4.8)	95 (0.5)	24	0.274 (52)	0.26
5	250 (1.2)	190 (1.0)	24	0.546 (104)	1.54
6	500 (2.4)	190 (1.0)	24	0.805 (153)	1.23
7	1 000 (4.8)	190 (1.0)	24	0.726 (138)	0.64

^aPerformed in 5 mL of solvent at room temperature for the indicated time under agitation. ^bDry Amberlyst A-21, 4.8 mmol N/g. ^cAfter filtration, washings and drying of the polymer *in vacuo*, evaluated by weight increase.¹³⁵

To run the Huisgen cycloaddition reaction by use of this Amberlyst A-21.CuI in an automated synthesis (synthesis robot), we tried the reaction first in acetonitrile as solvent, but we obtained some colored impurities, residual azide or a trace of copper released from the polymeric catalyst, which demand further purification. In the presence of MeOH that is a more polar solvent and the starting materials are better soluble in it, leaching of the copper from catalyst was observed again, so the reaction was repeated in dichloromethane as solvent, and this time all of the products were isolated pure by a simple filtration to remove catalyst and evaporation of solvent. Here, any traces of starting material or copper were observed on LC-MS analysis (**Table 3**).

Table 3. Automated synthesis of 1,4-Substituted 1,2,3-Triazoles using the A-21.CuI Catalyst at room temperature^a

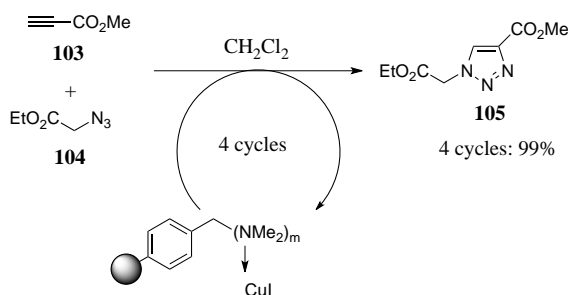


Alkyne	Azide/Product ^b	Yield ^c	Azide/Product ^b	Yield ^c	Azide/Product ^b	Yield ^c
	Bn-N ₃	(%)	HO(CH ₂) ₃ N ₃	(%)	EtO ₂ C(CH ₂) ₂ N ₃	(%)
	85		86		87	
		A: 91 B: 93		A: 27 B: 61 ^d		B: 76
		A: 80 B: 92		A: 62 B: 90		B: 99
		A: 78 B: 97		A: 70 B: 13 ^{d,e}		B: 99
		A: 50 B: 99		A: 37 B: 99		B: 99
		A: 74 B: 99		A: 87 B: 84 ^d		B: 99

^aReaction conditions: 0.5 mmol of alkynes, 0.55 mmol of azide, 31 mg of resin (1.23 mmol of CuI/g, 0.038 mmol of CuI, 8 mol%), 2 ml of solvent. ^bAll products gave correct analysis. ^cConditions A: Yields in CH₃CN after a needed purification for all products. B: Unoptimized isolated yields from CH₂Cl₂. ^dPurified yield. ^eSolubility problems for **95** in CH₂Cl₂.

II.2.1 Stability of Amberlyst A-21.CuI

The stability and ability of this polymeric catalyst was examined by use of propiolic acid methyl ester (**103**) and ethyl azidoacetate (**104**) as the starting materials, which led to the triazole **105** in quantitative yield (**Scheme 18**).



Scheme 18. Recycling the supported catalyst.¹³⁵

As is shown in **Scheme 18**, we reused the Amberlyst A-21.CuI through 4 cycles to produce triazole **105**, and in all cases the final triazole was obtained without decrease in yield. In addition, during our study on recycling of the catalyst we observed some stabilities of the catalyst in a way that no precaution is necessary to keep catalyst for a long time, because we just stored samples of Amberlyst A-21.CuI in a capped vial without protecting them from humidity or oxygen. Even in this condition the catalyst kept its activity after at least four months, which shows the ease of handle of this catalyst that makes it privilege to another reported catalysts for this reaction.

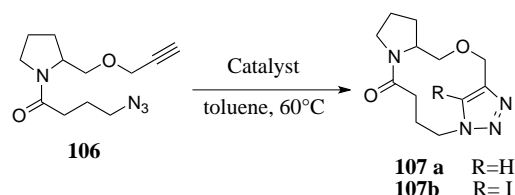
II.2.2. Limits of the Amberlyst A-21.CuI

Before using A-21.CuI we need to clarify some points of this catalytic system studies in literature. In a paper Marcaurelle *et al.*,¹³⁶ reported the use of Amberlyst A-21.CuI as catalyst to find macrocyclic triazole rings through an intermolecular cycloaddition reaction and by modifying the reaction condition (toluene as solvent and heating).

In this study, first they used a complex of ruthenium ($\text{Cp}^*\text{RuCl}(\text{PPh}_3)$) as catalyst, which conducted the intramolecular cycloaddition of an azido alkyne substrate (**Scheme 19**), but in this condition they observed formation of a dimer product (50%), then they decided to subject our proposed supported polymer catalyst (Amberlyst A-21.CuI) in this reaction, and this time pleasingly they

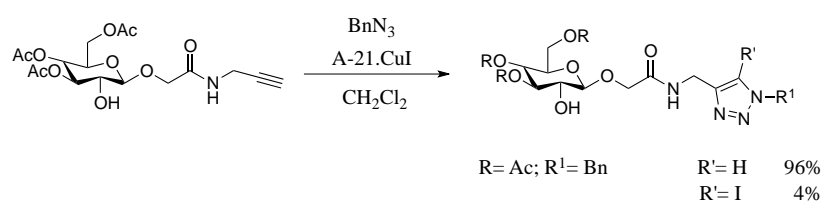
¹³⁶A. R. Kelly, J. Wei, S. Kesavan, J.-C. Marie, N. Windmon, D. W. Young, L. A. Marcaurelle *et al.*, *Org. Lett.* **2009**, *11*, 2257-60.

obtained only a monomeric 1,4-triazole, but they announced also observation of a side product, which was an iodine incorporation on triazole without mentioning the proportion of this side product that could be due to the stoichiometric amount of the A-21.CuI that they subjected to the reaction, in addition they performed the reaction in toluene as solvent and at 60°C and with the catalyst at 100 mol%.



Scheme 19. Intramolecular Cycloaddition of an azido alkyne.

In another paper reported by Queneau¹³⁷ where they worked on CuAAC reaction between a galactoside and benzyl or hexyl azide in the presence of A-21.CuI as catalyst (4%) (**Scheme 20**), they announced also this iodine incorporation on triazole as by-product (4%).



Scheme 20. Synthesis of triazoles from carbohydrates reported by Queneau¹³⁷

From these reported results, we decided to study the origin of this problem, because we haven't detected formation of any 5-iodine side product by using A-21.CuI in our laboratory.

For this study, we supposed that this iodation reaction could be due to modifying some parameters in the preparation of either the catalyst or reagents. In that order, we examined different factors and their influence on CuAAC reaction. For preparing the dried A-21, we tried different source of A-21 (Sigma Aldrich or Acros), washing with different solvents and different quality (distilled or not), drying the A-21 in the oven at 50°C and without protecting from oxygen or drying at 50°C by use of rotary evaporator (10 mm Hg), then for incubation of A-21 with CuI we used again different source of CuI (Sigma Aldrich or Acros), incubation in various qualities of acetonitrile (analytical grade (SDS), HPLC PLUS gradient grade (Carlo-Erba), HPLC grade (degassed before use)). Another factor that we changed during the incubation process was protecting or not protecting the

¹³⁷N. M. Xavier, M. Goulart, A. Neves, J. Justino, S. Chambert, A. Rauter, Y. Queneau, *Bioorg. Med. Chem.* **2011**, *19*, 926-38.

solution from light. After incubation of the dried A-21 with CuI in acetonitrile, the polymer was dried in vacuo by protecting from light and another time without any protection. By applying these modified factors in the procedure of preparing A-21.CuI, at the end we obtained the beads with different aspects (beads with yellow, beige, white, light-green or light-blue colors) and also with different amounts of copper loading on catalyst (between 1.06 up to 1.43 mmol CuI.g⁻¹). The results are summarized through Table 4 and Fig. 29.

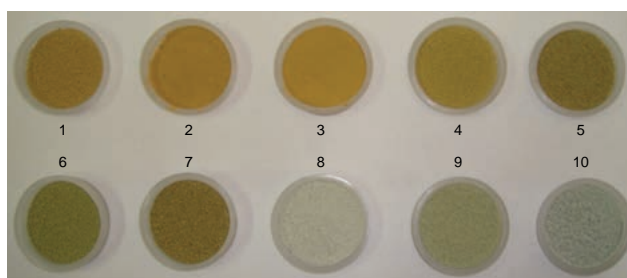


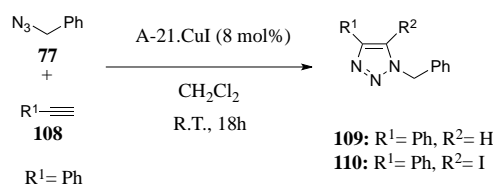
Fig. 29. Amberlyst A-21.CuI catalysts prepared by modifying preparation procedure. (Table 4)

Table 4. Preparation of A-21.CuI by modifying different factors in the preparation process.

Entry	A-21 source	Washes (agitation) ^b	Drying (50°C) ^c	CuI source	Incubation (light) ^e	Drying (light) ^e	Loading (mmolCuI.g ⁻¹)	Aspect
1	Acr	MeOH(MAG) CH ₂ Cl ₂ ^f (MAG)	Oven, air, overnight	S.-A.	CH ₃ CN ^h ,(+hv)	Büchi,(+hv)	1.06	Yellow beads
2	Acr	CH ₃ CN(MAG) CH ₂ Cl ₂ ^f (MAG)	Evaporator, 10mm Hg	S.-A.	CH ₃ CN ^h ,(+hv)	Büchi,(+hv)	1.30	Yellow powder
3	Acr	MeOH(MAG) CH ₂ Cl ₂ ^f (MAG)	Evaporator, 10mm Hg	S.-A.	CH ₃ CN ^h ,(+hv)	Büchi,(+hv)	1.20	Yellow powder
4	Acr	MeOH(MAN) CH ₂ Cl ₂ ^g (MAN)	Evaporator, 10mm Hg	S.-A.	CH ₃ CN ^h ,(+hv)	Büchi,(+hv)	1.43	Beige beads
5	Acr	MeOH(MAN) CH ₂ Cl ₂ ^g (MAN)	Evaporator, 10mm Hg	A.-C.	CH ₃ CN ^h ,(+hv)	Büchi,(+hv)	1.41	Beige beads
6	Ald	MeOH(MAN) CH ₂ Cl ₂ ^g (MAN)	Evaporator, 10mm Hg	S.-A.	CH ₃ CN ^h ,(+hv)	Büchi,(+hv)	1.36	Beige beads
7	Ald	MeOH(MAN) CH ₂ Cl ₂ ^g (MAN)	Evaporator, 10mm Hg	A.-C.	CH ₃ CN ^h ,(+hv)	Büchi,(+hv)	1.40	Beige beads
8	Acr	MeOH(MAN) CH ₂ Cl ₂ ^g (MAN)	Evaporator, 10mm Hg	S.-A.	CH ₃ CN ^h ,(-hv)	Büchi,(-hv)	1.37	White beads
9	Acr	MeOH(MAN) CH ₂ Cl ₂ ^g (MAN)	Evaporator, 10mm Hg	S.-A.	CH ₃ CN ⁱ ,(-hv)	Büchi,(-hv)	1.39	Light green beads
10	Ald	MeOH(MAN) CH ₂ Cl ₂ ^g (MAN)	Evaporator, 10mm Hg	S.-A.	CH ₃ CN ^j ,(-hv)	Büchi,(-hv)	1.33	Light blue beads

^aAcr= Acros, Ald= Aldrich. ^bMAN=manual agitation, MAG= magnetic agitation. ^cbefore being dried (10 mm Hg) and kept in a desiccator containing P₂O₅. ^dS.-A.= Sigma Aldrich; A.-C.= Ali-drich-Chemie. ^e-hv= protection from light by aluminium foil; +hv= without protection from light and incubation and drying in vials (40°C, 0.01 mm Hg, Büchi oven). ^fUntreated CH₂Cl₂. ^gCH₂Cl₂ distilled from P₂O₅. ^hAnalytical grade acetonitrile, SDS (France). ⁱHPLC PLUS Gradient grade acetonitrile Carlo-Erba (France). ^jHPLC grade acetonitrile, degased before use.

Once different samples of A-21.CuI were prepared by modifying some parameters, it was subjected to the CuAAC reaction between phenyl acetylene and benzyl azide as a model reaction (**Scheme 21**) and the reaction was followed on ^1H NMR. The results are shown in Table 5.



Scheme 21. Model reaction tested with samples of A-21.CuI for quantification of iodation products.

As is shown in Table 5, use of catalysts 1-3 (entries 1-3) result highest ratios of iodation (9-12%), but changing the source of A-21 (Acros or Aldrich) doesn't seem to have a great impact on the iodation levels (catalysts 4-5 vs. 6-7, entries 4-7), however the source of CuI influenced a little ratios of iodation in the way that by using a better quality of CuI the 5-iodine side product was obtained with less than 0.5% yield (catalyst 8, entries 8-9). Aging of the catalyst increases the iodation level from <0.5% to around 2% (entries 8-9 vs. 10-11), so presence of light and aging of the catalyst seem to be also responsible for more iodation.

Table 5. Reactions of phenylacetylene and benzyl azide in the presence of different samples of A-21.CuI

Entry	A-21.CuI	h ν ^b	5-H(%) ^c	5-I (%) ^c	Entry	A-21.CuI	h ν ^b	5-H (%) ^c	5-I (%) ^c
1	1	+	2 (91) ^d	3 (9)	10	8 ^e	+	2 (97.6)	3 (2.4)
2	2	+	2 (88) ^d	3 (12)	11	8 ^e	-	2 (98.2)	3 (1.8)
3	3	+	2 (88) ^d	3 (12)	12	9	+	2 (98.2)	3 (1.8)
4	4	+	2 (99)	3 (1)	13	9	-	2 (98.9)	3 (1.1)
5	5	+	2 (95)	3 (3)	14	10	+	2 (99.2)	3 (0.8)
6	6	+	2 (98)	3 (2)	15	10	-	2 (99.2)	3 (0.8)
7	7	+	2 (97)	3 (3)					
8	8	+	2 (>99.5)	3 (<0.5)					
9	8	-	2 (>99.5)	3 (<0.5)					

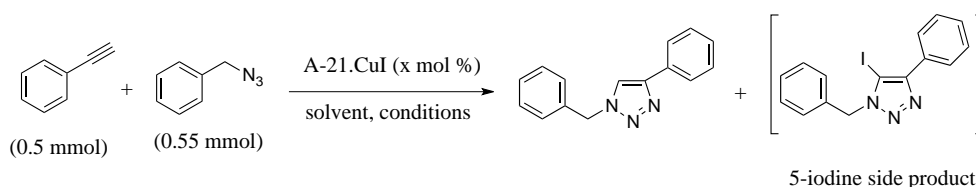
^a0.5 mmol alkyne/ 0.55 mmol azide in 2 ml CH₂Cl₂. ^bprotection from light (-) or not (+). ^cdefined by ^1H NMR. ^dresidual azide (8-15%). ^eOne year old sample.

Another factor that could cause the formation of 5-iodine was the quality of applied CH₃CN. Changing from analytical grade (entries 8-9) to HPLC (entries 12-15), which increased the iodation

from <0.5% to 0.8-1.8%, however the degased HPLC acetonitrile gave a better result (only 0.8%, entries 14-15). The main difference between analytical and HPLC grade C acetonitrile is that the latter is filtered, which increase the content in oxygen of the solvent and can explain both the light blue and green color of the catalyst that is due to the oxidation of copper.

We also found some other new results in the preparation of A-21.CuI catalysts and formation of the 5-iodine side product that are summarized through Table 6.

Table 6. Preparation of A-21.CuI with other modified parameters and obtained results for 1,2,3-dipolar cycloaddition reaction in the presence of this catalytic system.



Entry	A-21.CuI (mol%)	% I ₂ /A-21.CuI ^a	Solvent (ml)	Conditions	Yield %	5-iodine %
1	8	-	2	Dark	99	1.1
2	8	1.6	2	Dark	99	1.2
3	8	10	2	Dark	100	1.0
4	8	50	2	Dark	90	1.5
5	8	100	2	Dark	0 ^b	-
6	10	-	5	Dark	94	0.9
7	25	-	5	Dark	99	1.8
8	50	-	5	Dark	97	2.0
9	75	-	5	Dark	98	2.3
10	100	-	5	Dark	99	2.9
11	150	-	5	Dark	96	3.3
12	200	-	5	Dark	97	4.3
13	8	-	2	Dark/without stirring	88	0.8
14	8	-	2	hv 254nm/without stirring	88	0.8
15	8	-	2	hv 365nm/without stirring	95	0.9

^aA-21.CuI catalyst was doped with I₂. ^bThe reaction did not occur.

From these results we proved that formation of 5-iodine side-product is in a direct relation with the amount of used catalyst. When we doped A-21.CuI with more iodine (entries 2-4), an increase in formation of 5-iodine could be observed (1.2-1.5% of 5-iodine found when respectively 1.6 or 50% I₂/CuI was applied). Another remark was when 100 to 150% of A-21.CuI was subjected in the reaction. In this case the 5-iodine side-product was obtained with 2.9-4.3% yield respectively.

Also by reading the literature, this fact was proved that the iodation while using copper (I) iodide is a multi factor reaction, and may influenced by the solvent nature, the concentration of alkyne and/or azide, the temperature, the time of the reaction, the amount of the CuI, and also the amount and nature of the used base.¹³⁸ For example, through a study by Bock group^{139a} in which they varied some parameters like decreasing the amount of CuI (from 2 equiv. to 0.3 equiv.), changing the base DIPEA (2 equiv.) by DBU (20 equiv.), or changing the solvent (CH₃CN/THF by toluene), increasing the time of the reaction from 3 days to 7 days and at the end increasing the temperature from room temperature to 50°C, they could find a higher reaction yield (from 33% to 43%) and also a higher yield of triazolic product (1.4% to 24%) with a constant yield of 1% for 5-iodine. Pérez *et al.*^{139b} also demonstrated that decreasing the amount of CuI (from 2 equiv. to 0.1 equiv.) and the base DIPEA (from 50 equiv. to 2 equiv.) permit to increase the yield of the triazolic product (71% to 76%) and disappearance of the iodine by-product by passing from 13% to 0%.

Another study that was performed by Törnroos' group¹⁴⁰ revealed that in the case of a non-activated alkyne iodation side-products were observed with various ratios at the end of the reaction according to the type of used solvent and temperature of the reaction (**Fig. 30**). These results are in coherent with our obtained results in the case of phenylacetylene.

¹³⁸N. W. Smith, B. P. Polenz, S. B. Johnson, S. V. Dzyuba, *Tetrahedron Lett.* **2010**, *51*, 550-53. ^{139a}V. D. Bock, R. Perciaccante, T. P. Jansen, H. Hiemstra, J. H. Van Maarseveen, *Org. Lett.* **2006**, *8*, 919-22; b) I. Perez-Castro, O. Caamano, F. Fernandez, M. D. Garcia, C. Lopez, E. De Clercq, *Org. Biomol. Chem.* **2007**, *5*, 3805-13; c) K. Tanaka, C. Kageyama, K. Fukase, *Tetrahedron Lett.* **2007**, *48*, 6475-79. ¹⁴⁰T. Farooq, B. E. Haug, L. K. Sydnes, K. W. Toernroos, *Monatsh. Chem.* **2012**, *143*, 505-12.

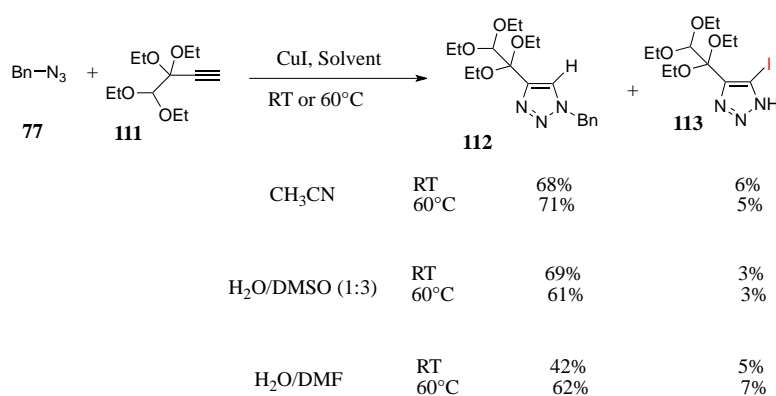


Fig. 30. Synthesis of triazoles from a non-activated alkyne at different temperatures and in the presence of different solvents.

In another paper published by Fukase group^{139c} was shown that, changing the solvent of the reaction (DMF) by an aqueous solution (H₂O/ CH₃CN 1:2), we could have appearance of the triazolic derivative with 100% yield without any formation of iodine, which showed the important role of solvent in the synthesis of triazolic derivatives.

From these reported results we found that all the used factors during the preparation of A-21.CuI can influence the appearance of the iodine by-product in the synthesis of triazoles. These factors contain the solvent, the used base, the amount of the catalyst, concentration of substrates, and temperature, which can play a role in the appearance of the 5-iodine side-product during the synthesis of triazole. Especially the amount of catalyst can play a critical role on this reaction, since we found that adding more A-21.CuI result formation of 5-iodine side product with higher yields.

II.3. Synthesis of 1,2,3-triazoles derivatives from alkynes or propargylic alcohols

II.3.1. Terminal alkynes

One of the basic functional groups is the carbon-carbon triple bond of alkynes and its reactions belong to the foundations of organic chemistry. Because of the existence of the alkynes in molecules at the border of organic chemistry like biochemistry or material sciences and also building blocks and multipurpose intermediates for the synthesis of an expanded assemblies of chemicals, this functional group found an importance in chemistry field.¹⁴¹ This improve in alkyne

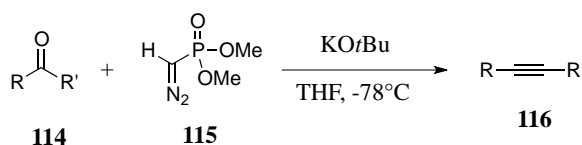
¹⁴¹a) *Modern Acetylene Chemistry*; P. J. Stang, F. Diederich, Eds.; VCH:Weinheim, **1995**; b) *Acetylene Chemistry*; F. Diederich, P. J. Stang, R. R. Tykwinski, Eds.; Wiley-VCH: Weinheim, **2005**.

chemistry has been fed by the evolution of new synthetic methodologies in the synthesis of terminal alkynes such as Corey-Fuchs,¹⁴² Seyferth-Gilbert,¹⁴³ Colvin rearrangement,¹⁴⁴ Bestmann-Ohira¹⁴⁵ modification of Seyferth-Gilbert reagent and alkyne zipper reactions.¹⁴⁶ In addition advances in synthetic chemistry like the Sonogashira cross-coupling reaction,¹⁴⁷ Grubbs olefin metathesis¹⁴⁸ and Ruthenium-catalyzed Alder-ene reaction¹⁴⁹ have greatly increased the synthetic utility of terminal alkynes.

Among these synthetic procedures to prepare terminal alkynes, we chose synthesis with Bestmann-Ohira reagent, which showed a significant advance in the synthesis of terminal alkynes directly from aldehydes.

II.3.1.1. Seyferth-Gilbert Homologation

The Seyferth-Gilbert Homologation is the base-developed reaction of dimethyl (diazomethyl)phosphonate with aldehydes and aryl ketones at low temperatures that provides a synthesis of alkynes (**Scheme 22**).¹⁴³



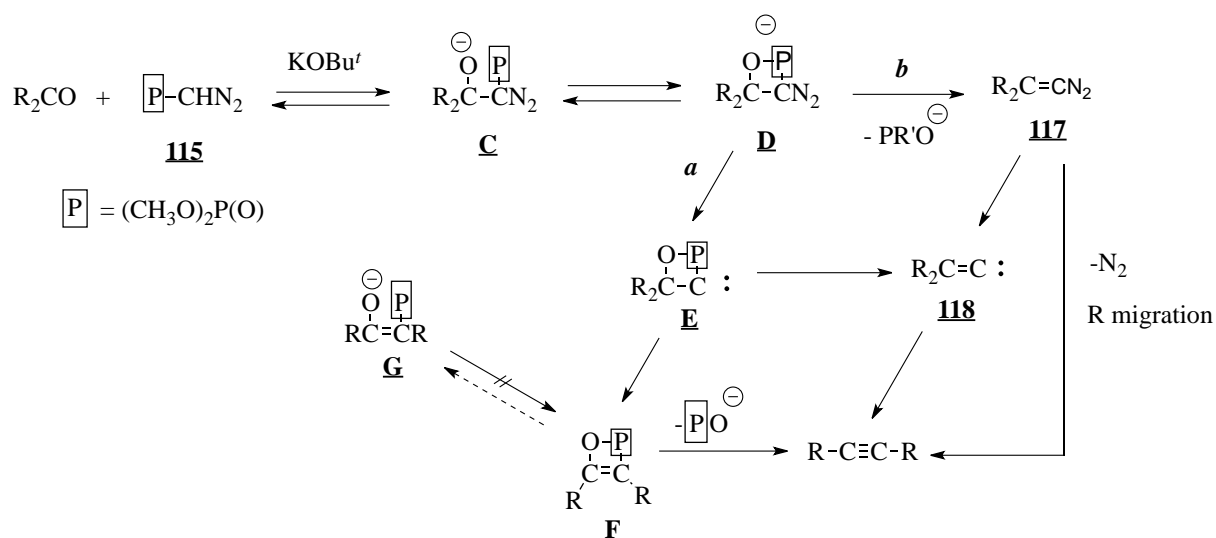
Scheme 22. Synthesis of alkynes in a Seyferth-Gilbert Homologation reaction

The Seyferth-Gilbert Homologation reaction needs a strong base and the reaction is done at low temperature.

II.3.1.2. Mechanism of the Seyferth-Gilbert Homologation

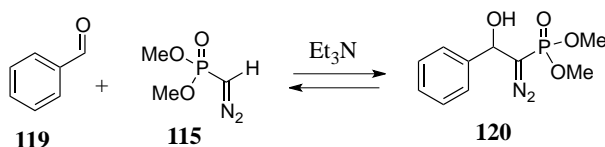
The mechanism of this reaction is well explained in a paper reported by Gilbert.¹⁴³ In this paper they proposed two possible pathways (**a** and **b**) for this reaction (**Scheme 23**). Both pathways show consecutive formation of intermediates **C** and **D** but they are different at the latter point.

¹⁴²E. J. Corey; P. L. Fuchs, *Tetrahedron Lett.* **1972**, *36*, 3769-72. ¹⁴³J. C. Gilbert, U. Weerasooriya, *J. Org. Chem.* **1982**, *47*, 1837-45. ¹⁴⁴K. Miwa, T. Aoyama, T. Shioiri, *Synlett* **1994**, *2*, 107-8. ¹⁴⁵a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561-4; b) S. Mueller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521-22. ¹⁴⁶S. R. J. Macaulay, *J. Org. Chem.* **1980**, *45*, 734-35. ¹⁴⁷A. Elangovan, Y.-H. Wang, T.-I. Ho, *Org. Lett.* **2003**, *5*, 1841-44. ¹⁴⁸S.-H. Kim, W. J. Zuerker, N. B. Bowden, R. H. Grubbs, *J. Org. Chem.* **1996**, *61*, 1073-81. ¹⁴⁹B. M. Trost, A. F. Indolese, T. J. J. Mueller, B. Treptow, *J. Am. Chem. Soc.* **1995**, *117*, 615-23.



Scheme 23. Proposed mechanism by Gilbert for Seyferth-Gilbert Homologation.

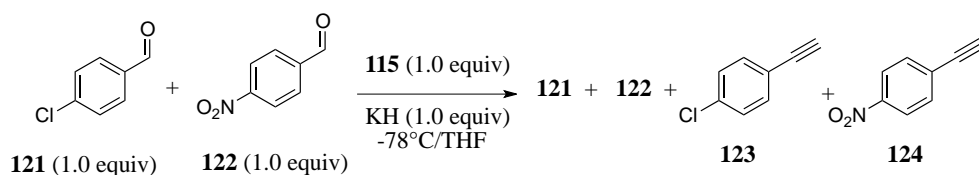
As an explanation of the mechanism, they proposed that formation of the tetrahedral intermediate **C** would be expected to be reversible, which was concluded from other studies containing other types of phosphonate anions¹⁵⁰ as the equilibria shown in Scheme 24.¹⁵¹



Scheme 24. Reversible formation of compound **120**.

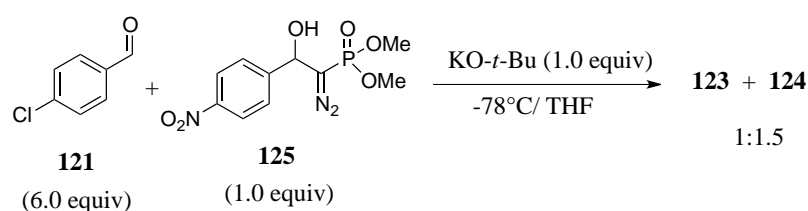
About this proposed equilibria Gilbert *et al.*¹⁴³ reported in their paper that this equilibria is true when the counterion of the conjugate base of the diazohydroxy phosphonate **120** (**Scheme 24**) is potassium. To prove this claim, they've done a reaction between **115** with an *equimolar* mixture of 4-chloro- and 4-nitrobenzaldehyde (**121** and **122**), which gave the corresponding alkynes **124** and **125** in a ratio of 1:5.3 respectively for alkyne **121** and **122** (**Scheme 25**).

¹⁵⁰M. Schlosser, A. Piskala, C. Tarchini, H. B. Tuong, *Chimia* **1975**, *29*, 341-2. ¹⁵¹W. Disteldorf, M. Regitz, *Chem. Ber.* **1976**, *109*, 546-61.



Scheme 25. The reaction between phosphonate **115** and a mixture of **121** and **122**.

In another experiments, they treated the diazo aldol **125** with potassium *tert*-butoxide and 6 equiv. of **121** that led to **123** and **124** with a ratio of 1:1.5 (Scheme 26).

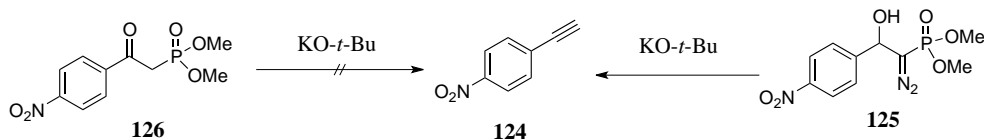


Scheme 26. The reaction between diazoaldol **125** and aldehyde **121** in the presence of *tert*-butoxide gave alkynes **123** and **124**.

By these studies, they could show that the attack of the anion **115** on the carbonyl-involved substrate is reversible, in addition they showed that the equilibrium, which gives **C**, happens first, before leading any other eventual irreversible step that results from this intermediate.

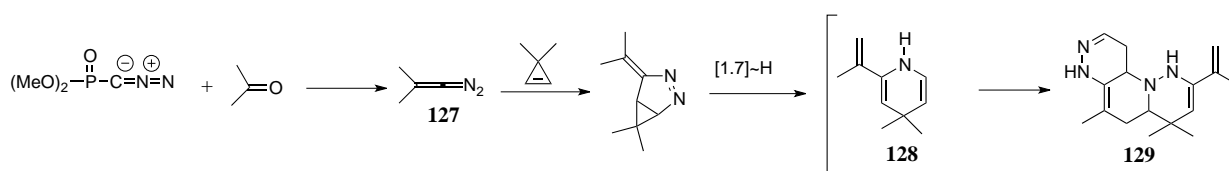
In this proposed mechanism, there is an intermediate **D** which is common for both pathway *a* and *b*. Pathway *a* shows the formation of a new carbene **E** and pathway *b* demonstrates the formation of a diazoethene **117**. Alkylidencarbene **118** is formed further by loss of nitrogen from **117** that expected to be rearranged to alkyne through a 1,2-migration (**Scheme 29**). In a same way, intermediate **E** resulting from path *a*, could give **118** by elimination of potassium dimethyl phosphate and gives alkyne thereafter. Another possible way is the formation of **F** followed by decomposition to alkyne. Although, transformation of **G** to **F** should be slower than its conversion to alkyne, as intermediate **G** is that kind of anion, which could not form alkyne, as it was found by Colvin and Hamill (**Scheme 27**).¹⁵²

¹⁵²a) E. W. Colvin, B. J. Hamill, *J. Chem. Soc., Chem. Commun.* **1973**, 151-2; b) E. W. Colvin; B. J. Hamill, *J. Chem. Soc., Perkin Trans. 1* **1977**, 869-74.



Scheme 27. Conversion of **125** to nitro alkyne **124** can not be performed in the presence of *tert*-butoxide.¹⁵²

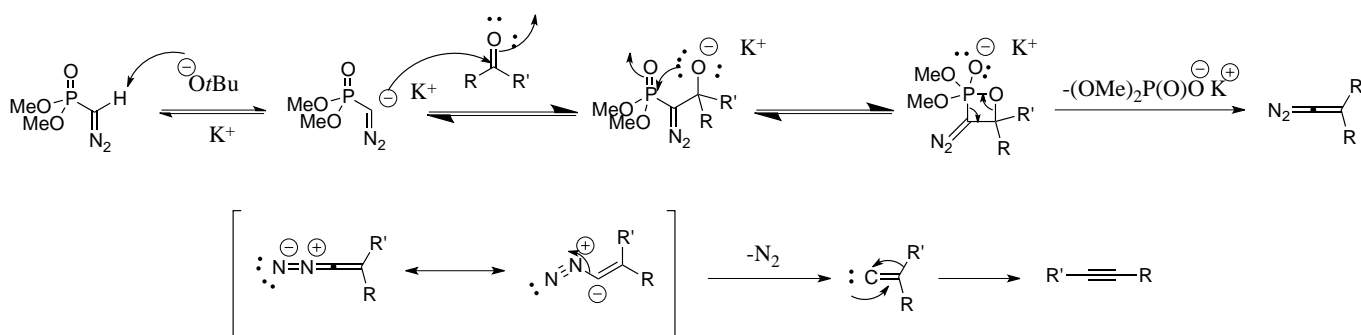
Gilbert *et al.* reminded in their paper¹⁴³ that the possibility of path *a* is not easy to be determined, but they justify the possibility of path *b* by mentioning some points: 1) intermediate **D** is less probable to lose nitrogen at -78°C while **115** is stable at this temperature; 2) another proof against path *a* resulted from a study on base-promoted reaction of dimethyl (diazomethyl)phosphonate **115** with acetone in the presence of 3,3-dimethylcyclopropene that gives molecule **129** (**Scheme 28**). This reaction is believed to result from dimerization of the unisolated dehydropyridazine **128**.¹⁵³



Scheme 28. Diasomethyl phosphonate-ketone-olefin reaction.¹⁵³

Gilbert *et al.*, supposed that formation of **128** is most probable as a result from reaction between 2-methyl-1-diazopropene (**127**), which supports the possibility of pathway *b* in favour of pathway *a*.

In conclusion, as mechanism of Seyferth-Gilbert Homologation, Gilbert *et al.* based their discussion on pathway *b* which leads to the mechanism in scheme **26**.



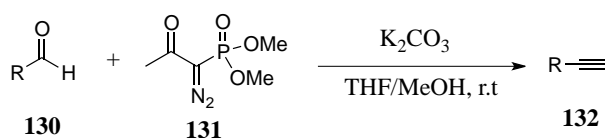
Scheme 29. Another presentation of Seyferth-Gilbert Homologation mechanism.

¹⁵³P. M. Lahti, J. Berson, *J. Am. Chem. Soc.* **1981**, *103*, 7011-12.

II.3.1.3. Bestmann-Ohira Reagent (BOR) reaction

The Bestmann-Ohira reagent reaction is a special case of the Seyferth-Gilbert Homologation reaction. This modification of the reaction, which is done by use of 1-diazo-2-oxopropylphosphonate, affords the conversion of base-labile substrates like enolizable aldehydes that would form aldol condensation under Seyferth-Gilbert conditions (**Scheme 30**).¹⁴⁵

The Bestmann-Ohira reagent reaction provides preparation of terminal alkynes in a one-pot manner and under mild conditions at room temperature using potassium carbonate as a base, which is advantageous against Seyferth-Gilbert homologation where we used to work at low temperature and in the presence of a strong base.

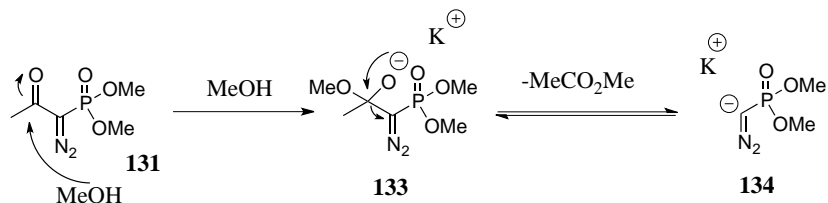


Scheme 30. Synthesis of terminal alkynes in the presence of Bestmann-Ohira reagent.

Another advantage of Bestmann-Ohira reagent is that this reagent is stable and can be prepared readily from available precursors¹⁵⁴ and the utility of this reagent in the synthesis of complex natural products is well established.¹⁵⁵

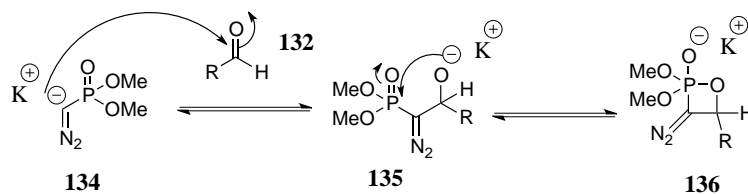
II.3.1.4. Mechanism of the alkynylation of an aldehyde with BOR

The mechanism of the reaction is similar to Seyferth-Gilbert's one. Here, the reaction starts by first formation of a (diazomethyl)phosphonate anion **134**, which is formed by a mild acyl cleavage of dimethyl diazo-2-oxopropyl phosphonate **131** in the presence of MeOH.

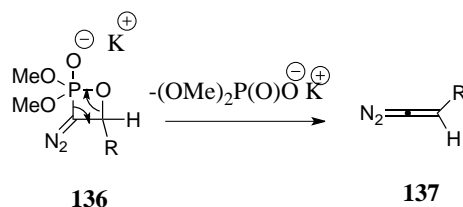


¹⁵⁴a) P. Callant, L. D'Haenens, M. Vandewalle, *Synth. Commun.* **1984**, *14*, 155-61; b) A. K. Ghosh, A. Bischoff, J. Cappiello, *J. Org. Chem.* **2003**, *(5)*, 821-32. ¹⁵⁵a) D. Dixon, S. V. Ley, D. J. Reynolds, *Chem. Eur. J.* **2002**, *8*, 1621-36; b) W. R. F. Goundry, J. E. Baldwin, V. Lee, *Tetrahedron* **2003**, *59*, 1719-29; c) Z. Xu, Y. Peng, T. Ye, *Org. Lett.* **2003**, *5*, 2821-24; d) J. A. Marshall, G. M. J. Schaaf, *J. Org. Chem.* **2003**, *68*, 7428-32; e) H. Maehr, M. R. Uskokovic, *Eur. J. Org. Chem.* **2004**, 1703-13.

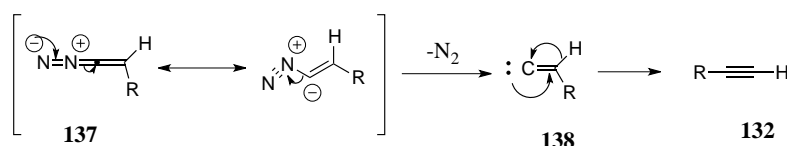
In the next step, the formed diazo anion **134** adds to the carbonyl compound (aldehyde) **130** forming an alkoxide **135** that forms further an oxaphosphetane **136**.



This oxaphosphetane **136** then conduct a Wittig¹⁵⁶ like rearrangement (cycloelimination) to form a dimethyl phosphate anion and a diazoalkene **137**.



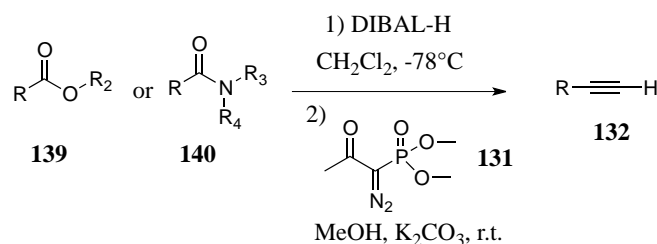
And finally, this intermediate **137** conducts a rearrangement followed by loss of nitrogen that gives a vinylidene carbene **138**, which yields the desired alkyne **132** after a hydrogen 1-2-migration on the carbene **138**.



II.3.1.5. Some Applications of Bestmann-Ohira Reagent

In a paper Dickson *et al.*¹⁵⁷ presented that Bestmann-Ohira reagent could be applied also in the synthesis of terminal alkynes from esters and Weinreb amides as the starting materials and in a one-pot way (Scheme 31).

¹⁵⁶a) G. Wittig, U. Schöllkopf, *Chem. Ber.* **1954**, 97, 1318-30; b) G. Wittig, Werner Haag, *Chem. Ber.* **1955**, 88, 1654-66. ¹⁵⁷D. Dickson, S. C. Smith, K. W. Hinkle, *Tetrahedron Lett.* **2004**, 45, 5597-99.



Scheme 31. Preparation of terminal alkynes from esters or Weinreb amides in the presence of Bestmann-Ohira reagent proposed by Dickson *et al.*.

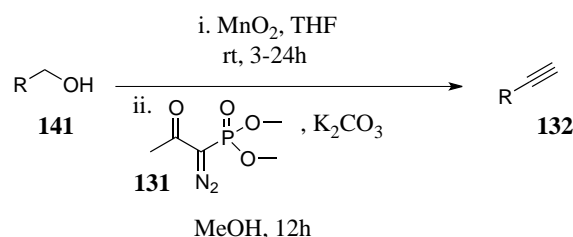
As is shown in Scheme 31, for this reaction the ester or amide were reduced first by DIBAL-H at low temperature followed by a quench with MeOH. The resulting aldehyde was then diluted with MeOH and treated with K_2CO_3 and the Bestmann-Ohira reagent. From both esters and Weinreb amides they could obtain terminal alkynes in high yields (71-88% yield). This reaction was done on esters containing non-conjugated double bonds (Table 7, entry a), ethers and carbamates (table 7, entries b, c). In another experiment they applied an ester derivative containing an unprotected hydroxyl group. In this condition reaction for which, they had to add an extra equivalent of DIBAL-H to first form an aluminium alkoxide of the free hydroxyl before reducing the ester (Table 7, entry d). In addition, for this reaction, Dickson *et al.*, subjected chiral substrates derived from aminoacids, which were transformed to the corresponding terminal alkynes with preservation of stereochemical integrity.

Table 7. Different esters transformed to terminal alkynes by first reduction of ester in the presence of DIBAL-H and then transformation of the obtained aldehyde by Bestmann-Ohira reagent to the terminal alkyne.

Entry	Substrate	Product	% Yield
a			76
b			72
c			71
d			75

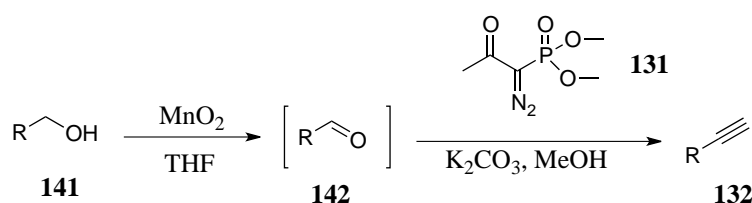
Another application of Bestmann-Ohira reagent that was reported by Taylor group¹⁵⁸ was its use in sequential one-pot MnO_2 oxidation of alcohols/ Bestmann-Ohira alkynylation to give terminal alkynes (Scheme 32).

¹⁵⁸E. Quesada, R. J. K. Taylor, *Tetrahedron Lett.* **2005**, 46, 6473-76.



Scheme 32. An example of a one-pot conversion of an activated alcohol to terminal alkynes in the presence of Bestmann-Ohira Reagent.

For this reaction, they first investigated on Tandem Oxidation Processes (TOP) sequence that is shown in Scheme 33. In this sequence, the alcohol **141**, MnO_2 and the Bestmann-Ohira reagent **131** were mixed together and the aldehyde **142** is trapped as soon as generated.

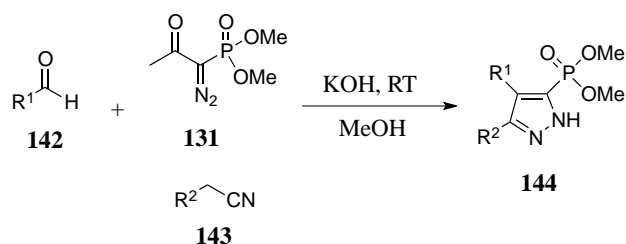


Scheme 33. Conversion of an alcohol to an alkyne through a tandem oxidation process.¹⁵⁸

Taylor *et al.* found that using only THF as solvent generates no alkyne, so they chose a mixture of THF-MeOH (1:1) as solvent. The presence of MeOH is necessary for deacetylation of Bestmann-Ohira reagent and the success of the reaction, but here they observed that presence of MeOH decrease the activity of MnO_2 and the reaction proceeded slowly in this case. Finally they decided to apply a sequential one-pot procedure as is shown in Scheme 32. In this method, the oxidation was carried out using MnO_2/THF before the addition of the Bestmann-Ohira reagent. Once all of the alcohol was converted into the intermediated aldehyde **142** (After 3-24h of reaction), MeOH was added followed by K_2CO_3 and the Bestmann-Ohira reagent **131**. After stirring for a further 12h, the terminal alkynes were obtained in good to excellent yield.

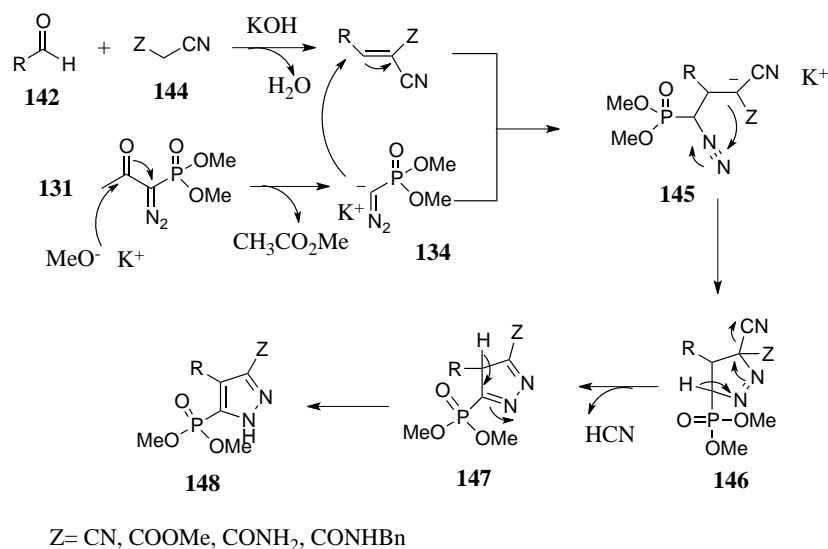
Vasseur *et al.*¹⁵⁹ also presented an application of Bestmann-Ohira reagent in the synthesis of phosphonyl pyrazole rings in a three-component manner (**Scheme 34**).

¹⁵⁹K. Mohanan, A. R. Martin, L. Toupet, M. Smietana, J.-J. Vasseur, *Angew. Chem. Int. Ed.* **2010**, *49*, 3196-99.



Scheme 34. Three-components synthesis of phosphonyl pyrazoles proposed by Vasseur et al..

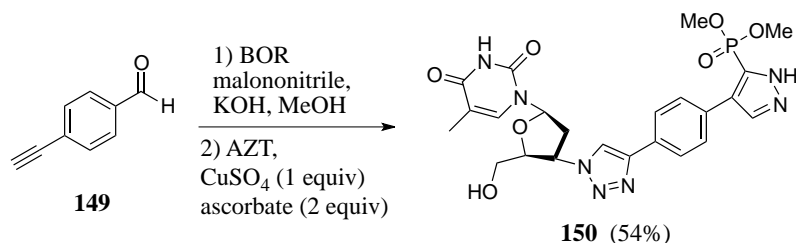
This proposed reaction is based on a domino Knoevenagel condensation/formal 1,3-dipolar cycloaddition resulted from the combination of the readily available reactents (aldehydes, Bestmann-Ohira reagent (BOR) and cyanoacetic derivatives), which generate small molecules with highly diversified structures and it was for the first time that they presented the use of BOR: 1) in a multicomponent reaction (MCR) and 2) in the presence of an aldehyde without forming the expected homologated alkyne, because this reaction afford 5-phosphonyl pyrazole scaffolds through the formation of two C-C bonds and one C-N bond. The mechanism of the reaction is presented in Scheme 35.



Scheme 35. Proposed mechanism for the formation of pyrazoles.¹⁵⁹

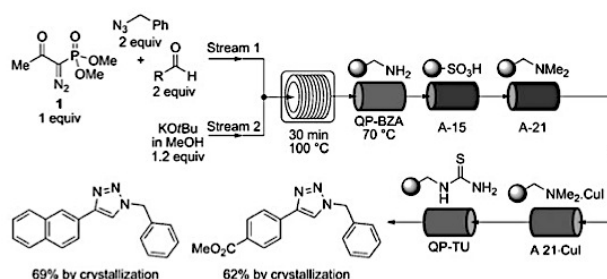
Vasseur *et al.* also explored the scope of this reaction in an efficient MCR/CuAAC reaction sequence in single step. In that order, aldehyde **149** was subjected to the MCR reaction conditions using BOR, and was then submitted to the copper-catalyzed click reaction in the presence of

azidothymidine (AZT) to yield the modified thymidine 3'-pyrazolyl phosphonate **155** in 54% yield (Scheme 36).¹⁵⁹



Scheme 36. One-pot MCR/CuAAC sequence.¹⁵⁹

BOR reagent could also be used in modular flow reactors in order to prepare terminal alkynes followed by triazoles through a multistep synthesis. This method was proposed by S. V. Ley¹⁶⁰ for which, they used a variety of immobilized reagents and scavenger materials to reach to a multicomponent, multistep coupling reaction (Scheme 37).



Scheme 37. Three-step synthesis of a triazole from alcohol.

Ley *et al.*,¹⁶⁰ could demonstrated successfully how a relatively complicated mixed component and by-product reaction stream could be controlled and automated to facilitate the preparation of alkynes using Bestmann-Ohira reagent and these product could be transformed to triazoles by treating the obtained alkynes with azides and flowing them through our prepared copper (I) catalyst system of A-21 (A-21.CuI)¹³⁵ to give the triazole product.

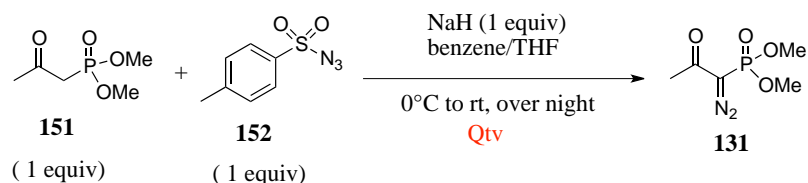
¹⁶⁰I. R. Baxendale, S. V. Ley, A. C. Mansfield, *Angew. Chem. Int. Ed.* **2009**, *48*, 4017-21.

II.3.1.6. Synthesis of alkynes

II.3.1.6.1. Synthesis of Bestmann-Ohira Reagent (BOR)

From these obtained results and developed methods by use of BOR in the synthesis of terminal alkynes, we also decided to apply this synthetic procedure to prepare our terminal alkynes.

For this reaction, Bestmann-Ohira reagent,¹⁶¹ which is a diazophosphonate derivative, was first prepared from a reaction between dimethyl (2-oxopropyl)-phosphonate (1 equiv.) and 4-methylbenzene-1-sulfonyl-azide¹⁶¹ (1 equiv.) in the presence of sodium hydride (1 equiv.) in THF/benzene as solvent (**Scheme 38**). This reaction resulted the expected diazo phosphonate with a quantitative yield.

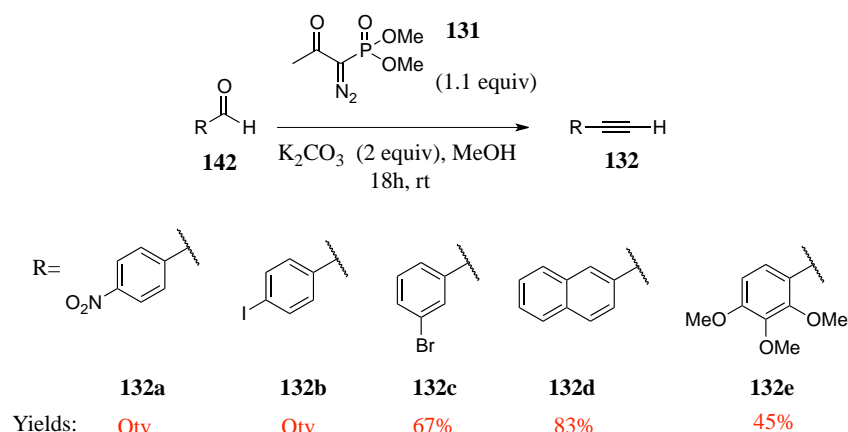


Scheme 38. Synthesis of BOR.

II.3.1.6.2. Synthesis of some terminal alkynes

Once the BOR was prepared, we subjected it into the reaction with aldehydes (**Scheme 39**) in order to prepare terminal alkynes. We subjected aromatic aldehydes with different functional groups such as electron withdrawing (EWG) or electron donating groups (EDG) in the reaction with BOR, in order to introduce different functional groups using these reaction conditions.

¹⁶¹M. Wijtmans, C. de Graaf, G. de Kloe, E. P. Istyastono, J. Smit, H. Lim, R. Boonak, S. Nijmeijer, R. A. Smits, A. Jongejan, O. Zuiderveld, I. J. P. de Esch, R. Leurs, *J. Med. Chem.* **2011**, *54*, 1693-1703.



Scheme 39. Synthesis of some terminal alkynes with BOR.

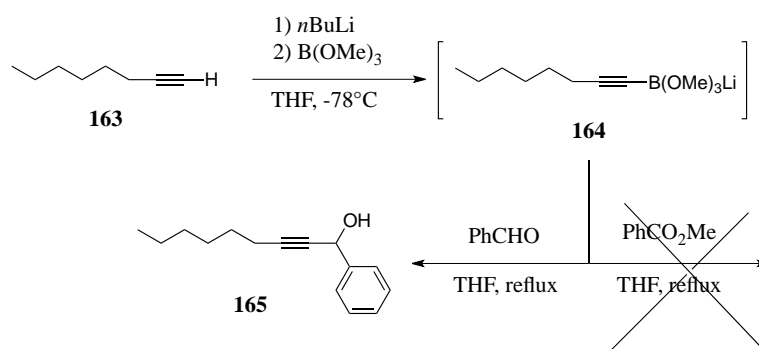
By running the reaction with these aldehydes, we found out that the nature of the existing functional groups (EWD or EDG) on the aryl doesn't have special effect on the yield of the reaction (**Scheme 39**, compounds **132a**, **132b**, **132d**), however the position of the substitution on the aryl (*ortho*, *meta* or *para*) has an influence on the yield as is found for alkyne **132e** (**Scheme 39**). For this aldehyde having a substitution on *ortho* position, we observed a decrease in yield of the reaction (45%) which can be the result of both electronic and steric effects.

II.3.2. Propargylic Alcohols

Propargylic alcohols are valuable building blocks and useful intermediates for the synthesis of many biologically active compounds and natural products like adociacetylene B,^{162a} longimicin D,^{162b} leukotriene B₄,^{162c} steroid,^{162d} prostaglandins,^{162e} and carotenoids.^{162f} In addition, synthesis of these compounds is in the center of attention because it corresponds to the fundamental principles of organic synthesis efficiency and reaction design. Most of these methods are based on the nucleophilic addition of the alkynylmetals such as alkynyllithium or magnesium to carbonyl compounds. These alkynyllithium or magnesium reagents are usually derived from acetylene derivatives and organolithium^{162a} and organomagnesium bases.^{162b} But such strong basic and nucleophilic reagents do not work always with a range of functional groups, because of that more studies are necessary to convert different aldehydes and ketones to their corresponding propargylic alcohols. In that order, some alkynylmetals containing metal species like Cs,¹⁶³ Zn,¹⁶⁴ In,¹⁶⁵ Rh,¹⁶⁶

^{162a}) B. M. Trost, A. H. Weiss, *Org. Lett.* **2006**, *8*, 4461-4; b) H. Tominaga, N. Maezaki, M. Yanai, N. Kojima, D. Urabe, R. Ueki, T. Tanaka, *Eur. J. Org. Chem.* **2006**, 1422-9; c) M. Treilhou, A. Fauve, J.-R. Pougny, J.-C. Promé, H. Veschambref, *J. Org. Chem.* **1992**, *57*, 3203-8; d) M. A. Sierra, M. R. Torres, *J. Org. Chem.* **2007**, *72*, 4213-19; e) W. S. Johnson, R. S. Brinkmeyer, U. M. Kapoor, T. M. Yarnell, *J. Am. Chem. Soc.* **1977**, *99*, 8341-3; f) K. K. Chan, N. C. Cohen, J. P. Denoble, A. C. Jr. Specian, G. Saucy, *J. Org. Chem.* **1976**, *41*, 3497-505. ¹⁶³D. Tzalis, D. Knochel, *Angew. Chem. Int. Ed.* **1999**, *38*, 1463-5. ¹⁶⁴N. K. Anand, E. M. Carreira, *J. Am. Chem. Soc.* **2001**, *123*, 9687-8. ¹⁶⁵a) R. Takita, Y. Fukuta, R. Tsuji, T. Ohshima, M. Shibasaki, *Org. Lett.* **2005**, *7*, 1363-6; b) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760-1. ¹⁶⁶P. K. Dhondi, J. D. Chisholm, *Org. Lett.* **2006**, *8*, 67-9.

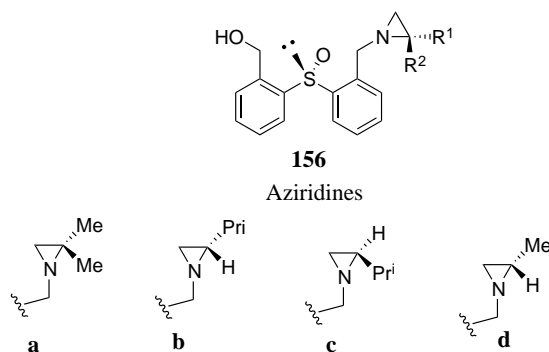
Ag,¹⁶⁷ Cu,¹⁶⁸ Ga,¹⁶⁹ Ce,¹⁷⁰ V,¹⁷¹ B¹⁷² and Ti¹⁷³ have been reported that can be used in large variety of enantioselective procedures with aldehydes and ketones. Between these metals, alkynyl borates have been used widely in organic synthesis because of their mildness, large availability and easy preparation.¹⁷⁴ In a paper, A. Wagner *et al.*¹⁷⁵ describes the use of *in situ* prepared lithium alkynylmethyl borate in a metal-free 1,2-addition to aldehydes as an efficient and selective straightforward way to synthesize propargylic alcohols (**Scheme 40**). As the advantages of this method, they mentioned functional-group tolerance, environmental sustainability and its economy. In this paper, they reported a good to excellent yield in the coupling reaction between lithium octynyl trimethyl borate and aliphatic or aromatic aldehydes. They also suggested that electronic properties of the borate intermediate also play a key role.¹⁷⁵



Scheme 40. Proposed reaction condition to prepare Propargylic alcohols in the presence of lithium alkynyltrimethyl borates.

Another method proposed by Rachwalski *et al.*¹⁷⁶ is the enantioselective addition of phenylacetylene zinc to aldehydes which led to chiral non-racemic propargylic alcohols that are again important building blocks in the synthesis of various biologically active and natural products.¹⁷⁷ This reaction was carried out by use of a chiral tridentate ligands involving two stereogenic centers, one located on the sulfinyl sulfur atom and the other on the carbon atom in the aziridine moiety (**Scheme 41**). Four chiral tridentate ligands containing aziridine moieties have been chosen by Rachwalski's group by which they could observe the best results during the

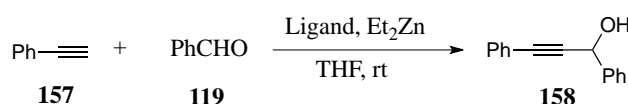
¹⁶⁷X. Yao, C.-J. Li, *Org. Lett.* **2005**, *7*, 4395-8. ¹⁶⁸Y. Asano, K. Hara, H. Ito, M. Sawamura, *Org. Lett.* **2007**, *9*, 3901-4. ¹⁶⁹X. Jia, H. Yang, L. Fang, C. Zhu, *Tetrahedron Lett.* **2008**, *49*, 1370-2. ¹⁷⁰T. Imamoto, Y. Sugiura, N. Takiyama, *Tetrahedron Lett.* **1984**, *25*, 4233-6. ¹⁷¹T. Hirao, D. Misu, T. Agawa, *Tetrahedron Lett.* **1986**, *27*, 933-4. ¹⁷²a) H. C. Brown, G. A. Molander, S. M. Singh, U. S. J. Racherla, *J. Org. Chem.* **1985**, *50*, 1577-82; b) M. D. Lewis, J. P. Duffy, J. V. Heck, R. Menes, *Tetrahedron Lett.* **1988**, *29*, 2279-82; c) J. C. Evans, C. Jonathan, C. T. Goralski, D. -L. Hasha, *J. Org. Chem.* **1992**, *57*, 2941-3. ¹⁷³a) H. Li, Y. Huang, W. Jin, F. Xue, B. Wan, *Tetrahedron Lett.* **2008**, *49*, 1686-9; b) R. M. Kamble, M. Rajesh, V. K. Singh, *Tetrahedron Lett.* **2003**, *44*, 5347-9; c) Z.-C. Chen, X.-P. Hui, C. Yin, L.-N. Huang, P.-F. Xu, X.-X. Yu, S.-Y. Cheng, *J. Mol. Catal. A* **2007**, *269*, 179-82. ¹⁷⁴M. Srebnik, *Tetrahedron Lett.* **1991**, *32*, 2449-52. ¹⁷⁵N. F. Irene, A. Renier, A. Wagner, F. Colobert, *Tetrahedron Lett.* **2010**, *51*, 1386-9. ¹⁷⁶M. Rachwalski, S. Lesniak, P. Kielbasinski, *Tetrahedron: Asymm.* **2010**, *21*, 2687-9. ¹⁷⁷B. Trost, M. J. Krische, *J. Am. Chem. Soc.* **1999**, *121*, 6131-41.



Scheme 41. Ligands for the asymmetric addition of phenylethynylzinc to aldehydes.

diethylzinc addition to aldehydes and enones (**Scheme 41** and **42**).

For this reaction, they chose addition of phenylacetylene and diethylzinc to benzaldehyde as a reference transformation (**Scheme 42**).



Scheme 42. The reaction condition of addition of phenylacetylene and diethylzinc to benzaldehyde.

From the obtained results, they found that the ligand **156b** catalyzes this reaction to give the appropriate propargylic alcohols in high yields with high enantiomeric excesses (**Table 8**).

Table 8. Obtained results by screening ligands **156** in the reaction of addition of phenylacetylene and diethylzinc to benzaldehyde.

Entry	Ligand (absolute configuration)	Propargylic alcohol			
		Yield(%)	$[\alpha]_D^{25}$ ^a	ee ^b (%)	Absolute Configuration ^c
1	156a (<i>R_S</i>)	62	-2.9	57	(<i>S</i>)
2	156b (<i>R_S</i> , <i>S_C</i>)	96	-5.05	98	(<i>S</i>)
3	156c (<i>R_S</i> , <i>R_C</i>)	94	+4.9	95	(<i>R</i>)
4	156d (<i>R_S</i> , <i>S_C</i>)	91	-4.7	92	(<i>S</i>)

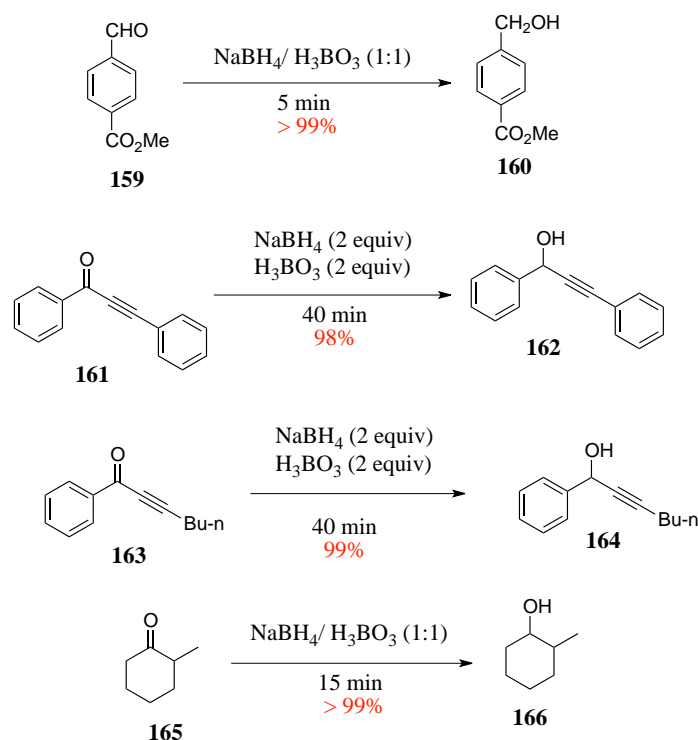
^aIn chloroform, *c* *l*. ^dDetermined using chiral HPLC. ^cTaken from the literature ¹⁷⁸

¹⁷⁸J.-C. Zhong, S.-C. Hou, Q.-H. Bian, M.-M. Yin, R.-S. Na, B. Zheng, Z.-Y. Li, S.-Z. Liu, M. Wang, *Chem. Eur. J.* **2009**, *15*, 3069-71.

Another result for this reaction was that the stereogenic center located on the aziridine moiety has an influence on the stereochemistry of the reaction and therefore on the absolute configuration of the addition product. This result was found from the reactions by two diastereoisomeric catalysts **166b** and **166c**, possessing opposite enantiomers of 2-isopropylaziridine that conducted the formation of the opposite enantiomers of propargyl alcohol.¹⁷⁶

A solvent free reduction of aldehydes and ketones using solid acid-activated sodium borohydride was also represented for the first time by Cho *et al.*¹⁷⁹ Sodium borohydride is an inexpensive, safe to handle, and environmental friendly reducing agent, and activated form of this reductive reagent could be used in reduction of α,β -unsaturated aldehydes and ketones, and stereoselective reduction of cyclic ketones (**Scheme 43**).¹⁷⁹

The sodium borohydride activated with boric acid (H_3BO_3) reduced α,β -ynones such as diphenylpropynone and 1-phenyl-2-heptyn-1-one to the corresponding propargylic alcohols in high yields and regioselectivities (**Scheme 43**).¹⁷⁹

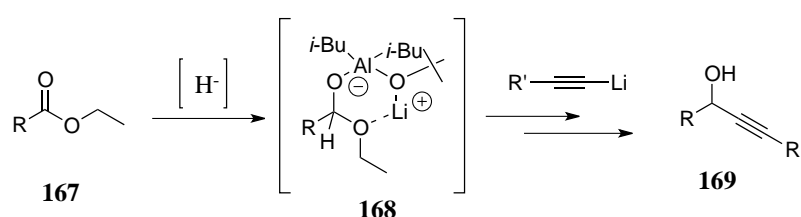


Scheme 43. Regio- and stereoselective reduction of α,β -ynones and cycloketones with solid acid-activated sodiumborohydride proposed by Cho *et al.*¹⁷⁹

¹⁷⁹B. T. Cho, S. K. Kang, M. S. Kim, S. R. Ryu, D. K. An, *Tetrahedron* **2006**, *62*, 8164-8.

This reduction reaction provides not only high chemoselectivity for functionalized aldehydes and ketones including other reducible functional groups, but also high regioselectivity for α , β -unsaturated aldehydes and ketones to give only the corresponding allylic alcohols.

D. Kuen An *et al.*¹⁸⁰ reported another synthetic method for the direct synthesis of propargylic alcohols by using the intermediate from partial reduction of carboxylic esters without isolating the intermediate aldehyde under mild reaction conditions. In this reaction they applied lithium diisobutyl-*t*-butoxyaluminium hydride (LDBBA) as the reducing agent by which they could perform the reaction at 0°C that is advantageous in comparison with other reducing agents like DIBALH where the reaction must be conducted at -78°C. This reducing agent was used to perform partial reduction of the carboxylic ester, here, ethyl caproate **177** and then reduction of the generated intermediate was completed by use of lithium phenylacetylide as a nucleophile which conducted the corresponding propargylic alcohol (**Scheme 44**).

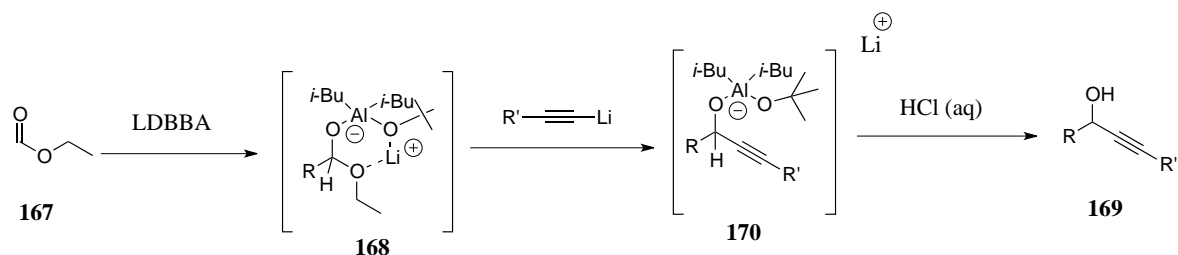


Scheme 44. Proposed one-pot synthesis of propargylic alcohols from esters¹⁷⁹

By this reaction condition, Kuen An *et al.*,¹⁸⁰ could prepare the corresponding propargylic alcohol without producing any tertiary alcohol from ethyl caproate.

As the mechanism of the reaction, they proposed this pathway shown in scheme **45**, where intermediate **168** first stabilized by coordination of lithium cation with the alkoxide oxygens in a six-membered chelate that was rapidly produced through attack of the hydride on the ester by LDBBA at 0°C, then used nucleophile which is a lithium acetylide decomplexes intermediate **168** that is an aldehyde equivalent to generate adduct **170** followed by the generation of the corresponding alcohol **169** upon hydrolysis.

¹⁸⁰M.-J. Chae, A.-R. Jeon, T. Livinghouse, D.-K. An, *Chem. Commun.* **2011**, 47, 3281-3.

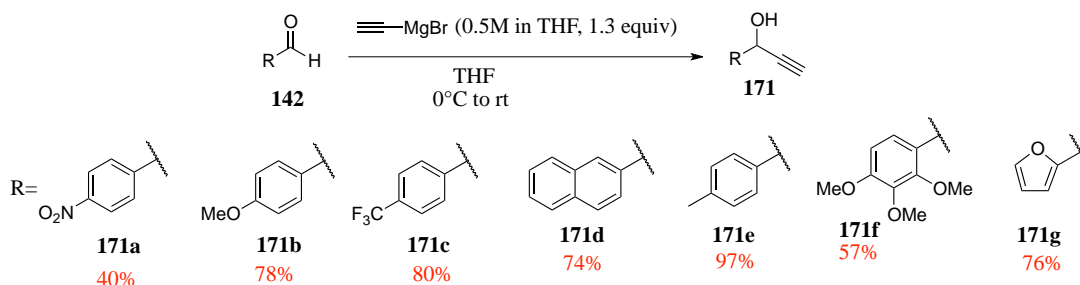


Scheme 45. Proposed mechanism by Kuen An *et al.* for the direct synthesis of propargylic alcohols from carboxylic esters in the presence of LDBBA.¹⁸⁰

II.3.2.1. Synthesis of some propargylic alcohols:

- with Ethynylmagnesium bromide:

By having the concept of DOS in mind, and as we already used different aldehydes to prepare terminal alkynes, here again we subjected these used aldehydes (**Scheme 39**) in order to produce the corresponding propargylic alcohols. For this aim, among different methods mentioned above, we applied a simple addition of ethynylmagnesium bromide to the aldehyde as the starting product (**Scheme 46**).

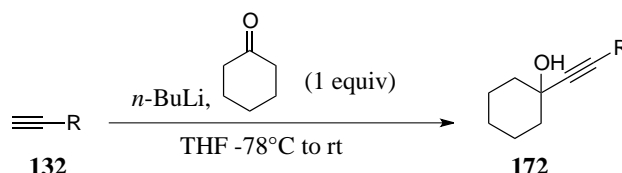


Scheme 46. Synthesis of propargylic alcohols from aldehyde in the presence of the Ethynyl magnesium bromide.

As is shown in Scheme **46**, the reaction was run in dry THF and by use of 1.3 equiv. ethynylmagnesium bromide solution (0.5M in THF). All of the propargylic alcohols were obtained from good to moderate yields.

- in the presence of *n*-BuLi:

We also prepared some internal propargylic alcohols by coupling between a terminal alkyne and a ketone in the presence *n*-BuLi which is a strong base (**Scheme 47**). The results are presented in **Table 9**.



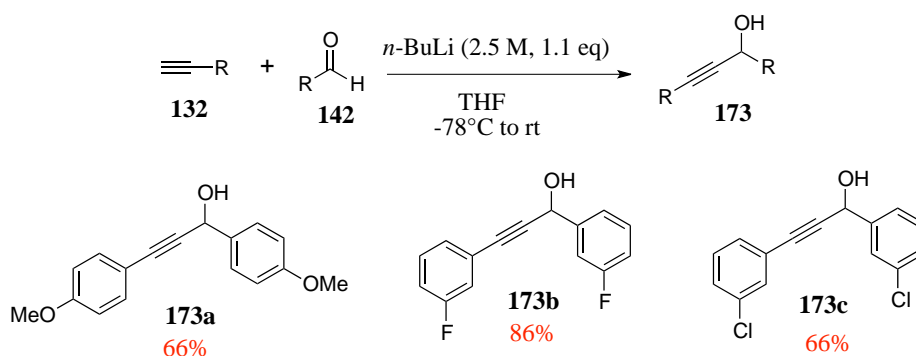
Scheme 47. Coupling between a cycloketone and a terminal alkyne by *n*-BuLi.

From this coupling reaction, the expected internal propargyl alcohols were obtained in good yields (50-78%) except for entry **3** where the reaction was run between an ethynyl benzyl alcohol containing a non-protected hydroxyl group and cycloketone. For this reaction the corresponding internal propargylic alcohol was obtained with only 23% yield where even if we performed deprotonation of the hydroxyl group by the use of 2 equiv. of BuLi.

Table 9. The obtained results for coupling between internal alkynes and cycloketone with BuLi.

Entry	Propargylic alcohol	Yield (%)	<i>n</i> -BuLi	Product
1	 132a	78	2.5M (1 equiv.)	 172a
2	 132b	71	2.5M (1 equiv.)	 172b
3	 132c	23	1.6M (2 equiv.)	 172c
4	 132d	50	2.5M (1 equiv.)	 172d

Some other internal symmetric propargylic alcohols were also prepared by reaction between a terminal alkyl lithium and its corresponding aldehyde generated by *n*-BuLi (**Scheme 48**).



Scheme 48. Preparation of internal alkynes with BuLi.

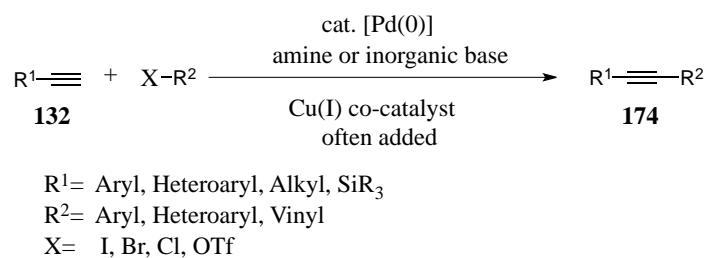
Here, the expected products could obtain with fair to good yield.

II.3.2.2. Sonogashira cross-coupling:

Another used method for the synthesis of internal alkynes is the classic Sonogashira cross-coupling reaction. This reaction is done using a Pd(II) complex as a catalyst. Today, palladium catalyzed reactions are amongst the most versatile processes to form carbon-carbon bonds. These reactions usually proved a high tolerance for many functional groups as well as high regio- and stereoselectivities.¹⁸¹

The coupling between aryl or vinyl halides and terminal acetylenes using palladium and other transition metals is known as Sonogashira cross-coupling reaction that is one of the most used reactions in organic synthesis to form sp^2 - sp carbon-carbon bonds. The name of the reaction was taken from a discovery in 1975 by Sonogashira, Tohda and Hagihara where they found that this reaction could be performed easily at room temperature in the presence of a palladium source as catalyst like $\text{PdCl}_2(\text{PPh}_3)_2$ combined with Cu(I) as co-catalyst and a base (**Scheme 49**).¹⁸² In addition this cross-coupling reaction is frequently employed in the synthesis of natural products, biologically active molecules, heterocycles, molecular electronics, dendrimers and conjugated polymers or nanostructures.

¹⁸¹*Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. I., de Meijere, A., Eds.; Wiley: New York, NY, **2002**. ¹⁸²K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, (50), 4467-70.



Scheme 49. Sonogashira cross-coupling reaction.

This finding came some months after the report of Cassar,^{183a} Dieck and Heck^{183b} where they announced that this reaction was only possible in the presence of palladium catalysis but working at high temperature. In comparison with these reactions, Sonogashira reaction was aimed to combine the copper-mediated transmetalation of alkynes that was studied, with a convertible metal and at the same time powerful catalyst like palladium that yielded a robust C-C bond formation procedure. One of the needed precautions for this reaction is the absence of the oxygen from the reaction medium, if not formation of a side-product which is an undesirable alkyne homocoupling may occur through a copper-mediated Hay-Glaser reaction.¹⁸⁴

Different applications and reaction conditions including catalytic systems for Sonogashira reaction has been studied since its discovery.¹⁷³

II.3.2.2.1. Sonogashira reaction's mechanism

The exact mechanism of palladium/copper-catalysed Sonogashira reaction is not fully understood because of the complications of analysing the combined action of the two present metal catalysts. However, the mechanism of the reaction is supposed to take place through two independent catalytic cycles (**Fig. 31**).^{185a} As it is shown in Figure 31, cycle **A** starts with catalytically active Pd(0)L_2 species. This palladium specie is supposed to be of colloidal nature or it could be a low-ligated Pd(0) -species that is stabilized by the present ligands such as base and/or solvent molecules.¹⁸⁶ Where the phosphanes were used in this reaction as ligands, the corresponding bis(phosphane)palladium was observed in the gas phase by negative-ion electrospray ionization mass spectrometry.¹⁸⁷ There are two hypothesis for the formation of $[\text{Pd(0)L}_2]$ complex: 1) it can be formed from Pd(0) complexes like $\text{Pd(PPh}_3)_4$ or, 2) from Pd(II) complexes like $\text{PdCl}_2(\text{PPh}_3)_2$

¹⁸³a) L. Cassar, *J. Organomet. Chem.* **1975**, *93*, 253-57; b) H. Dieck and F. Heck, *J. Organomet. Chem.* **1975**, *93*, 259-63. ¹⁸⁴G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054-3131. ¹⁸⁵a) R. Chinchilla, C. Najera, *Chem. Rev.* **2007**, *107*, 874-922; b) H. Doucet, J.-C. Hierso, *Angew. Chem., Int. Ed.* **2007**, *46*, 834-71. ¹⁸⁶R. Chinchilla, C. Najera, *Chem. Soc. Rev.* **2011**, *40*, 5084-5121. ¹⁸⁷K. L. Vikse, M. A. Henderson, A. G. Oliver, J. S. McIndoe, *Chem. Commun.* **2010**, *46*, 7412-14.

and by formation of a $[\text{Pd(II)L}_2(\text{CCR}^2)_2]$ species followed by a reductive-elimination and formation of a diyne that gives $[\text{Pd(0)L}_2]$. This route is notable by using an oxidant like molecular oxygen.¹⁸⁸

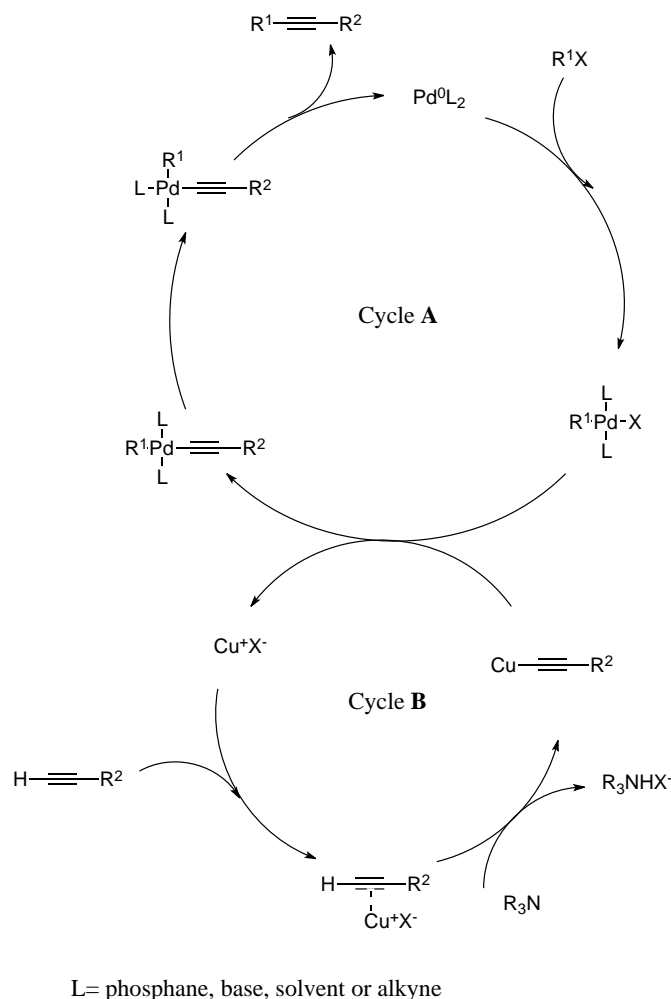


Fig. 31. Proposed mechanism cycles for Sonogashira cross-coupling reaction¹⁸⁶

Another remark about the mechanism of this reaction is the presence of amines that could also reduce Pd(II) to Pd(0) by forming an iminium cation. Structural confirmation of the reduction mechanism of Pd(II) to Pd(0) by inorganic bases has been already reported.¹⁸⁹

After formation of complex $[\text{Pd(0)L}_2]$, the first step in the catalytic cycle starts by oxidative addition of the aryl or vinyl halide. This step is taken as the rate-limiting step of the Sonogashira reaction. The rate of oxidative addition of ArX ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) increases in order of $\text{ArI} < \text{ArBr} < \text{ArCl}$.¹⁹⁰ After oxidative-addition step and formation of $[\text{Pd(II)R}_1\text{L}_2\text{X}]$ adduct is transmetalation step that the previous adduct will be converted to $[\text{Pd(II)L}_2\text{R}_1(\text{CCR}^2)]$ species. Here formation of a

¹⁸⁸G. P. McGlacken, I. J. S. Fairlamb, *Eur. J. Org. Chem.* **2009**, (24), 4011-4029. ¹⁸⁹H. Li, G. A. Grasa, T. J. Colacot, *Org. Lett.* **2010**, 12, 3332-5.

¹⁹⁰C. Gottardo, T. M. Kraft, M. S. Hossain, P. V. Zawada, H. M. Muchall, *Can. J. Chem.* **2008**, 86, 410-15.

copper acetylide, needed for the transmetallation, can also be observed through the copper-cycle (cycle **B**). This adduct then undergoes a reductive-elimination step through a cis/trans-isomerization to the final alkyne and the catalyst $[\text{Pd}(0)\text{L}_2]$ regenerates. The presence of the base (organic or inorganic) in this reaction is believed to help deprotonation after the formation of a π -alkyne copper complex through cycle **B** that makes the proton of the terminal alkyne more acidic. This cycle can be more complicated since CuI-phosphane adducts can also be formed and ligands can be transferred from one metal to other, which shows that copper-ligand interactions can also occur in this palladium/copper cross-coupling reaction.¹⁹¹

As is mentioned previously, another version of the coupling can be a copper-free reaction. The mechanism of this reaction also starts by oxidative addition of the aryl or vinyl halide to the catalytic species $[\text{Pd}(0)\text{L}_2]$ (**Fig. 32**),^{185a} followed by a reversible π -coordination of the alkyne which results in an alkyne-Pd(II) complex. This coordination renders the acetylenic proton more acidic and easy to be removed by the base. $[\text{Pd}(\text{II})\text{R}_1(\text{CCR}^2)\text{L}_2]$ complex then liberates the cross-coupled product by reductive-elimination and regeneration of the catalytic species $[\text{Pd}(0)\text{L}_2]$.

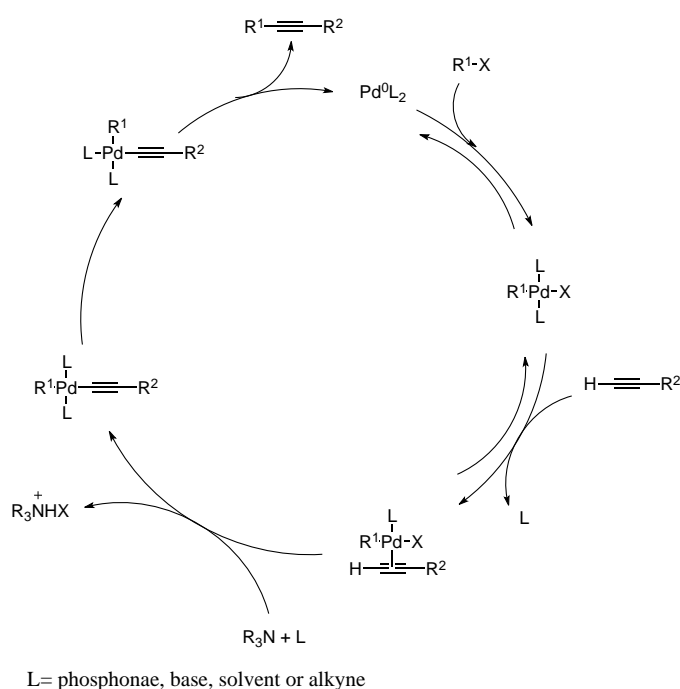


Fig. 32. Proposed mechanism for copper-free Sonogashira reaction.¹⁸⁶

The amine used in the copper-free Sonogashira reaction could have multiple roles that was shown

¹⁹¹a) M. Beaupérin, E. Fayad, R. Amardeil, H. Cattey, P. Richard, S. Brandes, P. Meunier, J.-C. Hierso, *Organometallics* **2008**, *27*, 1506-13; b) M. Beaupérin, A. Job, H. Cattey, S. Royer, P. Meunier, J.-C. Hierso, *Organometallics* **2010**, *29*, 2815-22.

by recent studies.¹⁹² Not only the amines can serve as deprotonating agents in this reaction, but they can also participate in different steps before the deprotonation one. For example, they can be involved in the oxidative addition step through formation of more reactive [Pd(0)L(amine)] complexes and they can also substitute one ligand in the complex formed after the oxidative elimination. Another possible mechanism that could occur is illustrated in Figure 33. This proposed mechanism depends highly on the rate of the competition between amine and alkyne in the substitution of one ligand on palladium in this mechanism. If the amine is a less good ligand than the alkyne for the palladium (II) center in [Pd(II)XR₁L₂] (*i.e.* L = PPh₃, amine = piperidine), mechanism of Figure 32 would be preferential in comparison with the one presented in Figure 33. In the case where the amine is a better ligand than the alkyne for the palladium (II) center in [Pd(II)XR₁L₂] (*i.e.* L = AsPh₃, amine = piperidine), the proposed mechanism in Figure 33 should occur.

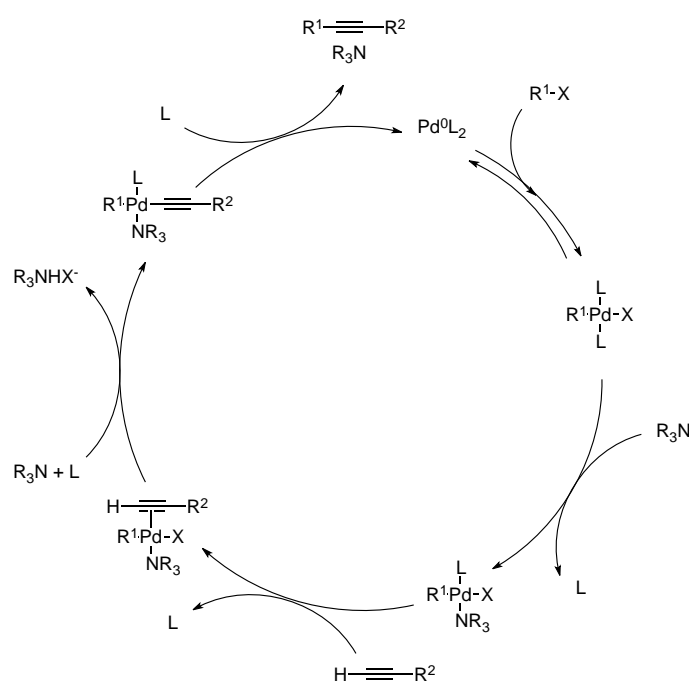


Fig. 33. Proposed mechanism involving amines for the copper-free Sonogashira reaction.¹⁸⁶

A possible mechanistic shift is also possible when going from electron-rich to electron-poor alkynes. This suggestion was proved by Hammett correlation studies where a model reaction with different *p*-substituted phenyl acetylenes and 4-iodobenzotrifluoride as coupling partners were used in the presence of Pd₂(dba)₃.CHCl₃/AsPh₃ as catalytic system in methanol.¹⁹³ This changeover point

¹⁹²A. Tougeri, S. Negri, A. Jutand, *Chem. Eur. J.* **2007**, *13*, 666-76. ¹⁹³T. Ljungdahl, T. Bennur, A. Dallas, H. Emténäs, J. Martensson, *Organomet.* **2008**, *27*, 2490-98.

was found to be dependent on the nature of the amine base and its concentration. It is thought that the reaction mechanism described in Fig. 32 changes from a pathway containing a fast proton transfer formed slowly from a cationic palladium complex (Fig. 34, cationic pathway) to a pathway containing a slow proton transfer from a neutral Pd complex (Fig. 34, anionic pathway) that occurs when going from electron-rich to electron-poor alkynes. In both pathways, amine base is suggested to act as both base and a nucleophile that facilitate the formation of the cationic complex in the reactions involving electron-rich alkynes, so the ideal choice of base depends on the substrate.

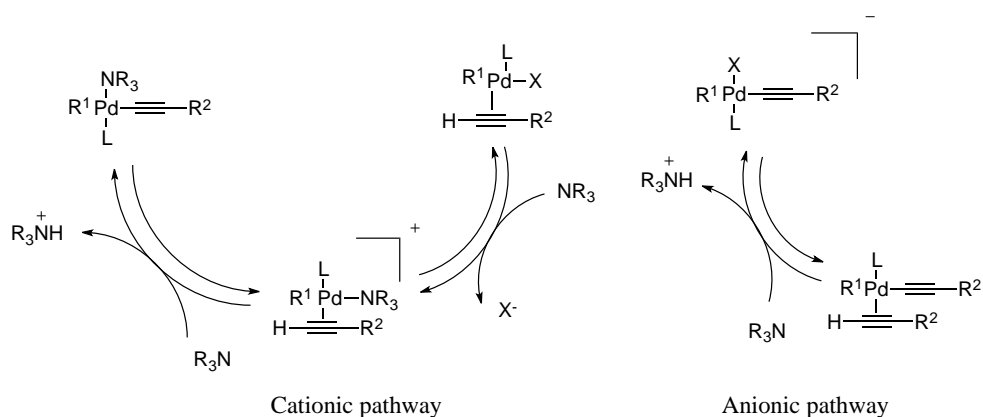
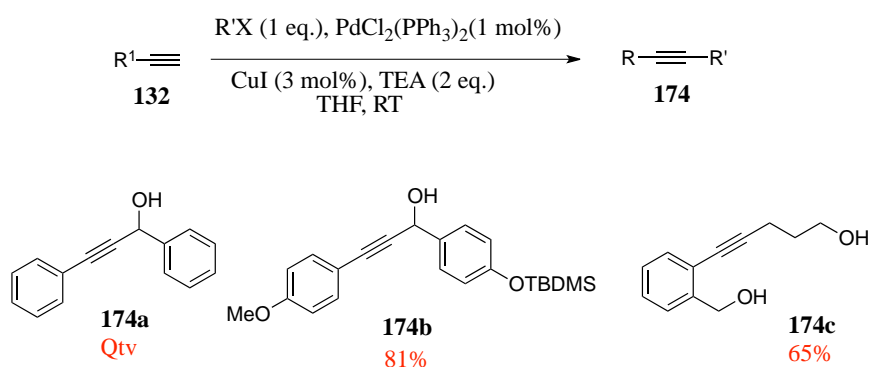


Fig. 34. Proposed mechanistic changeover in the mechanism of the Sonogashira reaction when going from electron-rich to electron-poor alkynes.¹⁸⁶

Therefore, in term of the mechanism of the Sonogashira reaction, it seems that depending on substrates or bases, different catalytic cycles can operate, and even that palladium-copper exchange of ligands could be present when possible.

II.3.2.2.2. Synthesis of internal alkynes

General Sonogashira reaction condition used to prepare our internal alkynes is shown in Scheme 50. By this reaction, we prepared either diols alkyne or hydroxy arylalkynes with different substitutions on the aromatic ring (Scheme 50).



Scheme 50. Preparation of internal alkynes by Sonogashira reaction condition.

As is shown in Scheme 50, the internal hydroxyl arylalkyne **174a** was obtained with a quantitative yield from a Sonogashira cross-coupling between iodobenzene as aryl halide and 1-phenyl-2-propyn-1-ol. Here, the reaction was not performed in THF as solvent, and Et_3N was used both as solvent and base in this reaction condition. In another try, a substituted hydroxyl arylalkyne **174b** was prepared with 81% yield which was produced from a reaction between a protected iodobenzyl alcohol and (methoxyphenyl)-prop-2-yn-1-ol. To prepare our dihydroxy arylalkyne, we ran this reaction between iodobenzyl alcohol and pentyn-1-ol that resulted in the desired internal alkyne **196c** with 65% yield. Therefore, with a classic Sonogashira reaction, we could prepare some internal alkynes with fair to good yield.

In order to conduct the *Click Chemistry* reactions which are Huisgen cycloaddition and its copper (I)-catalysed version (CuAAC), not only internal or terminal alkynes were necessary, but also we needed to prepare some organic azides that we will talk in the next part.

II.4. Azides

Greiss discovered the first azide that was phenyl azide, more than 100 years ago.¹⁹⁴ Different methods have been reported to prepare organic azides such as: 1) substitution or addition (insertion of the N₃ group); 2) diazo transfer (on amines); 3) diazotization (followed by azide reaction); 4) cleavage of triazines and analogous compounds; and 5) rearrangement of azides.¹⁹⁵

Amongst synthetic azides, azidonucleosides (*viz.*, AZT (3'-azido-3'-deoxythymidine) and CS-85) (**Fig. 35**) attracted international attention due to their application in the treatment of AIDS and ARC (AIDS-related complex).¹⁹⁶

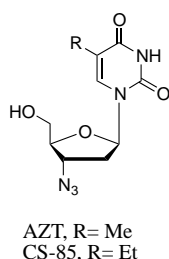


Fig. 35. Structure of AZT and CS-85.

It is also worth noting that, however most azides can be handled without any precautions, some of them are explosive, depending on the number of nitrogen atoms from the starting azide that end up in the final product. In another word, the more the azide compound is small, the more is possible to be explosive, and it is because of the liberation of the nitrogen molecule when there is structural possibility to easily eject N₂ and/or an external energy source like pressure or heat.

Some general guidelines to consider when working with organic azides are:

1) Carbon to nitrogen ratio; the total number of nitrogen atoms in an organic azide should not exceed that of carbon. The following equation helps to evaluate if the azide is stable enough to work with. Here, N represents the number of atoms:¹⁹⁷

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

- *n*-nonyl azide (C/N=3) is the smallest organic azide that can be isolated and stored in its

¹⁹⁴Griess, *Philos Trans. R. Soc. London* **1864**, *13*, 377. ¹⁹⁵E. F. V. Scriven, K. Turnbull, *Chem. Rev.* **1988**, *88*, 297-368. ¹⁹⁶a) T. S. Lin, W. H. Prusoff, *J. Med. Chem.* **1978**, *21*, 109-12; b) R. K. Robins, *Chem. Eng. News* **1986**, *64*, 28-40; c) R. M. Baum, *Ibid.*, p. 7; d) R. Dagani, *Ibid.*, p. 7; e) D. M. Barnes, *Science* **1986**, *234*, 15-16. ¹⁹⁷S. Bräse, C. Gil, K. Knepper, K. Zimmerman, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240.

pure form (up to 20 grams).¹⁹⁸

- Azides with a C/N ratio greater than one and no more than 3 can be synthesized and isolated but should be stored below room temperature at no more than 1M concentration and at a maximum of 5 grams of material.¹⁹⁸

- Organic azides with C/N <1 should never be isolated. It may be synthesized if the azide is a transient intermediate species and the limiting reagent in the reaction mixture has a maximum quantity of 1 gram.¹⁹⁸

2) Rule of six; Alternatively, follow the “rule of six”, six carbons (or other atoms of about the same size) per energetic functional group (azide, diazo, nitro, *etc.*) should provide enough dilution to render the compound relatively safe to work with given appropriate controls and safety procedure.⁴² In general, olefinic, aromatic, or carbonyl azides are much less stable than aliphatic azides.⁴²

Despite their explosive property, azides are used widely in organic synthesis because of their stability toward oxygen, water and also a multiple of reaction conditions. In term of industrial applications of azides we can mention their usage in the synthesis of heterocycles like triazoles and tetrazoles, in addition they have been utilized as functional group in pharmaceutical industry.

They are utilized as precursor of nitrene in the reaction of cycloaddition, aza-Wittig, Staudinger reaction, Mitsunobu and in different rearrangement reaction such as Curtius, Sundberg, Schmidt, Boyer-Aubé and Hemetsberger rearrangement.¹⁹⁷

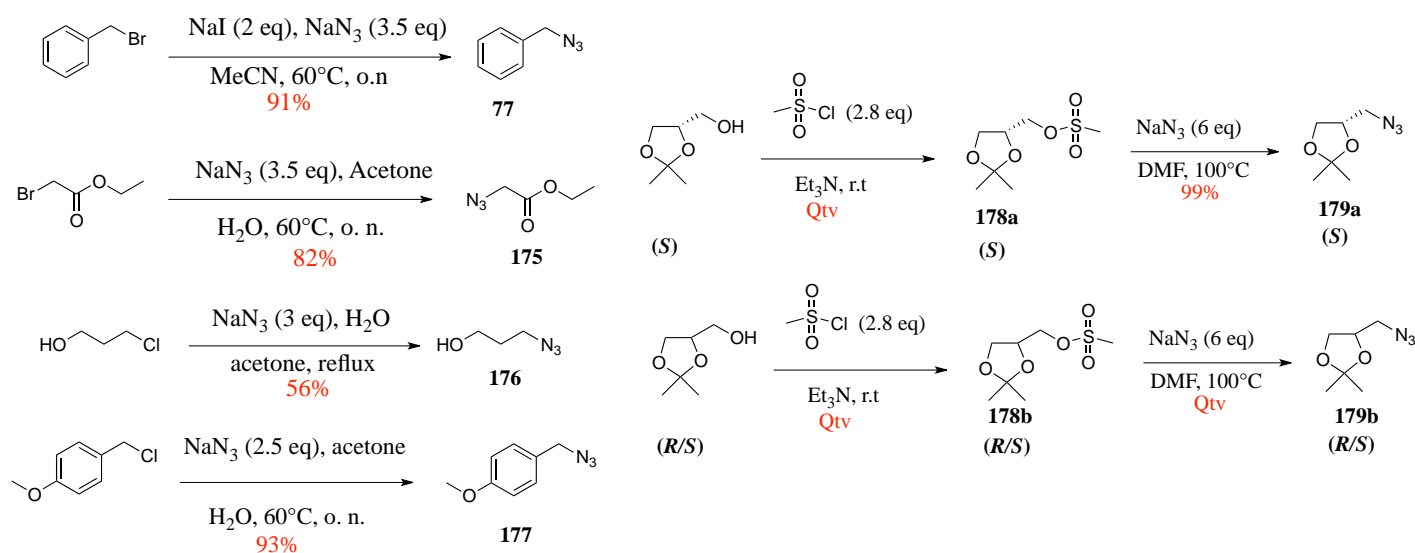
Azide functions are normally introduced into aliphatic compounds by a nucleophilic substitution reaction. In this case, the reaction is conducted by heating the corresponding halide compound and sodium azide. There are also some other preparation modes from alcohols as the starting material.¹⁹⁹

II.4.1. Synthesis of organic azides

As is mentioned above, the most commonly applied procedure to synthesize organic azide is displacement of halides by azide ion. In order to prepare azides, we applied this procedure between an organic halide and sodium azide, sometimes adding sodium iodide, in different solvents

¹⁹⁸University of California Santa Barbara, “Laboratory Safety Fact Sheet no. 26: Synthesizing, Purifying, and Handling Organic Azides”. ¹⁹⁹M. E. C. Biffin, D. B. Paul, *Aust. J. Chem.* **1974**, *27*, 777-88.

like acetonitrile, acetone or water (**Scheme 51**). By departing from different alkyl halides, a variety of corresponding azides with different functional groups have been prepared.

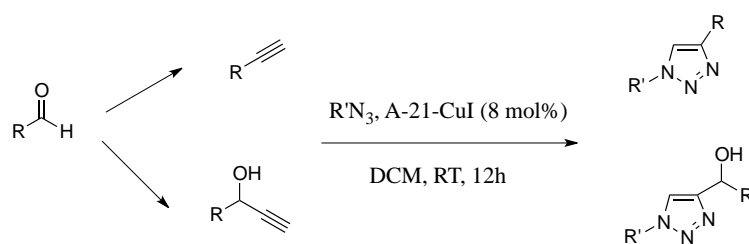


Scheme 51. Synthesis of organic azides from alkyl halides.

From this reaction procedure, the expected azides were prepared in a good yield except azide **177** which was found with an average yield of 56% that can be due to the solubility of the final product in water and lost of it in aqueous phase. In the case of azides **179a** and **179b**, they were prepared in two steps, first a mesylation reaction in the presence of methane sulfonyl chloride where the mesylated dioxolanes were obtained with a quantitative yield followed by an azidation reaction in the presence of sodium azide in DMF, which resulted the expected azidomethyl dioxolanes with 99% and quantitative yields respectively for *S* and *R/S*. Here, two forms of azidodioxolanes were prepared (*S* and *R/S*) to study their eventual effects on the reaction with alkynes.

II.5. Synthesis of small triazolic derivatives on a solid support catalyst (A-21.CuI)


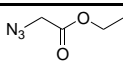
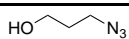
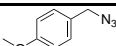
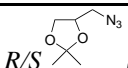
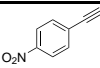
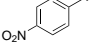
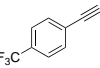
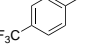
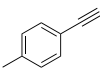
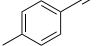
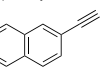
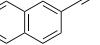
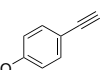
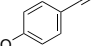
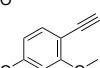
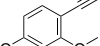
At the beginning of this chapter, solid support catalyst, especially A-21.CuI has been described. For the synthesis of triazole derivatives, from our prepared alkynes and azides, we subjected them to A-21.CuI (8 mol%) in CH_2Cl_2 at room temperature (**Scheme 52**).



Scheme 52. Reaction condition for the preparation of triazoles from propargylic alcohols or alkynes.


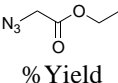
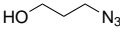
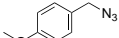
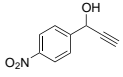
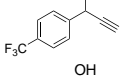
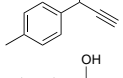
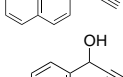
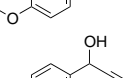
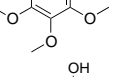
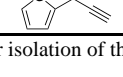
As shown in scheme **52**, this reaction could be performed easily at room temperature and without any special precautions like working under inert gas. The results are summarized through Table **10** and **11** respectively for terminal alkynes and propargylic alcohols.

Table 10. Synthesis of triazoles from the 1,3-dipolar cycloaddition reaction between terminal alkynes and azides in DCM at rt and for 12h and in the presence of A-21.CuI (8 mol%).

Entry	Terminal alkynes						
		% Yield	% Yield	% Yield	% Yield	R/S	S
1		93	91	38	Qtv	76	80
		180	181	182	183	184a	184b
2		97	92	Qtv	Qtv	86	43
		185	186	187	188	189a	189b
3		Qtv	92	Qtv	Qtv	82	66
		190	191	192	193	194a	194b
4		91	92	95	99	82	85
		195	196	197	198	199a	199b
5		Qtv	Qtv	99	Qtv	71	55
		200	201	202	203	204a	204b
6		100	96	Qtv	100	99	75
		205	206	207	208	209a	209b

*Yield after isolation of the final product on flash column chromatography.

Table 11. Synthesis of triazoles from the 1,3-dipolar cycloaddition reaction between propargylic alcohols and azides.

Entry	Propargyl alcohol	 % Yield	 % Yield	 % Yield	 % Yield	R/S	S % Yield*
1		90 210	98 211	82 212	98 213	84 214a	74 214b
2		92 215	93 216	62 217	Qtv 218	86 219a	67 219b
3		90 220	Qtv 221	95 222	99 223	87 224a	64 224b
4		92 225	99 226	81 227	Qtv 228	85 229a	75 229b
5		Qtv 230	99 231	87 232	Qtv 233	42 234a	43 234b
6		90 235	98 236	Qtv 237	96 238	59 239a	53 239b
7		Qtv 240	98 241	Qtv 242	Qtv 243	80 244a	38 244b

* Yield after isolation of the final product on flash column chromatography.

In the presence of our catalyst (A-21.CuI), all of the expected triazoles were prepared with a high yield (between 76% and 100%) for most of them after simple filtration and evaporation of solvent. However some problems were observed in the presence of azides such as 3-azidopropan-1-ol (**176**) where the final products were less soluble in the used solvent, so they remained onto the polymer (A-21.CuI), like in the case of the reaction between 1-ethynyl-4-nitrobenzene (**132a**) and 3-azidopropan-1-ol (**176**) (Table 10, entry 1), which resulted in isolation of the triazole with only 38% yield. In another case, in the reaction between our alkynes with (*S*)-4-azidomethyl-2,2-dimethyl-1,3-dioxolane (**179a**), the conversion of the alkynes into the triazoles was not total. Both the starting alkynes and azides remained with the triazole which required a further purification by flash column chromatography.

Once these triazoles were prepared, they were subjected into a cytotoxicity test in order to study their biological property. These small triazole derivatives were tested against cancer cells like *B16-melanoma cells* because during the course of our studies against cancer cells in our research unit, we found out triazolic derivatives with interesting anticancer activities²⁰⁰ that will be discussed in the next part.

²⁰⁰ a) N. M. Blanch, G. G. Chabot, L. Quentin, D. Scherman, S. Bourg, D. Dauzonne, *Eur. J. Med. Chem.* **2012**, *54*, 22-32. b) H. Elamari, R. Slimi, G. Chabot, L. Quentin, D. Scherman, C. Girard, *Eur. J. Med. Chem.* **2013**, *60*, 360-64.

II.6. Study of anticancer property of synthesized triazoles

In our study to find new biologically active compounds, we focused more on finding biological active molecules against murine B16 melanoma cell line. The choice of the B16 melanoma model is based on the urgent need to find new active compounds against metastatic melanoma, which is particularly resistant to chemotherapy in humans.²⁰¹ In addition, B16 melanoma is considered as a good model of the human disease because it is highly invasive and can metastasize when grafted into syngeneic mice.²⁰² This melanoma model is also particularly refractory to chemotherapy, just like the human disease.²⁰³ This model has also recently been shown to express $\alpha_v\beta_3$ and E-selectin, which are particularly important targets for antiangiogenic cancer therapy.²⁰⁴ Another point is that B16 melanoma has been used extensively in preclinical studies worldwide including the National Cancer Institute, and therefore allows a good comparison basis to numerous other published preclinical studies.

II.6.1. Melanoma

Melanoma is a malignant tumor of melanocytes. Melanocytes produce the dark pigment, melanin, which is responsible for the color of skin. These cells predominantly occur in the skin and in the soft tissue of the meninges, mucous membranes and upper oesophagus. Melanoma can originate in any part of the body containing melanocytes, and it is less common than other types of cancer but dangerous if it is not found in the early stages. Treatment of early-stage melanoma is associated with extremely high survival rates, but later invasive stages have proved considerably more difficult to treat.²⁰⁵ The incidence of melanoma is increasing rapidly in the US and Europe, particularly in young adults, mainly due to UV overexposure. Worldwide, doctors diagnose about 160,000 new cases of melanoma yearly. In women the most common site is legs, and for men is more common on the back.²⁰⁶

-Cause

In general, cancers can result from a DNA damage and in melanomas usually caused by exposure to ultraviolet (UV) light from the sun.

UVB have been suggested to generate melanin biosynthesis by activating keratinocytes in the skin

²⁰¹G. M. Boyle, *Expert Rev. Anticancer Ther.* **2011**, *11*, 725-37. ²⁰²D. P. Griswold, *Cancer Chemother. Reports Part 2 Supplement 3* **1972**, 315-24. ²⁰³F. Darro, C. decaestecker, J.-F. Gaussin, S. Mottier, R. Van Ginckel, R. Kiss, *Int. J. Oncol.* **2005**, *27*, 607-16. ²⁰⁴J. Seguin, C. Nicolazzi, N. Mignet, D. Scherman, G. Chabot, *Tumor Biol.* **2012**, *33*, 1709-17. ²⁰⁵Drugs in Clinical Development for Melanoma, *Pharm. Med.* **2012**, *26*, 171-183. ²⁰⁶Cancer Research UK Statistics Team **2010** (<http://www.cancerresearchuk.org>).

to secrete Nitric Oxide (NO), then this secreted NO activates melanin synthesis via the 3'-5'-cyclic guanosine monophosphate/protein kinase G (cGMP/PKG) pathway.²⁰⁷ Another possible reported mechanism is that UVB stimulates production of prostaglandin E₂ (PGE₂) in keratinocytes following by secretion of PGE₂, that in turn activates melanin synthesis via the 3'-5'-cyclic adenosine monophosphate/ protein kinase A (cAMP/ PKA) pathway.²⁰⁸ Overexposure to UV, can also lead to carcinogenesis through those misregulated pathways in cells.

II.6.2. Some synthesized molecules against B16 melanoma

Tan's group reported in 2006,²⁰⁹ synthesis, DNA binding and cytotoxicity of new pyrazole emodin derivatives. This group works on chemical modification of bioactive components of medicinal herbs. Among them Emodin (**Fig. 36**) is the major bioactive compound of a variety of herb species like *Rheum* and *Polygonum* (Polygonaceae), *Rhamnus* (Rhamnaceae) and *Senna* (Cassieae).²¹⁰

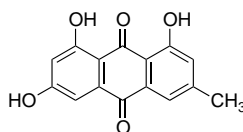


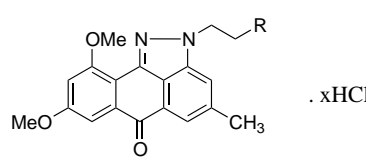
Fig. 36. Chemical structure of Emodin.

Emodin proved to exert a variety of biological effects such as anti-inflammatory, antibiotic, antiviral and antineoplastic activities.²¹¹ It has been shown to inhibit the growth of various cancer cells, and cause the apoptosis of certain cancer cells.^{211d, 212} Its function as noncovalent DNA binder is usually believed to be essential for its activity.

Emodin itself has low DNA binding affinity, and low or insignificant cytotoxicity against various cancer cells.²¹³ In their paper, Tan *et al.*,²⁰⁹ described that, because of its coplanar structure, the incorporation of a pyrazole ring into its anthraquinone structure might improve the electron density

²⁰⁷a) C. Romero-Graillet, E. Aberdam, M. Clement, J.-P. Ortonne, R. Ballotti, *J. Clin. Invest.* **1997**, *99*, 635-42; b) C. Romero-Graillet, E. Aberdam, N. Biagoli, W. Massabni, J.-P. Ortonne, R. Ballotti, *J. Biol. Chem.* **1996**, *271*, 28052-56. ²⁰⁸a) C. C. Miller, P. Hale, A. P. Pentland, *J. Biol. Chem.* **1994**, *269*, 3529-33; b) C. Bertolotto, P. Abbe, T. J. Hamesath, K. Bille, D. Fisher, J.-P. Ortonne, R. Ballotti, *J. Cell Biol.* **1998**, *142*, 827-35. ²⁰⁹J.-H. Tan, Q.-X. Zhang, Z.-S. Huang, Y. Chen, X.-D. Wang, L.-Q. Gu, J. Y. Wu, *Eur. J. Med. Chem.* **2006**, *41*, 1041-47. ²¹⁰D. S. Alves, L. Perez-Fons, A. Estepa, V. Micol, *Biochem. Pharmacol.* **2004**, *68*, 549-61. ²¹¹a) Y. C. Kuo, H. C. Meng, W.J. Tsai, *Inflamm. Res.* **2001**, *50*, 73-82; b) M. C. Fuzellier, F. Mortier, T. Girard, J. Payen, *Ann. Pharm. Fr.* **1981**, *39*, 313-18; c) D. L. Barnard, J. H. Huffman, J. L. B. Morris, S. G. Wood, B. G. Hughes, R. W. Sidwell, *Antiviral Res.* **1992**, *17*, 63-77; d) T.-L. Cha, L. Qiu, C.-T. Chen, Y. Wen, M. C. Hung, *Cancer Res.* **2005**, *65*, 2287-95. ²¹²a) Y.-C. Chen, S.-C. Shen, W.-R. Lee, F.-L. Hsu, H.-Y. Lin, C.-H. Ko, S.-W. Tseng, *Biochem. Pharmacol.* **2002**, *64*, 1713-24; b) D.-E. Shieh, Y.-Y. Chen, M.-H. Yen, L.-C. Chiang, C.-C. Lin, *Life Sci.* **2004**, *74*, 2279-90. ²¹³L. P. Mai, F. Gueritte, V. Dumontet, M. V. Tri, B. Hill, O. Thoison, D. Guenard, T. Sevenet, *J. Nat. Prod.* **2001**, *64*, 1162-68.

of the π system area that results in a higher resistance to enzymatic reduction to radical species, thus to lower the cardiotoxicity.²¹⁴ The quinonoid structure is not sufficient alone, but, the addition of side chains like polymethylenamine, sugar or heterocycles to the Emodin scaffold, usually results in a higher DNA binding affinity and antitumor activities.²¹⁵ Among different side chains, Tan and coworkers²⁰⁹ declare that, cationic amino side chains are most desirable as their distal amino group binds electrostatically to the phosphate moieties of DNA.^{214a,216} In addition, chains with different lengths, polarity, rigidity, charge and steric bulk cause different DNA binding affinities. Upon these claims, Tan's group synthesized a new family of Emodin derivatives with improved DNA binding affinity and antitumor activity by introducing a pyrazole ring into the anthraquinone chromophore, and then attaching various cationic amino side chains to the pyrazole ring (**Fig. 37**).





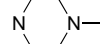
Compound	R	IC ₅₀ against B ₁₆ cells
Emodin		>100
245	N(CH ₃) ₂	2.7
246	N(CH ₂ CH ₃) ₂	3.6
247	NH(CH ₂) ₂ OH	1.8
248	NH(CH ₂) ₂ N(CH ₃) ₂	5.2
249	NH(CH ₂) ₂ N(CH ₂ CH ₃) ₂	10.1
250		6.9
251		n.d.
252		20.1

Fig. 37. Structures of Emodin derivatives **245-252**.²⁰⁹

IC₅₀ values (cytotoxicity potency index, compound concentration required to kill 50% of cancer cells) of these compounds against B16 melanoma are shown in Fig. 37. Through this study, they found that derivatives **245**, **246** and **247** were most effective in inhibiting the tumor cell growth with the lowest IC₅₀ values of 2.7, 3.6 and 1.8 μ M. Furthermore, these compounds have relatively large DNA binding constants, so they resulted that the higher cytotoxic activity of molecules against the tumor cells could be related, at least in part, to their high binding affinity with the DNA of tumor cells. In the term of structure activity relationship, compounds **245**, **246**, **247** and **250** containing mono-cationic side chains had a stronger cytotoxic activity than compounds **248**, **249** and **252**

²¹⁴W. M. Cholody, S. Martelli, J. Paradziew-Lukowicz, J. Konopa, *J. Med. Chem.* **1990**, *33*, 49-52. ^{215a)} R. K. Y. Zee-Cheng, C. C. Cheng, *J. Med. Chem.* **1978**, *21*, 291-4; b) R. K. Y. Zee-Cheng, E. G. Podrebarac, C. S. Menon, C. C. Cheng, *J. Med. Chem.* **1979**, *22*, 501-5. ²¹⁶J. Feigon, W. A. Denny, W. Leupin, D.R. Kearns, *J. Med. Chem.* **1984**, *27*, 450-65.

bearing the di-cationic side chains. As an explanation for lower activity of compounds **248**, **249** and **252**, Tan's group declared that this lower activity is due to the higher electrical charge of these three compounds which make them less lipophilic and so more difficult to diffuse through the cell membrane.

Other families of molecules were recently tested against B16 melanoma cells belong to APO (2-amino-3H-phenoxazin-3-one) and kojic acid derivatives (**Fig. 38**). These molecules were studied in Fukuda's group.²¹⁷

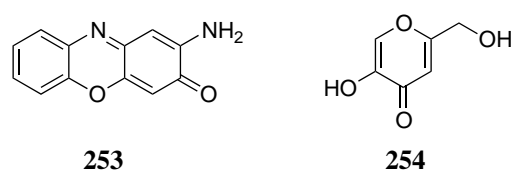


Fig. 38. Chemical structure of APO **253** and kojic acid **254**.

The first APO molecule **253** has been isolated as an antibacterial substance from Actinomycetes.²¹⁸ In addition, APO can be synthesized from *o*-aminophenol by human erythrocytes.²¹⁹ APO has also been found to exert various biological effects, including anticancer,²²⁰ antiviral,²²¹ and antichlamydia activities.²²²

From these observations, Fukuda and coworkers²¹⁷ decided to examine whether APO might show a depigmentation effect against sun-induced melanogenesis. To find that, they examined the inhibitory effect of APO on melanogenesis in the murine melanoma cell line B16, which is well-characterized as an *in vitro* model of melanin biosynthesis. For this study, they compared inhibitory effects of APO and Kojic acid (KA) on melanin biosynthesis (**Fig. 39**). Kojic acid **254**²²³ is an active ingredient available for medicated whitening cosmetics in Japan, and has antibacterial and antifungal activities. It is produced by *Aspergillus oryzae* and a by-product of rice malt fermentation (sake production).

In this study, they found out that APO inhibited the protein expression of tyrosinase and microphthalmia-associated transcription factor (MIFT), a melanogenic transcription factor that regulates the expression of tyrosinase. These results suggest that APO is a promising depigmenting

²¹⁷M. Miyake, S. Yamamoto, O. Sano, M. Fujii, K. Kohno, S. Ushio, K. Iwaki, S. Fukuda, *Biosc. Biotechnol. Biochem.* **2010**, *74*, 753-8. ²¹⁸K. Anzai, K. Isono, K. Okuma, S. Suzuki, *J. Antibiot.* **1960**, *13*, 125-132. ²¹⁹A. Tomoda, J. Yamaguchi, H. Kojima, H. Amemiya, Y. Yoneyama, *FEBS Lett.* **1986**, *196*, 44-8. ²²⁰S. Kato, K. Shirato, K. Imaizumi, H. Toyota, J. Mizuguchi, M. Odawara, X.-F. Che, S. Akiyama, A. Abe, A. Tomoda, *Oncol. Rep.* **2006**, *15*, 843-8. ²²¹K. Hayashi, T. Hayashi, A. Tomoda, *J. Pharmacol. Sci.* **2008**, *106*, 369-75. ²²²T. Uruma, H. Yamaguchi, M. Fukuda, H. Kawakami, H. Goto, T. Kishimoto, Y. Yamamoto, A. Tomoda, S. Kamiya, *J. Med. Microbiol.* **2005**, *54*, 1143-49. ²²³Y. Mishima, *Pigment Cell Res.* **1992**, *2*, 3-16.

agent with both therapeutic and cosmetic value in preventing melanogenesis. In another word, their obtained results revealing that APO is an effective inhibitor of tyrosinase and MIFT protein expression in B16 melanoma cells that cause a decrease in melanin biosynthesis. In addition they suggest that APO might be a useful inhibitor of melanogenesis, and further imply that it might have beneficial effects in the treatment of hyperpigmentation disorders.²¹⁷

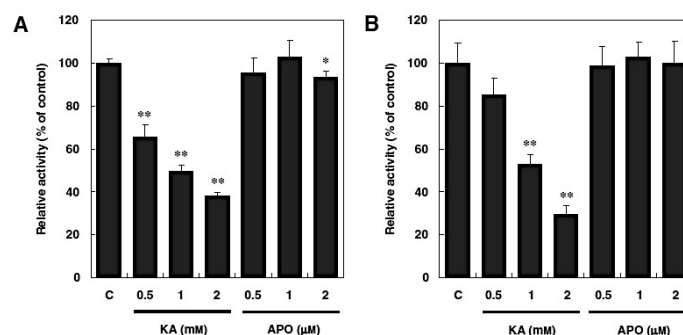


Fig. 39. Comparison of APO and Kojic Acid (KA) as to Cell-Free Tyrosinase activity.

The effects of Kojic acid (KA) and APO on the activities of tyrosinase from mushroom (A) and extracted B16 cells (B) were examined. * $p < 0.05$; ** $p < 0.01$; as compared with the control cultures.

II.7. *In vitro* evaluation of potential anticancer activity of synthesized triazolic derivatives

II.7.1. Synthesis of *Combretastatin A4* analogs containing a triazole core

In our sustained effort to find new methods for the synthesis of original and new biologically active compounds against cancer,²²⁴⁻²²⁸ in our research unit, we became interested in the evaluation of triazolic derivatives. Among these synthesized molecules, *cis*-constrained analogs of combretastatin A4 were synthesized at Curie institute in a collaborative project (**Fig. 40**).^{200a}

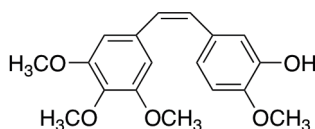
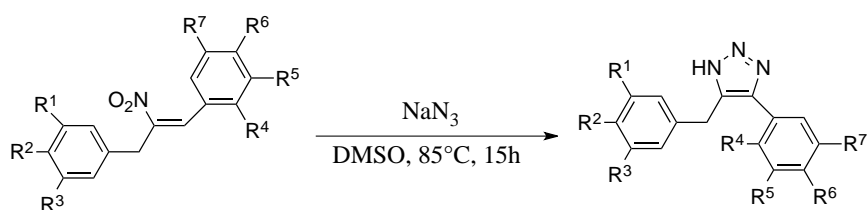


Fig. 40. Structure of Combretastatin A4 (CA4).

Structure of these molecules are shown in Scheme 53. Between these molecules, the one with a

²²⁴C. Girard, J. Doulat, A. Savarin, C. Surcin, S. Leue, V. Escriou, C. Largeau, J. Herscovici, D. Scherman, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3224-28. ²²⁵M. Aufort, J. Herscovici, P. Bouhours, N. moreau, C. Girard, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1195-98. ²²⁶H. Elamari, I. Jλία, C. Louet, J. Herscovici, F. Meganem, C. Girard, *Tetrahedron: Asymm.* **2010**, *21*, 1179-83. ²²⁷J.-P. Monserrat, G. Chabot, L. Hamon, L. Quentin, D. Scherman, G. Jaouen, E. A. Hillard, *Chem. Comm.* **2010**, *46*, 5145-47. ²²⁸M. Arthuis, R. Pontikis, G. G. Chabot, J. Seguin, L. Quentin, S. Bourg, L. Morin-Allory, J.-C. Florent, *Chem. Med. Chem.* **2011**, *6*, 1693-1705.

structure most similar to combretastin, meaning those bearing both aromatics with the same substituents as CA4 (with one exception) were among the most potent derivatives; such as compounds **260**, **262**, **264**, **267**.^{200a}



255: R¹= OH, R²= OCH₃, R³= H
R⁴= H, R⁵= OCH₃, R⁶= OCH₃, R⁷= OCH₃
256: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶-R⁷= OCH₂O
257: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= Cl, R⁵= H, R⁶= Cl, R⁷= H
258: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶= OCH₃, R⁷= NO₂
259: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶= OCH₃, R⁷= F
260: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶= OCH₃, R⁷= OH
261: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶= OH, R⁷= OCH₃

262: R¹= OH, R²= OCH₃, R³= H
R⁴= H, R⁵= OCH₃, R⁶= OCH₃, R⁷= OCH₃
263: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶-R⁷= OCH₂O
264: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= Cl, R⁵= H, R⁶= Cl, R⁷= H
265: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶= OCH₃, R⁷= NO₂
266: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶= OCH₃, R⁷= F
267: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶= OCH₃, R⁷= OH
268: R¹= OCH₃, R²= OCH₃, R³= OCH₃
R⁴= H, R⁵= H, R⁶= OH, R⁷= OCH₃

Scheme 53. Synthesized analogs of Combretastatin A4 (CA4).

The IC₅₀ obtained from the cytotoxicity test between these synthesized molecules against B16 melanoma cell lines are presented in Table 12. Some compounds show good activities, in the micromolar range, the best activity was found for compound **258**, but still less active than CA4 (3 nM).

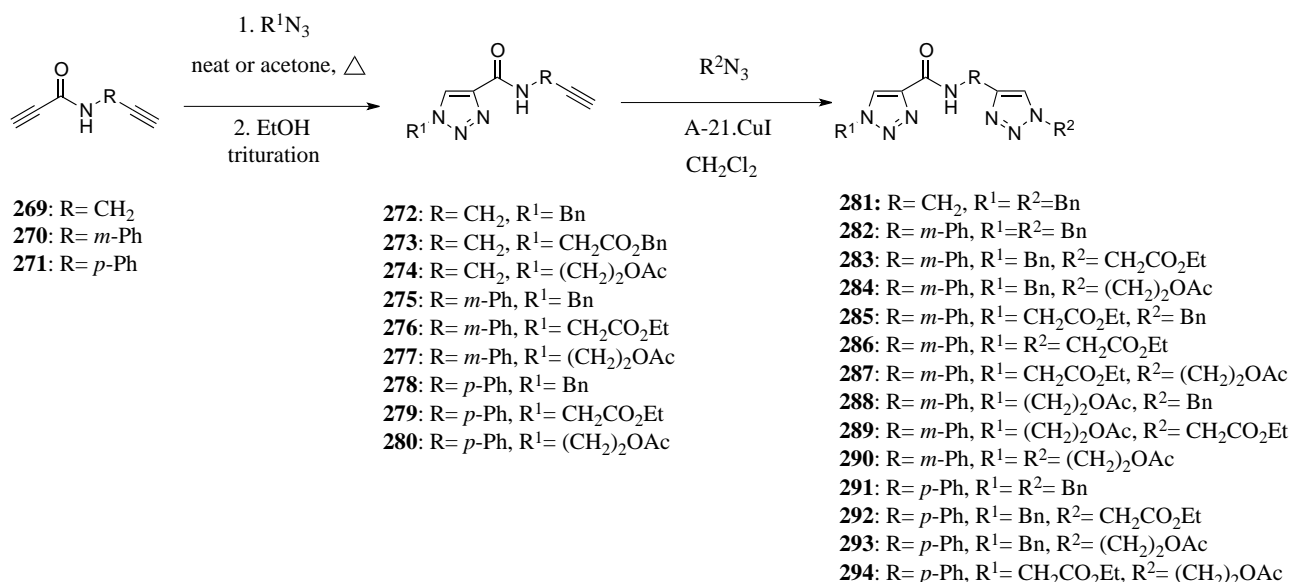
Table 12. Biological activities of new analogues of Combretastatin A4^{200a}

Entry	Compound	Cytotoxicity IC ₅₀ (μM) ^a	Entry	Compound	Cytotoxicity IC ₅₀ (μM) ^a
1	CA4	0.003	8	266	31 ± 2.6
2	267	1.6 ± 0.1	9	258	3.5 ± 0.1
3	260	4.0 ± 1.1	10	257	2.6 ± 0.2
4	256	3.0 ± 0.2	11	261	2.6 ± 0.3
5	255	2.9 ± 0.02	12	263	38.0 ± 3.4
6	262	22.9 ± 0.9	13	265	50.1 ± 10.7
7	259	2.9 ± 0.1	14	264	41.7 ± 1.3

^a Concentration required to kill 50% of cells after 48h incubation time (MTT assay). Mean ± SEM.

II.7.2. Mono- and bis-1,2,3-triazole derivatives of bis-alkynes

Another class of synthesized triazoles in our group was based on 1,4-disubstituted bis-1,2,3-triazole.²²⁹ Since 1,2,3-triazoles are recognized as important and efficient pharmacophores, investigation of new structures containing this nucleus as mono- and bis-triazoles prepared from bis-alkynes was at the center of our attention.²³⁰ The obtained IC₅₀ against B16 melanoma from these synthesized bis-alkynes are summarized in Scheme 54 and Table 13.



Scheme 54. Different synthesized mono- and bis-triazoles.²²³

²²⁹H. Elamari, F. Meganem, J. Herscovici, C. Girard, *Tetrahedron Lett.* **2011**, 52, 658-60. ²³⁰S. Agalave, G. Sandip, S. Maujan, V. S. Pore, *Chem. Asian. J.* **2011**, 6, 2696-2718.

Table 13. *In vitro* biological activity (IC₅₀) against B16 melanoma cells for the above presented bis-alkyne.²²³

N°	R	R ¹	R ²	IC ₅₀ (μM)	N°	R	R ¹	R ²	IC ₅₀ (μM)
269	CH ₂	-	-	38.0±0.4	282	<i>m</i> -Ph	Bn	Bn	4.5±0.3
270	<i>m</i> -Ph	-	-	0.3±0.008	283	<i>m</i> -Ph	Bn	CH ₂ CO ₂ Et	21.0±2
271	<i>p</i> -Ph	-	-	6.3±0.3	284	<i>m</i> -Ph	Bn	(CH ₂) ₂ OAc	25.1±0.3
272	CH ₂	Bn	-	65±5	285	<i>m</i> -Ph	CH ₂ CO ₂ Et	Bn	20.4±0.4
273	CH ₂	CH ₂ CO ₂ Et	-	>100	286	<i>m</i> -Ph	CH ₂ CO ₂ Et	CH ₂ CO ₂ Et	>100
274	CH ₂	(CH ₂) ₂ OAc	-	>100	287	<i>m</i> -Ph	CH ₂ CO ₂ Et	(CH ₂) ₂ OAc	>100
275	<i>m</i> -Ph	Bn	-	14.5±0.7	288	<i>m</i> -Ph	(CH ₂) ₂ OAc	Bn	>100
276	<i>m</i> -Ph	CH ₂ CO ₂ Et	-	91.0±6	289	<i>m</i> -Ph	(CH ₂) ₂ OAc	CH ₂ CO ₂ Et	63.0±9
277	<i>m</i> -Ph	(CH ₂) ₂ OAc	-	25.1±0.1	290	<i>m</i> -Ph	(CH ₂) ₂ OAc	(CH ₂) ₂ OAc	>100
278	<i>p</i> -Ph	Bn	-	>100	291	<i>p</i> -Ph	Bn	Bn	>100
279	<i>p</i> -Ph	CH ₂ CO ₂ Et	-	>100	292	<i>p</i> -Ph	Bn	CH ₂ CO ₂ Et	36.3±0.8
280	<i>p</i> -Ph	(CH ₂) ₂ OAc	-	79.0±2	293	<i>p</i> -Ph	Bn	(CH ₂) ₂ OAc	13.2±0.3
281	CH ₂	Bn	Bn	0.3±0.003	294	<i>p</i> -Ph	CH ₂ CO ₂ Et	(CH ₂) ₂ OAc	>100

From presented results in Table 13, we concluded that modification of the side chains could influence the value of IC₅₀ in a way that, for example, replacement of the propargyl side chain in **269** by a *m*-ethynylphenyl (compound **270**) caused a 127-fold increase in biological activity with an IC₅₀ of 0.3 μM (Table 13). Presence of an aromatic “linking” ring also increased the cytotoxic activity of **269** with an IC₅₀ of 6 μM (Table 13). In the R¹= benzyl series (molecules **272**, **274** and **278**), we observed an improved activity when going from **272** to **281** (with R²= benzyl). The bis-triazole **281** had an IC₅₀ of 0.3 μM, which was two-hundred and thirty times the activity of **272** and the same as the one of the bis-alkyne **270**. Introduction of this R¹= benzyl in **282**, starting from **275**, gave also an increase in activity going from 14.5 to 4.5 μM (three times). However the same effect was not observed when introducing a second triazole in **291**, obtained from **269**, since they have both IC₅₀>100 μM. Also in this R¹= benzyl series, the introduction of another type of chain like ethoxycarbonylmethyl and acetoxyethyl, had positive effects on the biological activity, but not as important as for **281**. In the R¹= benzyl / ethyloxycarbonyl (**273**, **276** and **279**) and acetoxyethyl (**274**, **277** and **280**) series, the introduction of another triazole ring only yielded compounds with IC₅₀ > 100 μM. So here, some of the synthesized products showed noteworthy activity against B16 melanoma cells. From these previous reported results,²²³ we subjected other synthesized triazoles reported in part II.4 of this dissertation in a biological assay (MTT) on B16.


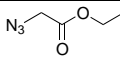
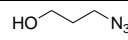
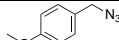

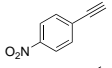
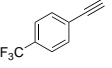
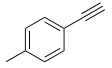
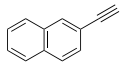
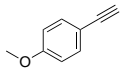
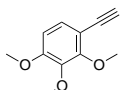
II.7.3. Mono-1,2,3-triazoles derived from terminal alkynes and propargylic alcohols

Tables **10** and **11** show the prepared triazoles from terminal alkynes and propargylic alcohols. For this biological test against B16 melanoma cell lines, a stock solution of triazoles (10mM) in DMSO was prepared and triazoles were incubated with B16 cells for 48h at different concentrations ranging from 100 to 3.13 μM , in order to study their IC_{50} (half maximal inhibitory concentration). The results are presented in Table **14** and **15**.

In the case of *p*-nitrobenzene triazolic derivatives (Table **14**, entry 1), when triazolic ring bears a benzyl group on the nitrogen (Table **14**, product **180**), a better IC_{50} could be observed (5.12 μM) compared with other substituents on nitrogen for which an IC_{50} higher than 100 μM was obtained, except for compound **183** where we could observe a higher IC_{50} of 19.05 μM (Table **14**, entry 1) when introducing a *p*-methoxy substituent on the benzyl.

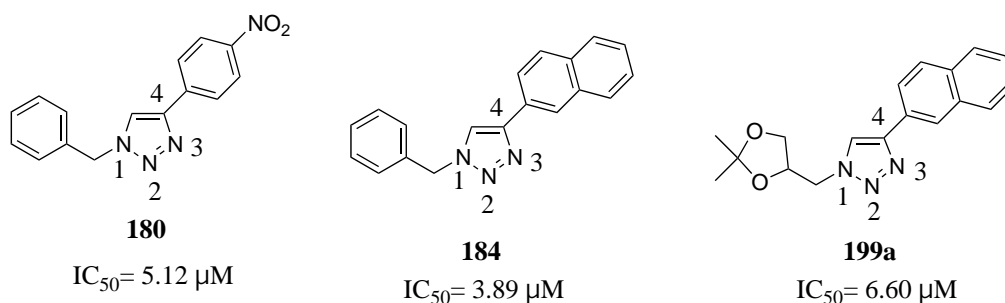
The best cytotoxicities for *p*- CF_3 -phenyl derivatives were obtained with compounds **188** and **189a** with respectively IC_{50} = 17.37 and 13.48 μM with *p*-methoxybenzyl and dioxolane substituents on the nitrogen. While triazole with dioxolane *S* has an IC_{50} of higher than 100 μM , for dioxolane *R/S* IC_{50} was decreased to 13.48 μM which could show a higher activity of form *R* compared to form *S*.

Table 14. Cytotoxicity of 1,2,3-triazoles obtained from terminal alkynes, was tested on B16 melanoma cell-lines.

Entry	Terminal alkynes	 IC_{50} (μM)	 IC_{50} (μM)	 IC_{50} (μM)	 IC_{50} (μM)	 IC_{50} (μM)
1		5.12±0.39 180	>100 181	n.d. 182	19.05±0.73 183	>100 184a >100 184b
2		>100 185	n.d. 186	>100 187	17.37±0.35 188	13.48±1.26 >100 189a >100 189b
3		>100 190	n.d. 191	>100 192	19.49±1.53 193	41.68±6.89 >100 194a >100 194b
4		3.89±0.31 195	>100 196	>100 197	>100 198	6.60±5.61 12.02 199a >100 199b
5		>100 200	n.d. 201	>100 202	>100 203	- >100 204a >100 204b
6		27.54±2.06 205	>100 206	n.d. 207	>100 208	- >100 209a >100 209b


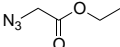
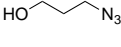
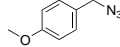

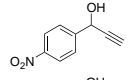
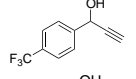
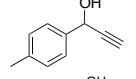
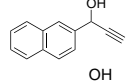
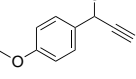
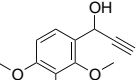
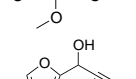
A decrease in IC_{50} could also be observed for *p*-methylphenyl derivatives (entry 3) from >100 to $19.49 \mu\text{M}$ when the triazole core bears a methoxy benzyl substituent on nitrogen (**Table 14**, entry 3, compound **193**). As previously observed, dioxolane stereochemistry seems to play a role even if IC_{50} for the racemate is higher than before ($41.68 \mu\text{M}$, **194a**, entry 3). With naphthalene derivatives, again a better IC_{50} was obtained with a triazole with a benzyl group on nitrogen ($IC_{50} = 3.89 \mu\text{M}$, **195**). Other triazoles showed an increase in IC_{50} , and only dioxolane *S* and *R/S* gave a readable IC_{50} of 12.02 and $6.60 \mu\text{M}$ respectively (**199b**, **199a**). For two other phenyl rings substituted by methoxy (**Table 14**, entries 5 and 6) only compound **205** with a benzyl ring on the nitrogen gave a measurable IC_{50} of $27.54 \mu\text{M}$.

With triazoles deriving from the reaction between propargylic alcohols and organic azide (**Table 15**) no good IC_{50} were obtained except for naphthalene derivatives where IC_{50} of 28.84 and $26.91 \mu\text{M}$ were respectively obtained for compounds **225** and **229a** (**Table 15**, entry 4). In other cases either a solubility problem occurred for which the IC_{50} couldn't be determined or an IC_{50} with high concentrations ($>100 \mu\text{M}$) was obtained. It thus seems that the introduction of a hydroxymethylene between the aryl substituent at the C-4 position of the triazole lowers considerably the activity. In the case of naphthyl derivatives, the extra CHOH increases the IC_{50} from 3.89 to $28.84 \mu\text{M}$ for the *N*-benzyl family and from 12.02 and $6.60 \mu\text{M}$ to n.d. and $26.91 \mu\text{M}$ for (*S*) and (*R/S*) dioxolane one. So compounds **180** with a *p*-nitrobenzene substituent on triazole ring and a methylbenzyl group on the nitrogen, **195** with a naphthyl substituent on triazolic ring and a methylbenzyl group on the nitrogen and **199a** with again a naphthyl substituent on triazole and a dimethyl dioxolane substituent on nitrogen remained as the most active products (**Scheme 55**).



Scheme 55. The most found active triazoles against B16 cells.

Table 15. Cytotoxicity of 1,2,3-triazoles obtained from propargylic alcohols, against B16 melanoma.

Entry	Propargyl alcohol						
		IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	R/S IC ₅₀ (μM)	S IC ₅₀ (μM)
1		n.d. 210	n.d. 211	n.d. 212	>100 213	n.d. 214a	>100 214b
2		>100 215	n.d. 216	n.d. 217	n.d. 218	>100 219a	n.d. 219b
3		>100 220	n.d. 221	n.d. 222	>100 223	>100 224a	>100 224b
4		28.84±1.33 225	>100 226	n.d. 227	n.d. 228	26.91±7.00 229a	n.d. 229b
5		n.d. 230	n.d. 231	>100 232	>100 233	n.d. 234a	>100 234b
6		n.d. 235	n.d. 236	>100 237	>100 238	- 239a	>100 239b
7		>100 240	>100 241	>100 242	>100 243	>100 244a	n.d. 244b

In addition of these triazolic derivatives, the starting terminal alkynes and propargylic alcohols were also subjected to this cytotoxicity test, but no interesting activity for these molecules could be obtained.

II.8. Molecular and bioactivity properties prediction by *Molinspiration* software

Molinspiration (Scheme 56) is a private company that is interested in development and application of modern cheminformatics techniques especially in connection with the web.²³¹ By use of this on-line program, different properties of chemical structures such as physicochemical properties or bioactivity of molecules can be predicted. There are many papers in which this software has been used to predict bioavailability or physicochemical properties of chemical molecules.²³²

In the development of bioactive molecules as therapeutic agents, high oral bioavailability is usually an important factor.²³³ Because of that, one of the important aims in drug research is to find sufficient understanding of the molecular properties that can cause boundaries for oral

Scheme 56. Page web of *Molinspiration* (WWW.molinspiration.com).²³¹

bioavailability, in that way the design of applicable new drug candidates will be facilitated.²³³

As properties of molecule we can mention physicochemical property that includes logP (octanol/water partition coefficient), TPSA (molecular polar surface area), Molecular Volume,

²³¹To find more information about molinspiration, you can visit their web-site: WWW.molinspiration.com. ²³²Some of these articles are: a) M. J. Ahsan, J. G. Samy, H. Khalilullah, M. d. Shivli Nomani, P. Saraswat, R. Gaur, A. Singh, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7246-50; b) B. J. Al-hourani, S. K. Sharma, M. Suresh, F. Wuest, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2235-8; c) C. Remes, A. Pahun, I. Zarafu, M. Tudose, M.T. Caproui, G. Ionita, C. Bleotu, L. Matei, P. Ionita, *Bioorg. Chem.* **2012**, *41-42*, 6; d) A. C. Pinheiro, M. N. Rocha, P. M. Nogueira, T. C. M. Nogueira, L. F. Jasmim, M. V. N. de Souza, R. P. Soares, *Diagnos. Microbiol. Infect. Disease* **2011**, *71*, 273-8; e) R. K. Verma, V. K. Prajapati, G. K. Verma, D. Chakraborty, S. Sundar, M. Rai, V. K. Dubey, M. S. Singh, *Med. Chem. Lett.* **2012**, *3*, 243-7. ²³³D. F. Veber, S. R. Johnson, H.-Y. Cheng, B. R. Smith, K. W. Ward, K. D. Kopple, *J. Med. Chem.* **2002**, *45*, 2615-23.

molecular weight, number of atoms, number of hydrogen bond acceptors, number of hydrogen bond donors, number of rotatable bonds and molecular lipophilicity potential (MLP).

- **Octanol/water partition coefficient (logP):** A pure substance may distribute itself between two partially miscible solvents in intimate contact, and the equilibrium ratio of solute concentrations in the two phases is also known as the distribution coefficient or partition coefficient.²³⁴ In the basic organic chemistry, the use of solvents with different polarities (*e.g.* hydrocarbon and water) accelerates the extraction and purification of desired products. In addition it was found that, the biological activity of simple organic compounds corresponds to their oil-water partition coefficients.²³⁵ It is supposed that, for biological aims a partition coefficient based on long chain ester or alcohol solvents was more suitable.²³⁶ Upon more studies on this subject, 1-octanol was chosen as the most useful lipophilic solvent in these applications. Further works have been done using the octanol-water pair, and this is the reason for its wide use and the existence of a great quantity of data on this subject. Octanol/water partition coefficient (logP) is used in QSAR (Quantitative Structure-Activity Relationship) studies and rational drug design as a measure of molecular hydrophobicity. This measure of hydrophobicity is important because hydrophobicity affects drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of molecules, as well as their toxicity. LogP has become also a key parameter in studies of the environmental fate of chemicals.

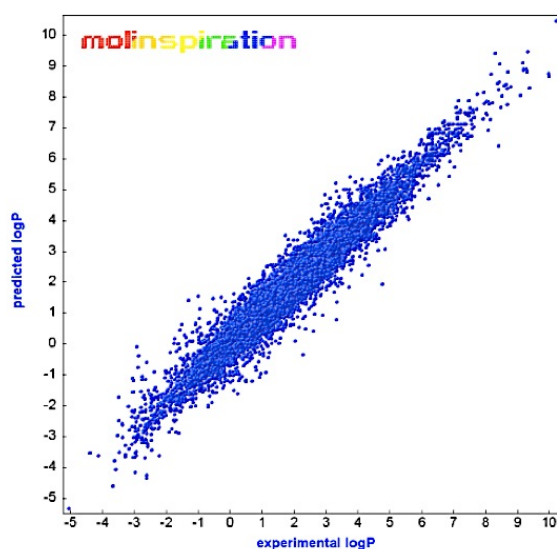
The octanol-water partition coefficient of a substance X at a given temperature is generally constant,²³⁵ represented by P and defined by:

$$P = [X]^{\text{org}}/[X]^{\text{aq}}$$

Superscripts « org » and « aq » indicate mutually saturated phases.²³⁶

The method for logP prediction developed at Molinspiration is based on group contributions.²³¹ This method is based on fitting calculated logP with experimental logP for a training set of more than twelve thousand, mostly drug-like molecules. In that way, hydrophobicity values for 35 small simple “basic” fragments have been obtained, as well as values for 185 larger fragments, characterizing intramolecular hydrogen bonding contribution to logP and charge interactions. Molinspiration methodology for logP calculation (**Scheme 57**) is very robust and is able to process practically all organic and most organometallic molecules.

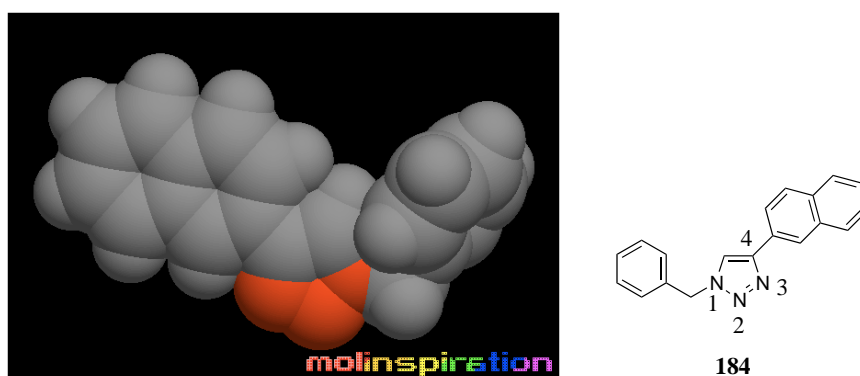
²³⁴A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525-616. ²³⁵C. Hansch, A. Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York **1979**. ²³⁶J. Sangster, *J. Phy. Chem. Ref. Data* **1989**, *18*, 1111-229.



Scheme 57. An example of correlation of calculated logP by *Molinspiration* program.²³¹

By the use of this program, logP is predicted with error < 0.25 for 50.5% of molecules, for 80.2% with error < 0.5 and for 96.5% with error < 1.0, and only for 3.5% of structures logP is predicted with error > 1.0. These statistical parameters place *Molinspiration* miLogP as one of the best existing methods for prediction of logP, and several users reported very good correlations between molinspiration calculated logP and various drug transport properties.

- **Molecular Molar Surface Area (PSA):**²³¹ is a very useful parameter for prediction of drug transport properties. Polar Surface Area is defined as a sum of surfaces of polar atoms (usually oxygens, nitrogens and attached hydrogens) in a molecule (**Scheme 58**). This parameter has been shown to correlate very well with the human intestinal absorption, Caco-2 monolayers permeability, and blood-brain barrier penetration.



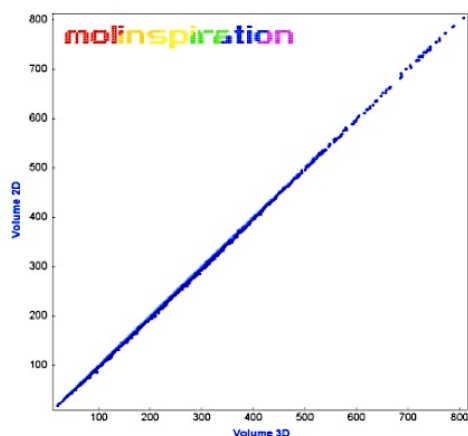
Scheme 58. Represented Polar Surface Area (PSA) for triazole **184** by *Molinspiration*.²³¹

The calculation of PSA in a classical way, however, is rather time consuming, because of the necessity to generate a reasonable 3D molecular geometry and the determine the surface itself. Additionally, calculations require specialized software to generate the 3D molecular structures and to determine the surface. In this era of drug development shaped by high-throughput screening and combinatorial chemistry, fast bioavailability screening of virtual libraries consisting of hundreds of thousands, even millions of molecules is required. That is the reason why in the molecular property prediction toolkit so called topological polar surface area - TPSA is implemented.

The methodology for the calculation of TPSA is described in details in a paper published by Selzer *et al.*²³⁷ Briefly, the procedure is based on the summation of tabulated surface contributions of polar fragments (atoms regarding also their environment). These fragment contributions were determined by least squares fitting to the single conformer 3D PSA for 34,810 drugs from the World Drug Index. Topological polar surface area provides results of practically the same quality as the classical 3D PSA, the calculations, however, are two to three orders of magnitude faster.

- **Molecular Volume:** ²³¹ Molecular volume determines transport characteristics of molecules, such as intestinal absorption or blood-brain barrier penetration. Volume is therefore often used in QSAR studies to model molecular properties and biological activity. Various methods may be used to calculate molecular volume, including methods requiring generation of 3D molecular geometries, or fragment contribution methods such as McGowan volume approximation. Method for calculation of molecule volume developed at Molinspiration is based on group contributions. These have been obtained by fitting sum of fragment contributions to "real" 3D volume for a training set of about twelve thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semiempirical AM1 method. Calculated volume is expressed in cubic Ångstroems (Å³). Molinspiration methodology for calculation of molecular volume is very robust and is able to process practically all organic and most organometallic molecules. Molinspiration fast 2D-based method for calculation of molecular volume provides identical results with computationally much more demanding 3D-based volume calculation for just a fraction of computing time (**Scheme 59**).

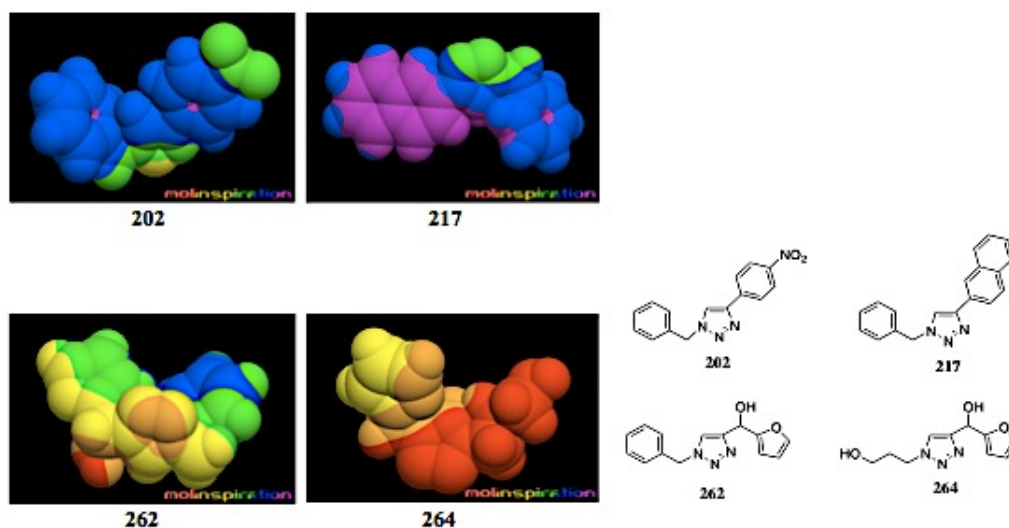
²³⁷P. Ertl, B. Rohde, P. Selzer, *J. Med. Chem.* **2000**, *43*, 3714-17.



Scheme 59. Correlation between the fast 2D volume calculation of *Molinspiration* corresponding to 3D evaluation.²³¹

- **Rotatable bonds:**²³¹ This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs.²³³ Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy (*i.e.*, non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier.

- **Molecular Lipophilicity Potential (MLP):** This method allows to see which parts of the molecule surface are hydrophobic (**Scheme 60**, encoded by violet and blue colors) and which are hydrophilic (**Scheme 60**, encoded by orange and red). On *Molinspiration* program,²³¹ the MLP is calculated from atomic hydrophobicity contributions, the same that are used to calculate the octanol-water partition coefficient (logP) by their *miLogP* method.



Scheme 60. Presented MLP of our triazoles 202, 217, 262, 264 on *Molinspiration*.²³¹

MLP is useful property to rationalize various molecular ADME (Absorption, Distribution, Metabolism, and Excretion) characteristics (like membrane penetration or plasma-protein binding). Analysis of 3-dimensional distribution of hydrophobicity on molecular surface is particularly helpful when explaining differences in observed ADME properties of molecules with the same logP, since, of course, 3D parameter contains much more information than logP expressed by just a single value.

Because of these utilities of *Molinspiration*, that makes us capable to calculate molecular property and predict bioactivity of molecules, and also considering the number of papers²³² used this on-line program, we decided to study the physicochemical properties of our synthesized molecules.

In order to predict drug-like molecules physicochemical property of chemical structures should respect *Lipinski's rule*²³⁸ or rule of 5. The rule was suggested for the first time by Christopher A. Lipinski in 1997 based on the observation that most medication drugs are rather small and they are lipophilic. This rule describes important molecular properties for a drug's pharmacokinetics such as their absorption, distribution, metabolism, and excretion (ADME). Precisely, upon *Lipinski's rule*, the most drug-like molecules have $\log P \leq 5$, molecular weight ≤ 500 Da, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5 . Molecules violating more than one of these rules may have problems with bioavailability. However this rule doesn't predict that a molecule can be pharmacologically active. The rule is called "Rule of 5", because the border values are 5, 500, 2*5, and 5.

We calculated molecular properties of our synthesized 1,2,3-triazoles for compliance to the Lipinski's rule of five by *Molinspiration*. Some of the results are shown in Table 16. The obtained results revealed that non of these molecules have any violation of the above criteria (Lipinski's violation =0), so all of our synthesized triazoles have a good potential for eventual development as oral agents, but only some of them presented a potential bioactivity, and are listed in Table 17.

²³⁸C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Feeney, *Adv. Drug Deliv. Rev.* **1997**, 23, 3-25.

Table 16. Calculated physical properties for our synthesized 1,2,3-triazolic derivatives with a measurable IC₅₀.

Compound	Volume	TPSA ^a	NROTB ^b	HBA ^c	HBD ^d	miLogP	MW ^e	nViol ^f
Rule	-	-	-	<10	<5	≤5	<500	≤1
180	244.05	76.54	4	6	0	3.08	280.287	0
183	269.59	85.77	5	7	0	3.13	310.31	0
188	277.56	39.95	5	4	0	4.04	333.31	0
189	270.98	49.18	4	5	0	3.03	327.30	0
193	262.82	39.95	4	0	0	3.56	249.31	0
194	256.25	49.18	3	5	0	2.58	273.33	0
195	264.70	30.71	3	3	0	4.30	285.35	0
199	283.68	49.18	3	5	0	3.32	309.36	0
205	297.35	58.42	6	6	0	2.94	325.36	0
225	295.83	69.41	5	6	1	2.52	357.33	0
229	308.52	69.41	4	6	1	2.80	339.39	0

^aPolar Surface Area ; ^b number of rotatable bond; ^c Number of hydrogen bond acceptors; ^d Number of hydrogen bond donors; ^eMolecular Weight; ^fLipinski's violations.

Table 17. Predicted biological activity for active compounds against B16.

Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
180	0.05	-0.11	0.01	-0.46	-0.22	0.16
183	0.03	-0.19	-0.00	-0.39	-0.21	0.09
188	0.26	-0.04	0.20	-0.10	-0.01	0.21
189	0.16	-0.19	0.16	-0.14	0.14	0.39
193	0.13	-0.21	0.09	-0.38	-0.18	0.18
194	-0.03	-0.41	-0.02	-0.47	-0.06	0.38
195	0.31	0.01	0.30	-0.22	0.03	0.36
199	0.15	-0.24	0.20	-0.24	0.15	0.45
205	0.17	-0.15	0.12	-0.35	-0.11	0.18
225	0.22	-0.09	0.12	-0.07	-0.07	0.21
229	0.06	-0.32	0.01	-0.10	0.02	0.30

As is shown in Table 17, by use of *Molinspiration*²³¹ program, we could find some molecules with a potential biological activities for our molecules such as GPCR ligand, kinase inhibitor or enzyme inhibitor (values are presented in red when a possible activity exists for values > 0.2). But we should remind that these activities are just a prediction and in *in vitro* or *in vivo* analysis it is possible that these found molecules behave in another way without showing any activity.

II.9. Conclusion

In this part of our work, some alkynes (terminal or internal) were prepared through different reaction conditions and different methods such as Bestmann-Ohira, coupling between an aldehyde and a terminal alkyne anion or through a classic Sonogashira cross-coupling reaction.

These obtained terminal alkynes were then subjected to a copper(I)-catalyzed Huisgen dipolar cycloaddition reaction with prepared organic azides in order to prepare triazolic derivatives. For this reaction, a new generation of heterogenous catalyst, copper doped Amberlyst A-21 which was prepared for the first time in our laboratory, was used. By doing the reaction between terminal alkynes and azides in the presence of A-21.CuI (8 mol%) in dichloromethane at room temperature, all of the expected triazoles could be obtained in a high yield, except for a few cases.

In the last part, these triazole products and their corresponding starting alkynes were subjected to a cytotoxicity test against B16 melanoma cell-line. In some cases a relative good IC_{50} could be obtained, especially for 4-substituted-nitrophenyl and naphthyl triazolic derivatives (IC_{50} = 3.89-6.60 μ M) (**Scheme 55**). However the starting terminal alkynes and propargylic alcohols were not active.

For other derivatives either high IC_{50} were found or the IC_{50} couldn't be determined due to a solubility problem of the triazoles. In addition, physical properties of these triazoles were calculated on *Molinspiration*, which showed that none of our molecules violate the Lipinski's rule of 5, meaning that all of our triazoles have a good potential to be developed as oral agents. Predicted biological activities like GPCR ligand, kinase or enzyme inhibitor could be found for our triazoles, again by using *Molinspiration* program, especially for our most active compounds (**184** and **188**) but not for **180**.

Chapter III

Microwave reactions

I. Preparation of trisubstituted triazolic derivatives

II. Catalyst- and Solvent-free Straightforward Synthesis of Propargylic Ethers From their carbonates and alcohols under microwave irradiation

III. Introduction

The microwave irradiation to accelerate organic chemical transformations was reported for the first time in 1986.²³⁹ The microwave radiation region in the electromagnetic spectrum is located between infrared radiation and radio waves. Wavelengths of microwaves are between 1mm-1m, that corresponds to frequencies, which are found between 0.3 and 300 GHz. In this region, telecommunication and microwave radar equipment cover many of the band frequencies,²⁴⁰ because of that, in order to prevent disturbance, the wavelength at which industrial and domestic microwave apparatus used for heating operates is adjusted on 12.2 cm, that corresponds to a frequency of 2.450 (± 0.050) GHz, but other frequency allocations do exist.

III.1. Use of microwaves in chemistry

In inorganic chemistry, microwave technology has been used since the late 1970s, however in organic chemistry as is mentioned in above, the use of microwave returns to mid-1980s. Since that time, the development of the technology in the field of organic chemistry was slow that can be due to its lack of controllability, safety aspects and a lack of understanding of the basics of microwave dielectric heating.²⁴⁰ In the term of the operation of microwave, the debates turn around this question whether the observed effects can be related to thermal/kinetic phenomena (thermal microwave effects) that arises from the fast heating and high volume reaction temperatures attained with microwave dielectric heating, or whether some effects are connected to a specific or nonthermal microwave effects.^{241,242} There is not yet a determined definition for a specific and nonthermal microwave effect and different scientific communities may in fact have different definition,²⁴² but most scientists today agree that the energy of microwave photon is too low to directly break molecular bonds, and so microwaves cannot make the molecules to conduct chemical reactions by direct absorption of electromagnetic energy, against to ultraviolet and visible radiation (photochemistry).²⁴² However, the organic community claims the existence of nonthermal microwave effects²⁴¹ that results from a direct, and often stabilizing interaction of the electromagnetic field with particular molecules, intermediates, or even transition states in the

²³⁹a) R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, *Tetrahedron Lett.* **1986**, 27, 279; b) R. J. Giguere, T.L. Bray, S. M. Duncan, G. Majetich, *Tetrahedron Lett.* **1986**, 27, 4945. ²⁴⁰P. Lidström, J. Tierney, B. Wathey, J. Westman, *Tetrahedron* **2001**, 57, 9225-83. ²⁴¹For leading reviews on microwave effects in organic synthesis, see : a) L. Perreux, A. Loupy, *Tetrahedron* **2001**, 57, 9199 ; b) A. De La Hoz, A. Diaz-Ortiz, A. Moreno, *Chem. Soc. Rev.* **2005**, 34, 164 ; c) L. Perreux, A. Loupy, *Microwaves in organic synthesis*, 2nd ed. (Ed. : A. Loupy), Wiley-VCH, Weinheim, **2006**, chap. 4, pp. 134-218 ; d) A. De La Hoz, A. Diaz-Ortiz, A. Moreno, *Microwaves in Organic Synthesis*, 2nd ed. (Ed. : A. Loupy), Wiley-VCH, Weinheim, **2006**, chap. 5, pp. 219-277 ; e) L. Perreux, A. Loupy, A. Petit, *Microwaves in Organic Synthesis*, 3rd ed. (Eds. : A. De La Hoz, A. Loupy), Wiley-VCH, Weinheim, **2013**, chap. 4, pp. 127-208. ²⁴²a) C. O. Kappe, *Angew. Chem.* **2004**, 116, 6408; *Angew. Chem. Int. Ed.* **2004**, 43, 6250 ; b) C. O. Kappe, A. Stadler, D. Dallinger, *Microwaves in Organic and Medicinal Chemistry*, 2nd ed., Wiley-VCH, Weinheim, **2012**, Chap. 2, pp. 9-39.

reaction medium that doesn't have any relation to a macroscopic change in reaction temperature.^{241,242} For example, it has been discussed that the presence of an electric field influences the orientation of dipolar molecules or intermediates and consequently changes the pre-exponential factor A or the activation energy (entropy term) in the Arrhenius equation (**eq. 1**) for some kinds of reactions.^{241, 242}

$$\text{Arrhenius' equation: } K = Ae^{-Ea/(RT)} \quad \text{eq. 1}$$

Where : Ea = activation energy ; R = Universal gas constant ; T = temperature in Kelvin

Moreover, a similar effect was proposed for polar reaction mechanisms, where the polarity increases going from the ground state to the transition state that leads to an increase in reactivity by a decrease of the activation energy.^{241, 242}

Despite of this incertitude for microwave operations, the number of publications that report use of this technique in inorganic or organic synthesis increased significantly (**Fig. 41**),²⁴⁰ because of the availability of commercial microwave equipment aimed to be applied in organic chemistry and the development of the solvent-free technique, that has improved the safety aspects, but are mostly because of a shorter time of the reaction by use of microwave radiations.

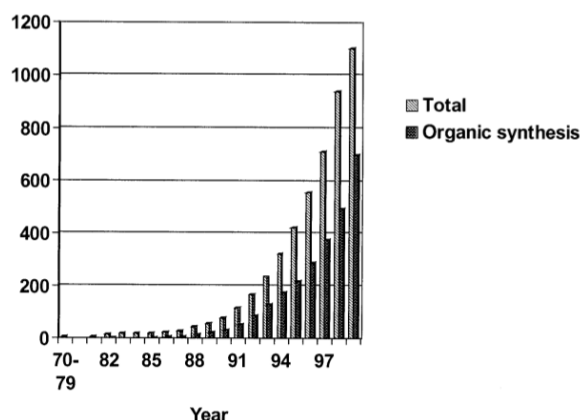


Fig. 41. The collected number of published articles containing organic and inorganic microwave assisted synthesis between 1970-1999.²⁴⁰

This increase for the use of microwave in industry is due to the short reaction times and the wide variety of reactions that can be performed by the microwave irradiation. As an example, in

pharmaceutical industry, the need for a large number of chemical entities to be produced, force chemists to apply new synthetic methods to decrease the time for the production of compounds; as an example, as the applied techniques in organic chemistry to increase the throughput, one can mention chemistry data bases, software for diversity selection, on-line chemical ordering systems, open-access and high throughput systems for analysis and high-speed, and also parallel and combinatorial synthesis equipment. In all these mentioned techniques, the common factor that can be considered is the automation and computer-aided control. However, they don't accelerate the chemistry itself, and today the improvements in chemistry only involve the highly reactive reagents in solution or on solid support.

In the context of heating organic reactions, traditionally these reactions have been heated by use of heat transfer equipment like oil baths, sand baths and heating jackets. These techniques are quite slow and a temperature gradient can appear within the sample. In addition, this local heating can lead to the decomposition of product, substrate or reagent. However, in microwave dielectric heating, the microwave radiation proceeds through the walls of the vessel and there are only reactants and solvent under heat not the reaction vessel itself,²⁴⁰ and the temperature increase will be constant all over the sample in the case the apparatus is well designed that can cause less by-products and/or decomposition products (**Fig. 42**). Another possibility in pressurized systems is that the temperature can increase rapidly even far above the standard boiling point of the used solvent.

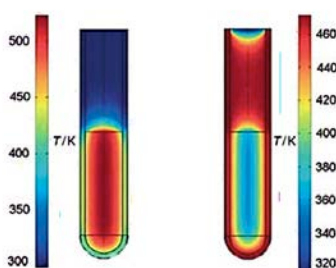


Fig. 42. Temperature gradients in microwave versus oil-bath heating: Difference in the temperature sides after 1min of microwave irradiation (left) and heating in an oil-bath (right). Microwave radiation increases the temperature of the whole volume simultaneously (volume heating) but in the oil-bath tube, only the reaction mixture in contact with the vessel wall is heated first.²⁴³

Another point about heating by microwave is that, on microwave, the materials are heated by “dielectric heating effects”.^{242a} This effect is based on the ability of the particular materials (solvent

²⁴³J.-S. Schanche, *Mol. Diversity* **2003**, 7, 293-300; Biotag AB (formerly Personal Chemistry AB), www.personalchemistry.com; www.biotag.com.

or reagent) to absorb microwave energy and convert it into heat. There are two mechanisms by which the electric component ²⁴⁴ of an electromagnetic field causes heating: dipolar polarization and ionic conduction. When a sample is subjected to the irradiation by microwave the dipoles or ions align in the applied electromagnetic field. This applied field oscillates so the dipole or ion field tend to realign itself with the existing electromagnetic field (Fig. 43), in this step of realigning energy is released in the form of heat through molecular abrasion and dielectric loss. The amount of this released heat is related to the ability of the matrix to align itself with the frequency of the applied field, and if the dipole does not have enough time to realign, or reorients itself quickly with the applied field, no heating takes place.



Fig. 43. Dipolar molecules that try to align with an oscillating electromagnetic field. ²⁴⁰

The frequency of 2.45 GHz that devoted to all commercial systems gives the molecular dipole time to align in the field, but not to follow the alternating field precisely. ²⁴⁵ To calculate the ability of a material to convert electromagnetic energy into heat at a given frequency and temperature, the equation $\epsilon''/\epsilon' = \tan \delta$ is used. ²⁴⁶ In this equation δ represents dissipation factor, and ϵ'' is the dielectric loss that measures the efficiency with which heat produced from electromagnetic radiation and ϵ' shows the dielectric constant or the ability of a molecule to be polarised by an electric field. The larger the dielectric constant, the greater the coupling with microwaves. In Table 18 the dielectric constant ($\epsilon_s =$ relative permittivity) and loss tangent δ of some solvents are presented. ²⁴⁰

²⁴⁴a) D.V. Stass, J.R. Woodward, C.R. Timmel, P.J. Hore, K.A. McLauchlan, *Chem. Phys. Lett.* **2000**, 329, 15-22; b) C.R. Timmel, P.J. Hore, *Chem. Phys. Lett.* **1996**, 257, 401-408; c) J.R. Woodward, R.J. Jackson, C.R. Timmel, P.J. Hore, K.A. McLauchlan, *Chem. Phys. Lett.* **1997**, 272, 376-382.
²⁴⁵a) D.R. Baghurst, D.M.P. Mingos, *Chem. Soc. Rev.* **1991**, 20, 1-47; b) C. Gabriel, S. Gabriel, E.H. Halstead, D.M.P. Mingos, *Chem. Soc. Rev.* **1998**, 27, 213-223. ²⁴⁶S. Caddick, *Tetrahedron* **1995**, 51 (38), 10403.

Table 18. Dielectric constants and loss tangent values for some solvents relevant to organic synthesis.

Solvent	Dielectric constant (ϵ_s) ^a	Loss tangent ($\tan \delta$) ^b
Hexane	1.9	
Benzene	2.3	
Carbon tetrachloride	2.2	
Chloroform	4.8	
Acetic acid	6.1	0.091
Ethyl acetate	6.2	0.174
THF	7.6	0.059
Methylene chloride	9.1	0.047
Acetone	20.6	0.042
Ethanol	24.6	0.054
Methanol	32.7	0.941
Acetonitrile	36	0.659
Dimethylformamide	36.7	0.062
DMSO	47	0.161
Formic acid	58	0.722
Water	80.4	0.123

^aThe dielectric constant ϵ_s , equals the relative permittivity, ϵ' , at room temperature and under the influence of a static electric field. ^b Values determined at 2.45 GHz and room temperature.

It is believed that, the more polar the solvent or in another word when the solvent possesses a higher dielectric constant, the more the microwave irradiation can be absorbed by the solvent and consequently the higher the temperature can be obtained. Upon this discussion, even two solvents with comparable dielectric constants, ϵ_s , like acetone and ethanol (**Table 18**) when they are heated at the same radiation power and for the same period of time, the final temperature obtained for ethanol is much higher than the obtained temperature for acetone (**Fig. 41**).

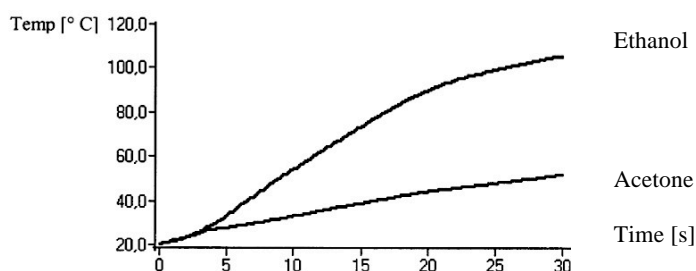


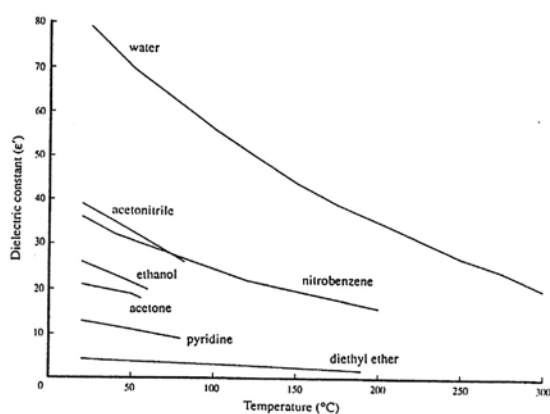
Fig. 41. The temperature increase of ethanol and acetone, respectively, at 150 W microwave irradiation. The upper curve corresponds to ethanol and the lower plot represents acetone.

III.2. Solvents in microwave assisted synthesis

As mentioned before, the frequency for most kinds of microwave apparatus is adjusted on 2.45 GHz,²⁴⁰ and the dielectric constant can only change with temperature. While a solvent is heated on microwave, the dielectric constant decreases as the temperature increases. As an example, water has

a dielectric constant that decreases from 78 at 25°C to 20 at 300°C (**Fig. 42**), the latter value is comparable to that of solvents like acetone at ambient temperature,²⁴⁷ therefore water can act as a pseudo-organic solvent at high temperatures, but this property is rational in pressurized systems. It was said in the above that non-polar solvents are not heated by microwave due to their so low dielectric constants, but addition of a small amount of polar solvent with an elevated loss tangent, usually cause higher heating rates for the whole mixture, and the energy transfer between the polar molecules that couple with the microwave radiation and the non-polar solvent bulk is fast. This method makes us capable to use non-polar solvents in microwave organic synthesis. Another

Fig. 42. Plots of dielectric constants against temperature for various solvents.²⁴⁸



method to increase heating rates is to add some salts to the solvent. But in this case, unfortunately, a solubility problem can be observed in heterogeneous mixture, because of that, in microwave synthesis, always a homogeneous mixture is privileged to obtain a uniform heating pattern. There are also ionic liquids that have recently been reported as a new class of environmentally friendly and recyclable alternatives to dipolar aprotic solvents for organic synthesis.^{247, 249} The use of this class of solvents is so advantageous in microwave assisted organic synthesis because of their excellent dielectric properties. Ionic liquids absorb not only microwave irradiation in a very efficient manner, but they show also a very low vapour pressure which results in their suitability even for microwave heating. However the ionic liquids are salts, but they can be dissolved in a wide range of organic solvents like water and alcohols.^{247, 249} In addition, some ionic solvents are even soluble in many non-polar organic solvents and so they can be used as microwave coupling agents when microwave transparent solvents are used (**Fig. 43**).

²⁴⁷C.R. Strauss, R.W. Trainor, *Aust. J. Chem.* **1995**, *48*, 1665-92. ²⁴⁸J.A. Dean Ed.; *Lange's Handbook of Chemistry*, 13th ed.; McGraw-Hill: New York, **1985**, p 99. ²⁴⁹K.R. Seddon, *Kinet. Katal.* **1996**, *37*, 743-48.

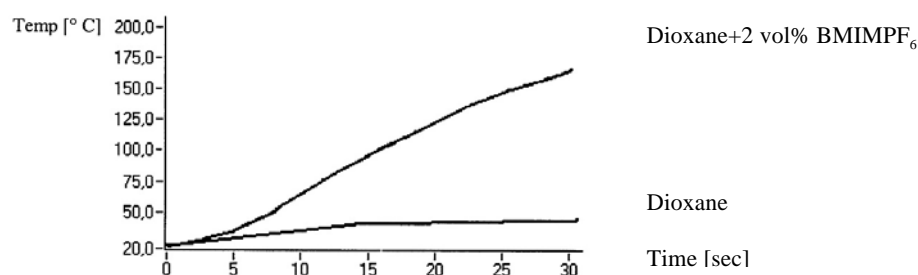


Fig. 43. The effect of the addition of ionic liquids on the temperature increase of dioxane at 300W microwave irradiation. The lower curve represents dioxane and the upper one shows dioxane with the addition of 2 vol% 1-butyl-3-methyl-imidazolium hexafluorophosphate.

III. 3. How does microwave irradiation increase the rate of the chemical reactions?

After the introduction of microwave assisted synthesis in 1986, the main discussion among the organic chemists society turns around this subject that what exactly effects the result of the synthesis on microwave mode. Is it only an effect of the thermal heat resulted by microwaves or is it a specific effect for microwave heating?

The main advantage of using microwave assisted synthesis is the shorter reaction times. As is shown in Part III in Eq. 1, the rate of a reaction is calculated by the Arrhenius equation. Upon this equation, there are two ways to increase the rate of a reaction. First, the pre-exponential factor A , that shows the molecular mobility depending on the frequency of vibrations of the molecules at the reaction interface. It has been described previously how microwaves generate an increase in molecular vibrations and is proposed that this factor A also plays a role on this vibration increase.²⁵⁰ However some other scientists suggested that microwave irradiation results a change in the exponential factor by affecting the free energy of activation ΔG .²⁵¹

In most other published examples, the specific microwave effects declared can be a result of thermal effects. Heating through microwave to obtain the desired temperature can be so rapid in a way that is not easy accessible by other heating techniques. Therefore, the experiments ran with microwave assisted organic synthesis may result in a different outcome in comparison with ordinary heated reactions, even in the case where the final temperature is the same. It has been reported, as an example, that the heating profile can change the regioselectivity in the sulfonation of

²⁵⁰a) F. Langa, P. de la Cruz, A. de la Hoz, A. Diaz-Ortiz, E. Diez-Barra, *Contemp. Org. Synth.* **1997**, *4*, 373-86; b) J.G. Binner, N.A. Hassine, T.E. Cross, *J. Mater. Sci.* **1995**, *30*, 5389-93. ²⁵¹J. Berlan, P. Giboreau, S. Lefevre, C. Marchand, *Tetrahedron Lett.* **1991**, *32*, 2363-66.

naphthalene.²⁵² Lidström *et al.* declare in a review²⁴⁰ that even if there is a ‘specific microwave effect’ other than heating effect, this effect would appear less important than stated in earlier publications.

III.4. Different techniques of microwave assisted organic synthesis

As used techniques in microwave synthesis one can mention ‘solvent-free’ open vessel reactions, reflux systems, pressurized systems and continuous flow systems.

A) Domestic household ovens—‘solvent-free’ open vessel reactions: Most of the reported organic synthesis done on microwave are performed on domestic microwave ovens just because of the availability and cheap price of this apparatus, however upon the CE code for electrothermal appliances (IEC 335-2-25, IEC 335-2-220) the domestic microwaves are not considered to be used to conduct the organic synthesis due to the increased risk for the user.²⁵³ So, the lack of control in domestic microwave ovens for organic synthesis led to a vast number of incidents including explosions. To avoid such problems, one method is to omit solvent from the reaction and to run the reaction on solid supports like clays, aluminium oxides and silica. Very interesting syntheses have been reported using this method.²⁵³ As this method (solvent-free technique) requires a simpler method of work-up and it prevents the use of solvents,²⁴⁰ it is considered as environmentally friendly, but undoubtedly, an easier work-up can be declared only when the support has been engaged in the reaction as a reagent and can be removed from the reaction mixture by a simple filtration like the solid-supported reagents. The difficulty of a good temperature control at the surface of the solids is accepted in the case of solvent-free technique but there are still advantages from using solvent-free approaches such as high safety by avoiding low-boiling solvents that can result unwanted pressure increases during heating.

B) Reflux systems: In order to use solvents in microwave assisted organic synthesis without having any serious problem like the risk of explosion, a number of reflux systems have been developed. Some of these systems are only modified domestic ovens but there are also some that designed with single mode cavities. On reflux systems small risk of explosions exists as the systems are at atmospheric pressure and flammable vapors cannot be liberated into the microwave cavity. Here, by use of this method, the temperature cannot be increased by more than 13-26°C above the normal boiling point of the solvent and only for a limited time. However this special superheating

²⁵²D. Stuerge, K. Gonon, M. Lallemand, *Tetrahedron* **1993**, 49, 6229-34. ²⁵³a) H.M. Kingston, P.J. Walter, W.G. Engelhart, P.J. Parsons, Laboratory microwave safety. In *Microwave-Enhanced Chemistry Fundamentals, Sample Preparation and Applications*; b) H.M. Kingston, S.J. Haswell; Eds.; Am. Chem. Soc.: Washington, DC, **1997**, pp. 697-745.

effect will, of course, increase the rate of the reactions to some extent, but it will not result in the same effects than can be achieved at much higher temperature.²⁵⁴

C) Pressurized systems: Pressure results from a rapid increase in temperature of volatiles and so reactions conducted under pressure in a microwave cavity benefit from the rapid heating rates and distant heating of microwave dielectric heating. This method led to the early developments using microwave assisted organic synthesis.²³⁹ As is discussed in above, the lack of control could make microwave assisted organic synthesis very unpredictable, that often results in explosions, but modern microwaves with the ability of controlling pressure defeated these possible problems. Today most of these instruments are equipped with good temperature control and pressure measurement that prevents a great concern of the failures which results from the thermal runaway reactions and poor heating (**Fig. 44**).

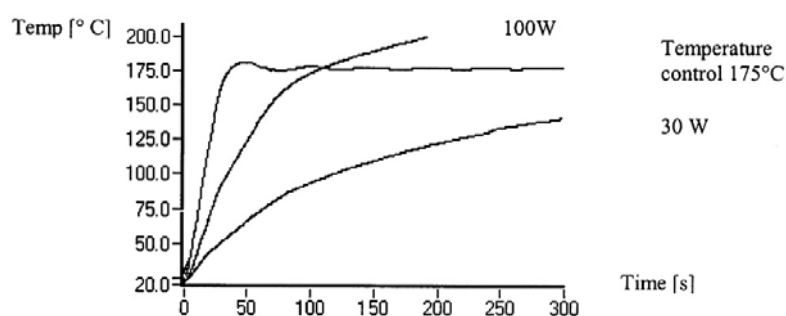


Fig. 44. The different temperature profiles obtained when a sample of DMF is heated with temperature control or effect control, respectively.²⁴⁰

D) Continuous flow systems: It is supposed that if the yield of the reaction is dependent on the heating profile of the reaction mixture, it is critical to keep the heating profile when scaling up the reaction. As an example, if 3 ml of a solvent is heated to 150°C during 20 s with a microwave irradiation at 300W, it will be necessary to use at least 15 kW power for heating 150ml of the same solvent, with the purpose to keep the same heating profile. For non-synthetic process purposes, high power microwave equipment is widely used, but the problem with such equipment is that they are large and is not easy to be adapted, and they usually requires water cooling when working with volumes >500 ml, so the single mode cavity microwaves are no longer the best choice and there is a necessary to use multi-mode cavity microwaves. Another method is that the use of continuous flow systems.²⁵⁵ By this method, the reagents are pumped through the microwave cavity, which allows

²⁵⁴a) C.R. Strauss, *Aust. J. Chem.* **1999**, *52*, 83-96; b) C.R. Strauss, R.W. Trainor, *Aust. J. Chem.* **1998**, *51*, 703-705. ²⁵⁵T. Cablewski, A.F. Faux, C.R. Strauss, *J. Org. Chem.* **1994**, *59*, 3408-12.

only a portion of the sample to be irradiated at a time, so it allows us to keep exactly the same heat profile, even for large-scale synthesis. Despite of this advantage of continuous systems there exist also disadvantages that the main one is that, for some reactions not all substances will be in solution before or after microwave irradiation and this can result the flow to stop, because the pipes becoming blocked.

By considering these mentioned characteristics of microwaves, in our laboratory, we decided to apply this method first in the synthesis of tri-substituted triazoles (**Fig. 45**) from their corresponding internal propargylic alcohols and without use of any catalyst, in order to study the possibility of doing this kind of synthesis under microwave condition. In the absence of catalyst, we expected to find mixture of isomers 1,4- and 1,5-trisubstituted triazoles (**Fig. 45**).

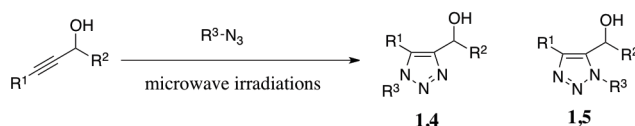
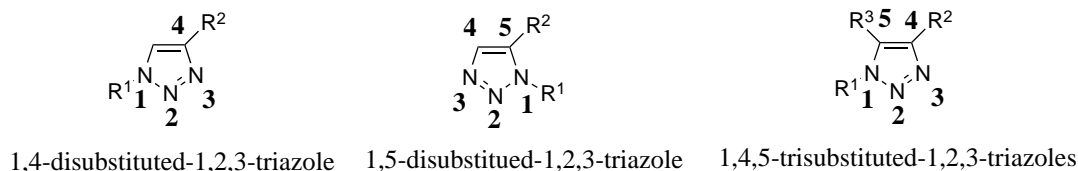


Fig. 45. Synthesis of trisubstituted triazoles from internal propargylic alcohols.

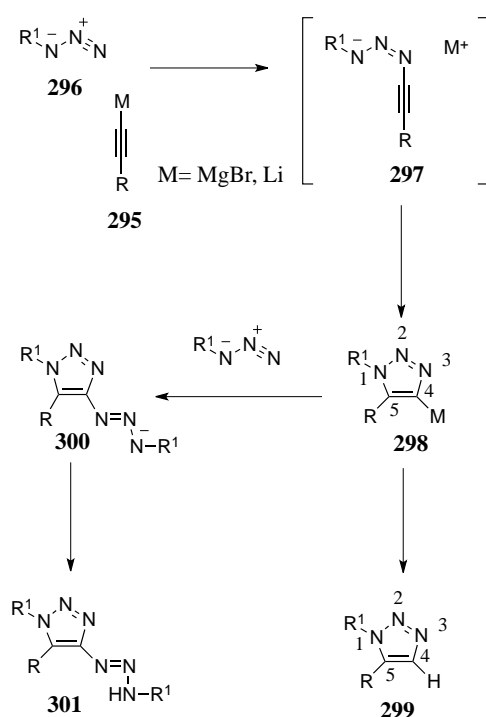
III.5. Preparation of tri-substituted triazoles

The cycloaddition of alkynes and azides is usually done by starting from terminal alkynes with/without catalyst [a source of Cu(I)] that result 1,4-disubstituted 1,2,3-triazoles in the case of CuAAC and a mixture of 1,4- and 1,5-disubstituted 1,2,3-triazoles (**Scheme 61**) where the reaction is done without Cu(I) as catalyst. There are not a lot of reports in the literature for the preparation of 1,4,5-trisubstituted 1,2,3-triazoles (**Scheme 61**).



Scheme 61. Structures of 1,4-, 1,5- and 1,4,5-triazoles.

One of the reported methods for the synthesis of 1,4,5-trisubstituted-1,2,3-triazoles was the reaction between a bromomagnesium acetylide and an azide.²⁵⁶ Reactions of sodium, lithium or magnesium acetylides with organic azides have been reported over 70 years ago.^{257, 258} 1,5-disubstituted-1,2,3-triazoles (**Scheme 61**) are the major products of these reactions. The scope of this transformation was investigated by Akimova *et al.* in the 1960s.²⁵⁸ The proposed mechanism of this reaction is shown in Scheme 62.²⁵⁸ Here, the mechanism begins with the nucleophilic attack of the acetylide **295** on the terminal nitrogen atom of the azide **296** followed by spontaneous closure of the linear intermediate **297** to the 4-metallotriazole species **298**.

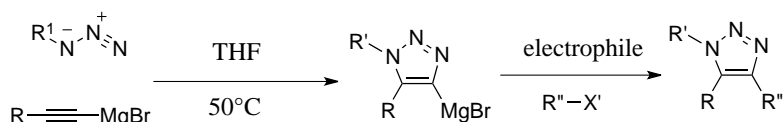


Scheme 62. Proposed mechanism for the synthesis of 1,5-disubstituted-1,2,3-triazoles by lithium or bromomagnesium acetylides.²⁵⁸

The reaction of the bromomagnesium acetylides with azides gave, after hydrolysis, 1,5-disubstituted triazoles **299** as the only product, however, the yields were low. In addition, formation of by-product **301** was reported in some cases that was a result from a reaction with unreacted starting materials. On the other hand, the use of lithium acetylides favoured further attack by intermediate **298** on a second molecule of azide, resulting from hydrolysis, in the 4-triazene-substituted triazoles **301**, often in high yields.²⁵⁸

²⁵⁶A. Krasinski, V. V. Fokin, K. B. Sharpless, *Org. Lett.* **2004**, *6*, 1237-40. ²⁵⁷a) S. G. Fridman, N. M. Lisovska, *Zap. Inst. Khim. Akad. Nauk. U.R.S.R., Inst. Khim.* **1940**, *6*, 353; b) N. M. Boyer, C. H. Mack, N. Goebel, L. R. Morgan, *J. Org. Chem.* **1958**, *23*, 1051; c) G. S. Akimova, V. N. Chistokletov, A. A. Petrov, *Zh. Org. Khim.* **1965**, *1*, 2077. ²⁵⁸a) G. S. Akimova, V. N. Chistokletov, A. A. Petrov, *Zh. Org. Khim.* **1967**, *3*, 968; b) G. S. Akimova, V. N. Chistokletov, A. A. Petrov, *Zh. Org. Khim.* **1967**, *3*, 2241; c) G. S. Akimova, V. N. Chistokletov, A. A. Petrov, *Zh. Org. Khim.* **1968**, *4*, 389.

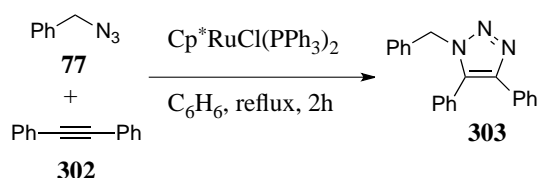
About 30 years after this first application of bromomagnesium acetylides, Sharpless *et al.*²⁵⁶ took advantage of this synthetic method to synthesize 1,4,5-trisubstituted-1,2,3-triazoles. For this reaction, they used different electrophiles to capture 4-halomagnesiatriazole intermediate in order to regioselectively form 1,4,5-trisubstituted-1,2,3-triazoles (**Scheme 63**) and they performed the reaction in THF at 50°C.



Scheme 63. Synthesis of 1,4,5-trisubstituted-1,2,3-triazoles from bromomagnesium acetylides.²⁵⁶

As the used electrophiles for this reaction we can mention DCI/D₂O, PhCHO, I₂, CO₂, etc. by which the final trisubstituted triazoles were found with yields between 76 and 95%. Despite, they²⁵⁶ observed that all electrophile compounds are not suitable to trap 4-halomagnesiatriazole intermediate, for example the use of sulfamoyl and sulfonyl chlorides results in partial chlorination of the triazole ring at C-4. Sharpless²⁵⁶ also reported that, due to the very strong basicity of 4-magnesiatriazoles, reactions with electrophiles, which also possess acidic C-H bonds usually fail as a result of competing protonation at C-4, but these drawbacks can be overcome by transmetalation prior to the coupling.²⁵⁹

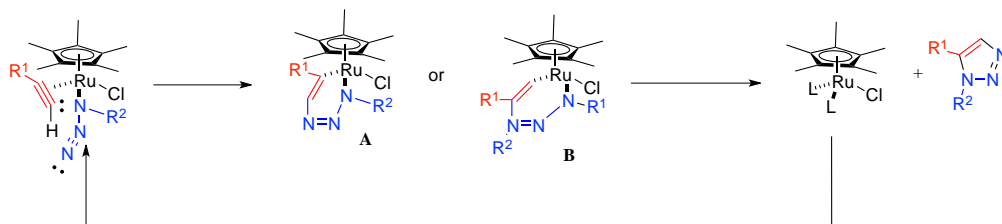
Another proposed synthetic method again by Sharpless²⁶⁰ group, was the reaction between internal alkynes and organic azides in the presence of Ru(II) catalyst (**Scheme 64**).



Scheme 64. Proposed reaction condition by Sharpless for the preparation of 1,4,5-trisubstituted-1,2,3-triazoles.²⁶⁰

As presented in Scheme 64, when a mixture of diphenylacetylene and benzyl azide (1.1:1 equiv., 0.15M) was refluxed in benzene in the presence of *ca.* 1% mol of Cp^{*}RuCl(PPh₃)₂ for 2h, the azide was completely converted to the triazole. In the term of the mechanism of the reactions, Sharpless²⁶⁰ proposed a tentative hypothesis (**Scheme 65**) however, it needs more study.

²⁵⁹J. Felding, P. Uhlmann, J. Kristensen, P. Vedø, M. Begtrup, *Synthesis* **1998**, 1181. ²⁶⁰L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998-9.

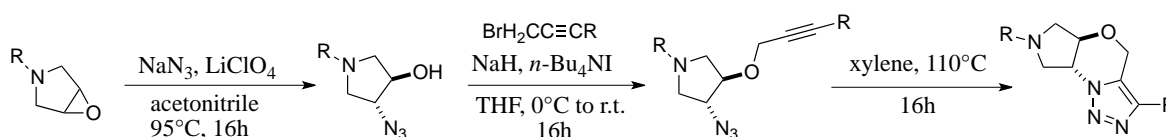


Scheme 65. Proposed intermediates by Sharpless²⁶⁰ in the catalytic cycle.

In this proposed mechanism, oxidative coupling of an alkyne and an azide on ruthenium can initially give a six-membered ruthenacycle (**Scheme 65**; **A** is more possible than **B**) that conducts further a reductive elimination by liberating triazole product.²⁶⁰ This reaction is also regio-selective like the case of terminal alkynes when a catalyst (Cu(I) or Ru(II)) is used.

III.6. Microwave-assisted intra/intramolecular Huisgen Cycloaddition of azides and alkynes

The intramolecular version of the Huisgen cycloaddition is a potentially useful reaction for the stereocontrolled preparation of 1,5-disubstituted and 1,4,5-trisubstituted triazoles. Several intramolecular Huisgen cycloadditions, which lead to polycyclic triazoles, have been reported in literature. These strategies are all based on multi-sequence syntheses. For example, in a paper published by Pericàs *et al.*,²⁶¹ they presented a synthetic strategy in order to find tricyclic 1,2,3-triazoles via an intramolecular cycloaddition reaction of alkyne and azide. This synthetic method starts from cyclic epoxides via the sequential azidolysis, propargylation and at the end 1,3-cycloaddition (**Scheme 66**).²⁶¹



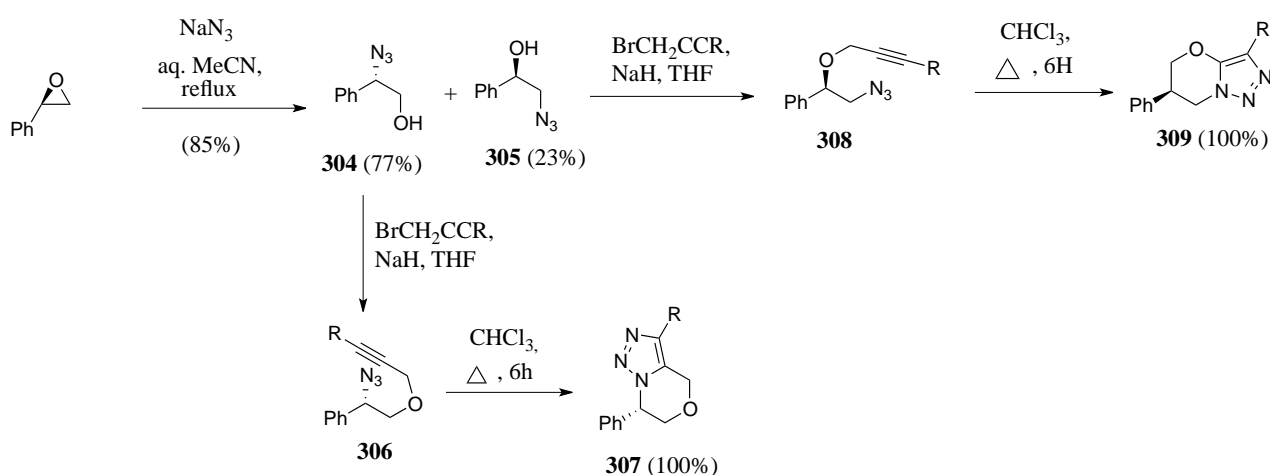
Scheme 66. Sequential synthesis of tricyclic 1,2,3-triazoles via an internal cycloaddition reaction.²⁶¹

As is presented in **Scheme 66**, this proposed synthesis is based on a sequential epoxide ring-opening with azide, *O*-propargylation and intermolecular azide-alkyne cycloaddition. In the last step, the intramolecular azide-alkyne cycloaddition was performed in good yields after heating in toluene or xylene to afford tricyclic triazole derivatives.²⁶¹ It must be mentioned that the cycloaddition was

²⁶¹ A. I. Oliva, U. Christmann, D. Font, F. Cuevas, P. Ballester, H. Buschmann, A. Torrens, S. Yenes, M. A. Pericàs, *Org. Lett.* **2008**, *10*, 1617.

performed without use of any metal catalyst when compared to the intermolecular cycloaddition reaction between azide and alkyne, and as it was expected, only 1,5-regioisomers were obtained. They ran also the intramolecular cycloaddition step in the presence of a copper catalyst and taking a *O*-propargyl where R is a hydrogen, but in this condition the reaction was not done that can be due to geometry restrictions in the formation of the 1,4-regioisomer.²⁶¹

In another attempt by Datta *et al.*,²⁶² another synthetic method for the preparation of polycyclic triazoles has been proposed. This approach involved initial installation of azide and alkyne moieties on a common structural framework, followed by their intramolecular cycloaddition studies. In this sequential synthesis, the intermediate, which conducts the internal azide-alkyne cycloaddition is a pivotal azidoalkyne (**306** and **308**).



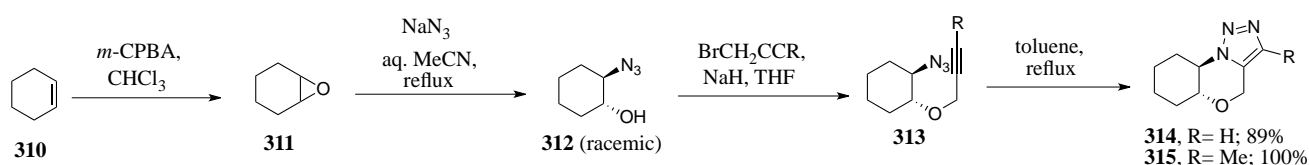
Scheme 67. Sequential synthesis of polycyclic triazoles via an internal alkyne-azide cycloaddition.²⁶²

Like the proposed synthesis by Pericàs,²⁶¹ this synthetic procedure begins with a ring opening of epoxide with azide nucleophiles, which is among the most frequent reaction for the formation of vicinal azido alcohols (azidoalcohols). For this ring-opening epoxide step, Datta²⁶² subjected (*R*)-styrene oxide compound in the synthesis sequence and in the presence of sodium azide in acetonitrile, which led to a mixture regioisomers of **304** and **305** (**Scheme 67**) with as the major and minor products respectively **304** and **305**, and then they used both of regioisomers for the synthesis of polycyclic triazoles. In the next step, an *O*-alkylation reaction was performed on azidoalcohol in the presence of an appropriate propargylic bromide in order to install the alkyne functionality, which then led to the formation of the pivotal azido-alkynes **306** and **308** (**Scheme 67**). Having obtained the suitable substrates for intramolecular cycloaddition studies, in the next step thermally

²⁶²R. Li, D. J. Jansen, A. Datta, *Org. Biomol. Chem.* **2009**, *7*, 1921.

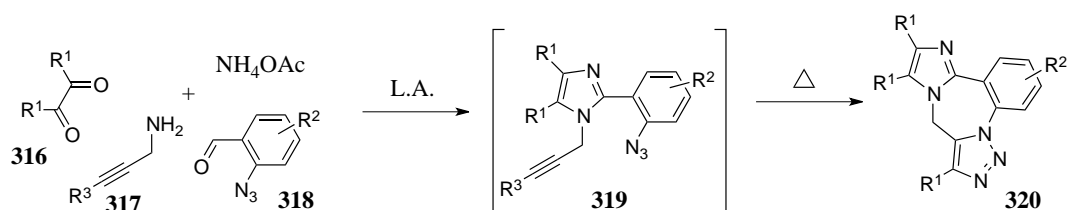
induced cyclization of these azido-alkynes was investigated. The cycloaddition reaction was performed efficiently and at a moderate temperature without any catalyst.

Datta *et al.*²⁶² also tried cyclic azido alcohols in this synthetic strategy by departing from cyclohexene-derived epoxide (**Scheme 68**, compound **311**). This approach was also conducted by a sequence including *O*-alkylative installation of the propargylic functionalities and cycloaddition in refluxing toluene that provided the corresponding tricyclic triazolooxazine derivatives in high yields.



Scheme 68. Preparation of tricyclic triazoles from cyclic azido alcohols.²⁶²

Not only these sequential procedures have been reported in order to prepare polycyclic triazole derivatives via an intramolecular azido-alkyne cycloaddition reaction, but also one-pot multicomponent reactions have been reported in the literature. As an example, Kurth and co-workers²⁶³ proposed a multicomponent reaction for the preparation of imidazotriazolobenzodiazepine that proceeded by tandem InCl_3 -catalyzed cyclocondensation followed by intramolecular Huisgen 1,3-dipolar cycloaddition reactions (**Scheme 69**).

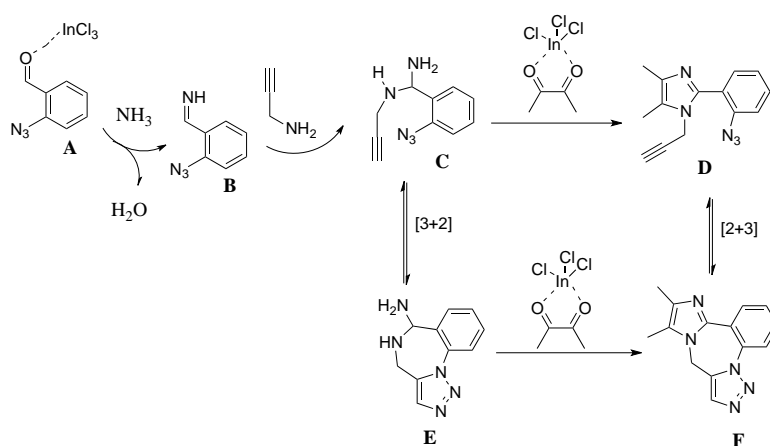


Scheme 69. Synthetic strategy toward Imidazo-[1,2,3]triazolo[1,4]benzodiazepines, proposed by Kurth.²⁶³

Kurth proposed a synthetic pathway via the Lewis acid-catalyzed multicomponent reaction of symmetrical α -diketones, *o*-azidobenzaldehydes, propargylic amines, and ammonium acetate (**Scheme 69**). However, there are different procedures for the synthesis of imidazoles,²⁶⁴ but Kurth's group²⁶³ was especially interested in cyclocondensations of α -diketones, aldehyde, primary

²⁶³H. H. Nguyen, T. A. Palazzo, M. J. Kurth, *Org. Lett.* **2013**, *15*, 4492-95. ²⁶⁴a) H. Bredereck, G. Theilig, *Chem. Ber.* **1953**, *86*, 88-96; b) F. R. Japp, H. H. Robinson, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 1268-70; c) B. Radziszewsky, *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 1493; d) H. Debus, *Justus Liebigs Ann. Chem.* **1858**, *107*, 199-208; e) F. Kunckell, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 637; f) A. M. Van Leusen, J. Wildeman, O. H. Oldenzien, *J. Org. Chem.* **1977**, *42*, 1153-9.

amine, and ammonia reactions, which was conventionally catalyzed by different Brønsted/ Lewis acids to promote imine formation and subsequent heterocyclization.²⁶⁵ As the applied acid Lewis in this reaction we can mention, I₂, Cu(OAc)₂, FeCl₃, Zn(ClO₄)₂, Sc(OTf)₃, CeCl₃, InBr₃, InCl₃, but higher yields were obtained when InCl₃ (10 equiv.) was subjected to the reaction. The proposed mechanism of the reaction by Kurth²⁶³ is illustrated in Scheme 70.

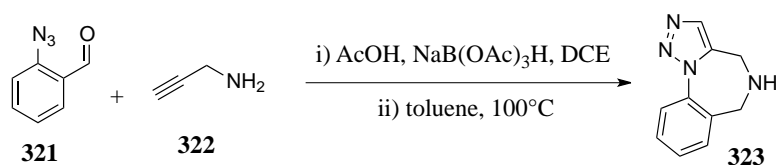


Scheme 70. Proposed mechanism by Kurth.²⁶³

The tandem process takes place by initial InCl₃-catalyzed imine formation (**A** → **B**) followed by nucleophilic addition of propargylamine to the resulting imine (**B** → **C**). There are then two possible pathways from intermediate **C** to result **F**: **C** → **D** → **F** that proceeds with imidazole formation first, while **C** → **E** → **F**, which proceeds with triazole formation first.

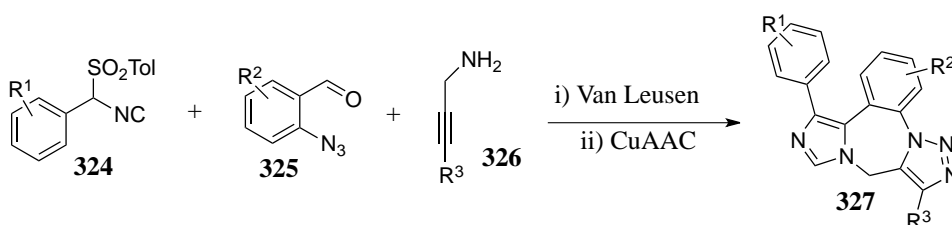
Before this proposed pathway by Kurth, there were also some other reports for the construction of imidazole /triazole/ diazepine-fused skeletons. Martin^{266a,b} and co-workers reported an effective route to 1,2,3-triazole-fused 1,4-benzodiazepines **323** from a cascade reductive amination and intramolecular Huisgen cycloaddition^{266c} (Scheme 71).

²⁶⁵ a) S. D. Sharma, P. Hazarika, D. Konwar, *Tetrahedron Lett.* **2008**, *49*, 2216-20; b) J. N. Sangshetti, N. D. Kokare, S. A. Kothrkara, D. B. Shinde, *J. Chem. Sci.* **2008**, *120*, 463-7; c) S. Samai, G. C. Nandi, P. Singh, M. S. Singh, *Tetrahedron* **2009**, *65*, 1015-61; d) B. Sadeghi, B. B. F. Mirjalili, M. M. Hashemi, *Tetrahedron Lett.* **2008**, *49*, 2575-7; e) M. Kidwai, P. Mothra, V. Bansal, R. K. Somvanshi, A. S. Ethayathulla, S. Dey, T. P. Singh, *Mol. Catal. A: Chem.* **2007**, *265*, 177-182; f) M. M. Heravi, F. Derikvand, M. Haghghi, *Monatsh. Chem.* **2008**, *139*, 31-33. ²⁶⁶ a) J. R. Donald, S. F. Martin, *Org. Lett.* **2011**, *13*, 852-5; b) J. R. Donald, R. R. Wood, S. F. Martin, *ACS Comb. Sci.* **2012**, *14*, 135-43; c) G. Hooyberghs, H. De Coster, D. D. Vachhani, D. S. Ermolat'ev, E. V. Van der Eycken, *Tetrahedron* **2013**, *69*, 4331-7; d) A. Kumar, Z. Li, S. K. Sharma, V. S. Parmar, E. V. Van der Eycken, *Org. Lett.* **2013**, *15*, 1874-7; e) V. Gracias, D. Darczak, A. F. Gasielki, S. W. Djuric, *Tetrahedron Lett.* **2005**, *46*, 9053-6.



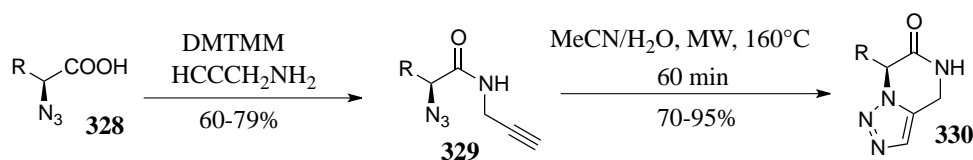
Scheme 71. Proposed internal cycloaddition by Martin *et al.*^{266a,b}

Djuric^{266e} has also demonstrated an interesting postmodification of the van Leusen imidazole synthesis using an intramolecular azide-alkyne cycloaddition to construct **327**, which incorporates imidazole, triazole, and diazepine rings in one scaffold (**Scheme 72**).



Scheme 72. Proposed intramolecular azide-alkyne cycloaddition by Djuric.^{266e}

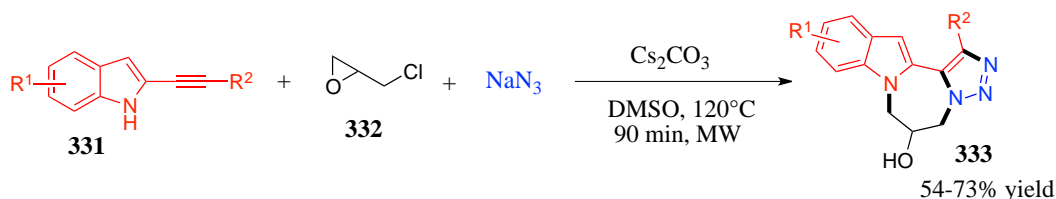
In addition of these thermic intramolecular azide-alkyne cycloadditions, there are also some examples of intramolecular formation of triazolic derivatives under microwave irradiation conditions. In a paper published by Taddei and co-workers,²⁶⁷ they reported an internal Huisgen cycloaddition under microwave condition by introducing a labile template (ester or amide) between the azide and the alkyl moieties in order to force the regiochemistry (**Scheme 73**).



Scheme 73. The intramolecular cycloaddition of azido alkynes by introducing an amide template linkage and under microwave condition.²⁶⁷

It must be mentioned too, here, the formed alkyne was a terminal one, but in another attempt by Kundu group,²⁶⁸ this intramolecular cycloaddition was performed with an internal alkyne. In that order, they proposed a strategy based on a three component domino reaction (**Scheme 74**).

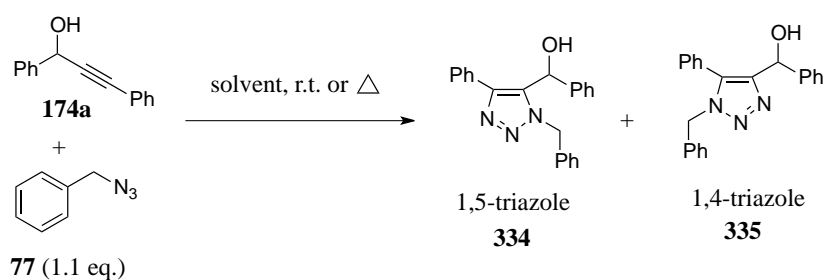
²⁶⁷E. Balducci, L. Bellucci, E. Petricci, M. Taddei, A. Tafi, *J. Org. Chem.* **2009**, *74*, 1314-21. ²⁶⁸R. K. Arigela, S. K. Sharma, B. Kumar, B. Kundu, *Beilstein J. Org. Chem.* **2013**, *9*, 401-5.



Scheme 74. Internal cycloaddition of azido alkynes departing from an internal alkyne.²⁶⁸

This strategy starts with a N-1 of 2-alkynylindole, which was first functionalized with epoxide by reacting 2-alkynylindole with epichlorohydrin, which was then followed by a ring opening of the oxirane by azide to result a bis-functionalized indole intermediate having azides and alkyne groups in close proximity. This intermediate may then undergo annulation following an intramolecular 1,3-dipolar cycloaddition pathway that in turn lead to the sequential formation of 7- or 5-membered diazepine and triazole rings in a single step.

Upon these proposed strategies, and because of the potential biological activity of polycyclic triazoles, for our research project, we decided to conduct intermolecular cycloaddition of alkynes and azides by departing from internal propargylic alcohol (**202**) described in chapter 2 and benzylazide (**77**). For this aim, we first decided to perform the reaction at room temperature and without use of any catalyst. As it was mentioned before, in the absence of catalyst a mixture of isomers 1,4 and 1,5-triazoles would be expected to be generated from 1,3-dipolar cycloaddition reactions. The reaction was carried out between benzylazide and propargylic alcohol (**Scheme 75**).



Scheme 75. 1,3-dipolar cycloaddition reaction between benzylazide and propargylic alcohol.

The reaction was performed in different solvents such as DCM, methanol, acetonitrile and toluene, but at room temperature, generation of the expected triazoles weren't detected, so the reaction was repeated under reflux and here, toluene was chosen as solvent in order to conventionally heat the reaction at higher temperature (110°C), by supposing that at higher temperature the 1,3-dipolar cycloaddition can be conducted easily due to the high needed energy for formation of triazole

cycles. Even under these reaction conditions, the expected triazoles were not formed and only a trace of triazoles could be observed.

In another experiment, and in order to study the feasibility of the 1,3-cycloaddition reaction between azides and internal alkynes, this reaction was run under microwave condition. To this aim, different parameters have been tested, like different microwave methods, different temperatures, and different solvents. The results are summarized through Table 19.

Table 19. The obtained results for 1,3-dipolar cycloaddition between 1,3-diphenylprop-2-yn-1-ol (**174a**) and benzyl azide

Entry	Solvent	Method	Temperature (°C)	Time (min)	Power (W)	Product(%) ^a		Conversion(%) ^a	
						1,4	1,5	1,4	1,5
1	DCM	Standard	110	25	260	-	-	0	-
2	DCM	Standard	120	15	260	-	-	0	-
3	Toluene	Standard	200	100	260	11	5	18	7
4	DCM	Dynamic	80	180	300	-	-	0	-
5	THF	Dynamic	100	180	300	-	-	-	-
6	Acetonitrile	Dynamic	120	180	300	trace	-	n.d.	-
7	Toluene	Dynamic	170	90	300	9	4	17	7
8	Toluene	Dynamic	170	190	300	28	12	50	23
9	Toluene	Fixed Power	170	190	300	Decomp.	-	-	-

^aThe yields and the conversion were determined by ¹H-NMR.

The applied microwave methods depend on the type of the apparatus. In our case, the existed methods for our microwave were, *Standard*, *Dynamic* and *Fixed Power (FP)* method. In each method there are some parameters than can be or cannot be modified. For example, in *Standard* mode there are only temperature and hold time that can be modified and the irradiation power is always adjusted on 260W by default. However in *Dynamic* and *Fixed Power* method, the power of irradiation can also be modified in addition of the temperature and hold time. The only difference between *Dynamic* and *Fixed Power* method is that, when the reaction is run on *FP* and on a precised power, the irradiation begins on the adjusted power for example 260W at time 0 (**Fig. 46, b**), but in the case of *Dynamic* method, the irradiation begins from power 0W and increases progressively during the reaction to reach to the max adjusted power (**Fig. 46, a**).

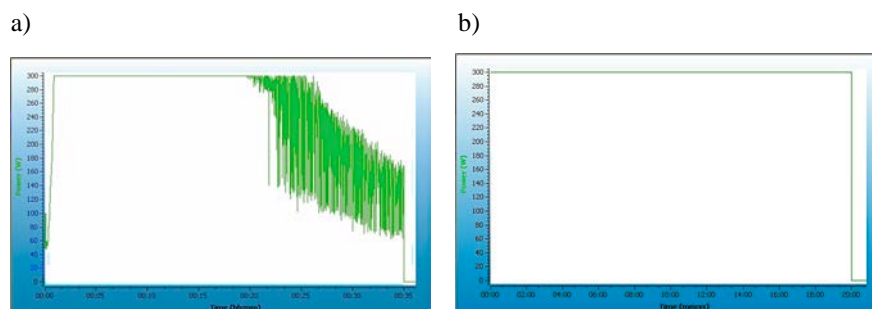
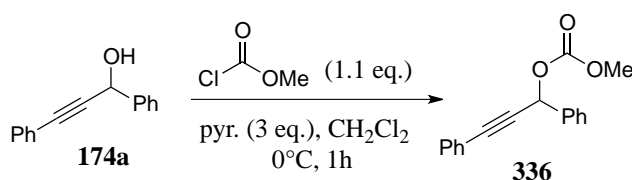


Fig. 46. a) The observed power graph in Dynamic mode, which increases progressively during the reaction; b) The observed power graph for Fixed Power mode, which begins on the adjusted watt from the very beginning of the reaction.

As is presented in Table 19, even under microwave irradiations, the cycloaddition reaction cannot be performed as expected. In the presence of solvents like DCM, methanol and acetonitrile, the starting products were only recovered at the end of the reaction without formation of any triazolic derivatives, but when the toluene was used as solvent, formation of triazoles could be observed, however the yield remains low. In the best case where the reaction was conducted at 170°C for 1h30 and under Dynamic method condition (Table 19, entry 8), isomers of 1,4- and 1,5-trisubstituted triazoles were obtained in 28% and 12% yields respectively. It is worth to note that, at higher temperatures (*e.g.* 170°C), decomposition of the product could also be observed (Table 19, entry 9).

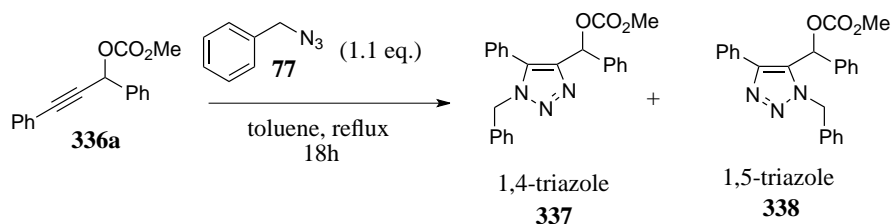
Since the reaction with propargylic alcohol did not give good results even under microwave condition, we decided to insert a carbonate group on hydroxyl in order to activate the alkyne and by supposing that triazoles could be constructed with a better yield. For this reason, first the internal propargylic carbonate (Scheme 76, 336)²⁶⁹ was prepared from the reaction between 1,3-diphenylprop-2-yn-1-ol (174a) and methyl chloroformate in the presence of pyridine.



Scheme 76. Preparation of propargylic carbonate from propargylic alcohol.²⁶⁹

This prepared propargyl carbonate was then subjected to the 1,3-dipolar cycloaddition reaction with benzyl azide (Scheme 77).

²⁶⁹M. Yoshida, M. Higuchi, K. Shishido, *Org. Lett.* **2009**, *11*, 4752-55



Scheme 77. 1,3-dipolar cycloaddition between propargyl bicarbonate and benzyl azide.

First, the reaction was run at room temperature and with solvents like MeOH and toluene, dichloromethane, and acetonitrile but the expected triazoles could not be formed under these conditions. The reaction was then repeated at room temperature but without any solvent to see if azide and internal alkyne can react with each other in a concentrated medium, but after 18h the starting materials were only recovered.

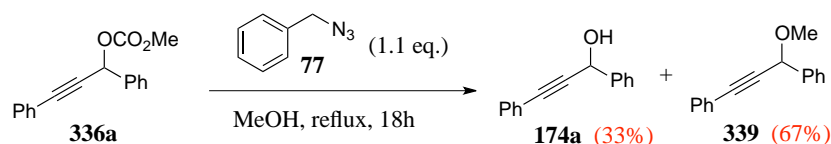
We decided then to perform the reaction under conventional reflux for 18h. The results are shown in Table 20.

Table 20. 1,3-dipolar Huisgen cycloaddition between propargylic carbonate (319a) and benzylazide under reflux for 18h.

Entry	Solvent	T (°C)	Product (%) ^a		By-product (OMe) (%)
			1,4	1,5	
1	Acetone	56	-	-	-
2	MeOH	64	-	-	67
3	Toluene	110	31	21	-
4	-	95	41	31	-

^aThe conversion was determined on ¹H-NMR.

Under reflux condition, the expected triazolic derivatives could be obtained only by using toluene as solvent (Table 20, entry 3), however the conversions were still low, 31% and 21% respectively for 1,4- and 1,5-trisubstituted triazoles, and the starting propargylic carbonate was recovered with 48% conversion. The reaction was then repeated neat at 95°C, but similar results were found, 41% for 1,4-triazole and 31% yield for 1,5-trisubstituted triazole (Table 20, entry 4). An interesting result was observed in the case of the reaction with MeOH as solvent. Here the reaction didn't perform as we expected. Instead of finding triazolic derivatives at the end of the reaction, we observed formation of methyl ether (67% conversion) and the starting propargylic alcohol (33% conversion) (Scheme 78).



Scheme 78. The reaction between propargyl carbonate and benzylazide in MeOH gave internal propargylic alcohol and methyl ether.

After a classic heating of the reaction, we subjected the medium reaction under microwave irradiation, in order to study the effects of microwave on formation of the triazoles. As the best results were obtained in toluene as solvent, we decided to conduct the reaction in the same solvent. The results are summarized in Table 21.

Table 21. Reaction between propargylic carbonate (**336a**) and benzylazide (**77**) (1.1 equiv.) under microwave condition.

Entry	Solvent	Method	Power (W)	Temperature (°C)	Time	Propargyl carbonate	Benzylazide	Pdct (%) ^a		Conversion (%) ^a	
								1,4	1,5	1,4	1,5
1	MeOH	Standard	260	120	42min	-	100	-	-	-	-
2	Toluene	Standard	260	150	1h30	100	100	-	-	-	0
3	Toluene	Dynamic	120	150	1h30	44	42	9	7	57	43
4	Toluene	Dynamic	260	200	4h10	28	20	30	22	57	43
5	Toluene	Fixed power	300	138 ^b	1h10	77	28	8	8	50	50

^aThe conversions were determined by ¹H-NMR. ^bThe temperature was fixed on 200°C, but the obtained temperature was 138°C.

The reaction was carried out changing different parameters, like microwave methods, temperatures and time of the reaction. In the best case, when the reaction was performed on a dynamic method at 200°C and with an irradiation power of 260 W (Table 21, entry 3), the expected triazoles were obtained in 30% and 22% respectively for 1,4- and 1,5-trisubstituted triazoles. So the reaction wasn't done better even under microwave conditions.

Since using MeOH as solvent under reflux, we could obtain the methoxy ether as the major product, we decided to repeat the reaction in MeOH and under microwave condition. Like the previous experiment, methoxy ether was obtained as the final product only after 52 min instead of 18 h, and with 100% yield, without formation of any propargylic alcohol like it was observed using standard reflux.

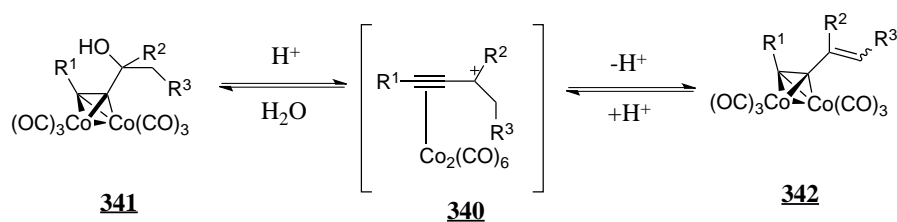
From these obtained results, we became interested to perform more studies on this nucleophilic substitution under microwave conditions, because to the best of our knowledge this kind of reaction has not been reported in the literature. All existing reported reactions are based on metal-catalyzed reactions and will be presented in the following part of this manuscript.

III.7. Catalyst- and solvent-free straightforward synthesis of propargylic ethers from carbonates and alcohols under microwave irradiation

III.7.1. Introduction

For more than a decade, studies about nucleophilic substitution of propargylic carbonates or alcohols started, because these compounds are important building blocks in organic synthesis and used widely to obtain a variety of structures. To this end, different studies were performed with different catalysts, like cobalt catalyst,²⁷⁰ Lewis acids,²⁷¹ Brønsted acids,²⁷² and other metal complexes like ruthenium,^{273,274} rhenium,²⁷⁵ copper,²⁷⁶ palladium²⁷⁷ and recently gold catalyst;²⁷⁸ which have been used from stoichiometric to catalytic amount to lead to the desired product.

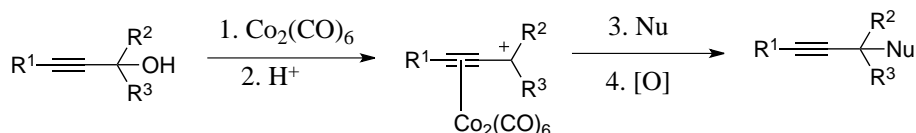
III.7.2. Direct propargylic substitution by Nicholas reaction:²⁷⁰ the direct propargylic substitutions have traditionally and efficiently been carried out under Nicholas conditions in the presence of stoichiometric amounts of a cobalt complex.²⁷⁰ During the studies on the dicobalthexacarbonyl ($-\text{Co}_2(\text{CO})_6$) unit as a protecting group for the C-C triple bond, Nicholas *et al.*²⁷⁰ discovered the ready acid-promoted hydration/dehydration equilibrium connecting the complexes of propargylic alcohols and 1,3-enynes (**Scheme 79**) which suggested that the intermediates (propargyl) $\text{Co}_2(\text{CO})_6^+$ cations (**340**), possessed an important stability.



Scheme 79. Formation of the stabilized intermediate **340** through acid-promoted hydration/dehydration, suggested by Nicholas group.²⁷⁰

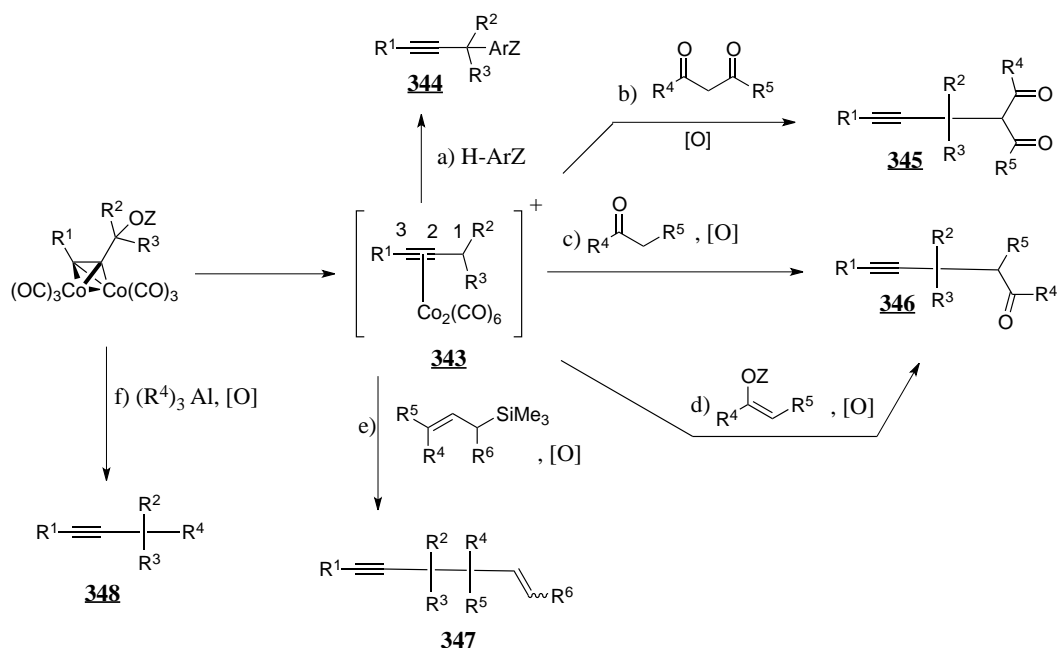
²⁷⁰K. M. Nicholas, *Acc. Chem. Res.* **1987**, *20*, 207–14. ²⁷¹a) E. Emer, R. Sinisi, M. G. Capdevila, D. Petruzzello, F. De Vincentiis, P. G. Cozzi, *Eur. J. Org. Chem.* **2011**, 647–66; b) P. G. Cozzi, F. Benfatti, *Angew. Chem., Int. Ed.* **2010**, *49*, 256–9; c) F. Bisaro, G. Prestat, M. Vitale, G. Poli, *Synlett* **2002**, 1823–6. ²⁷²R. Sanz, D. Miguel, A. Martínez, J. M. Álvarez-Gutiérrez, F. Rodríguez, *Org. Lett.* **2007**, *9*, 727–30. ²⁷³a) Y. Nishibayashi, S. Uemura, *Curr. Org. Chem.* **2006**, *10*, 135–150; b) Y. Nishibayashi, M. D. Milton, Y. Inada, M. Yoshikawa, I. Wakiji, M. Hidai, S. Uemura, *Chem. Eur. J.* **2005**, *11*, 1433–51; c) Y. Yamauchi, G. Onodera, K. Sakata, M. Yuki, Y. Miyake, S. Uemura, Y. Nishibayashi, *J. Am. Chem. Soc.* **2007**, *129*, 5175–9; d) H. Matsuzawa, K. Kanao, Y. Miyake, Y. Nishibayashi, *Org. Lett.* **2007**, *9*, 5561–4; e) S. C. Ammal, N. Yoshikai, Y. Inada, Y. Nishibayashi, E. Nakamura, *J. Am. Chem. Soc.* **2005**, *127*, 9428–38. ²⁷⁴a) H. Matsuzawa, Y. Miyake, Y. Nishibayashi, *Angew. Chem., Int. Ed.* **2007**, *46*, 6488–91. b) Y. Nishibayashi, A. Shinoda, Y. Miyake, H. Matsuzawa, M. Sato, *Angew. Chem., Int. Ed.* **2006**, *45*, 4835–9; c) Y. Inada, Y. Nishibayashi, S. Uemura, *Angew. Chem., Int. Ed.* **2005**, *44*, 7715–17. ²⁷⁵a) R. V. Ohri, A. T. Radosevich, K. J. Hrovat, C. Musich, D. Huang, T. R.H. olman, F. D. Toste, *Org. Lett.* **2005**, *7*, 2501–4; b) B. D. Sherry, A. T. Radosevich, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 6076–7; c) J. J. Kennedy-Smith, L. A. Young, F. D. Toste, *Org. Lett.* **2004**, *6*, 1325–7. ²⁷⁶ Y. Imada, M. Yuasa, I. Nakamura, S.-I. Murahashi, *J. Org. Chem.* **1994**, *59*, 2282–4. ²⁷⁷E. Keinan, E. Bosch, *J. Org. Chem.* **1986**, *51* (21), 4006–16. ²⁷⁸a) M. Georgy, V. Boucard, J.-M. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180–1; b) M. Georgy, V. Boucard, O. Debleds, C. Dal Zotto, J.-M. Campagne, *Tetrahedron* **2009**, *65*, 1758–66.

From this finding, they became interested in synthetic prospects for these compounds, especially the possibility that they could be used as electrophilic propargyl synthons as is presented in Scheme 80.



Scheme 80. Use of cobalt complex as electrophilic propargyl synthons.²⁷⁰

The reactions of the parent (propargyl) $\text{Co}_2(\text{CO})_6^+$ complexes (isolated or generated *in situ*) have been explored by Nicholas²⁷⁰ with a wide variety of carbon-centered nucleophiles (**Scheme 81**). They observed that, in all cases, attack by the nucleophile occurs exclusively at the propargylic carbon (C-1), providing a versatile propargylation method when followed by mild oxidative demetalation.



Scheme 81. Carbon-carbon bond formation with (propargyl) $\text{Co}_2(\text{CO})_6^+$ complexes.²⁷⁰

III.7.3. Palladium(0)-catalyzed substitution of propargylic acetates by different nucleophiles: Kenian and Bosch²⁷⁷ reported a propargylic substitution in the presence of Pd(0)-catalyst. Through their studies on this reaction, three modes of reactivity have been observed dependent on the utilized nucleophiles (**Table 22**): 1) sodium dimethyl malonate, which is a

stabilized carbanion does not react with propargylic acetates, however it reacts easily with allylic acetates (**Table 22**, entry 1) ; 2) Phenyl zinc chloride used as non-stabilized organometallic, reacts with propargylic and allylic acetates at comparable rates, here the reaction results exclusively in the allenic product (**Table 22**, entry 2); 3) Allyl- and allenyl-stannanes that are known to react only with allylic acetates, did not show a reaction with propargylic acetates except in a few cases where the propargylic system was conjugated to an adjacent olefin (**Table 22**, entry 3).

Table 22. Palladium(0)-catalyzed substitution of conjugated bifunctional substrates.

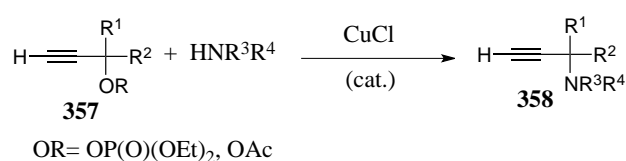
$\text{Ph}-\text{CH}=\text{CH}-\text{C}(\text{OAc})-\text{C}\equiv\text{C}-\text{R} \xrightarrow[\text{THF}]{\text{nucleophile, Pd(PPh}_3)_4 (5-7 \text{ mol}\%)} \text{Substituted products}$

349a, R= Me
349b, R= Ph

Entry	Substrate	Nucleophile	Time (h)	Products	Yield (%) ^a	
1	349b	NaCH(CO ₂ CH ₃) ₂	10	<p>350</p>	<p>351 (E:Z= 1:3)</p>	90
2	349a	PhZnCl	2		<p>352</p>	94
3	349a	Bu ₃ Sn-CH=CH ₂	2	<p>353 (E:Z= 3:1)</p>	<p>354</p>	73
4	349a	(CH ₂ =CH) ₄ Sn	3	<p>355 (E:Z= 1:3)</p>	<p>356</p>	75

III.7.4. Copper(I)-catalyzed amination of propargyl esters: Murahashi and co-workers²⁷⁶

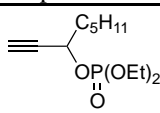
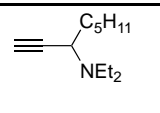
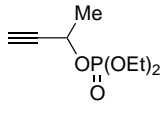
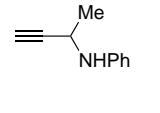
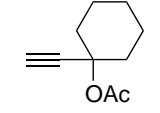
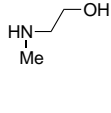
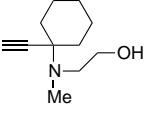
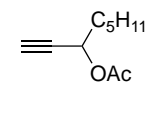
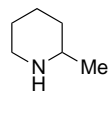
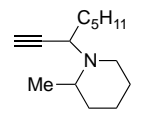
showed that propargylamines could be obtained through amination of propargyl phosphates or acetates efficiently and under mild reaction conditions (Scheme 82).



Scheme 82. Amination of propargyl esters proposed by Murahashi.²⁷⁶

They reported that cuprous chloride as the best catalyst among the examined catalysts for this reaction, however in the presence of other copper salts such as CuBr, CuI, CuCl₂ and CuSO₄, they could also obtain the propargyl amine with good yields. Some of their results from the reaction of propargyl phosphate or acetate with amines are presented in Table 23.

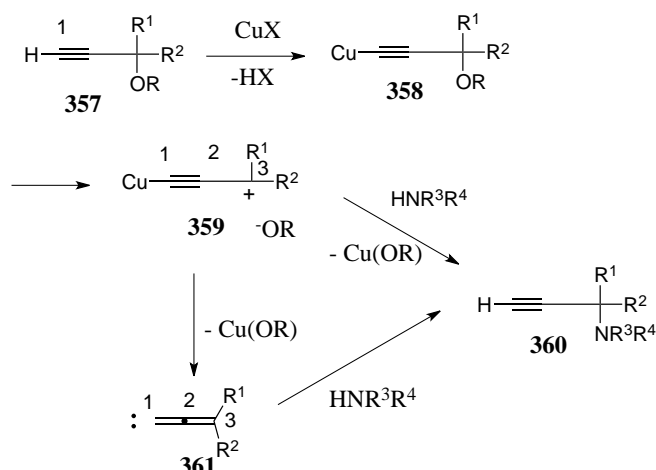
Table 23. Copper-catalyzed amination of propargyl phosphates^a and acetates^b.

Entry	Propargyl phosphate/acetate	Amine	Propargyl amine	Yield ^c
1		HNEt ₂		91
2		H ₂ NPh		85
3				80
4				72

^aThe reaction of propargylic phosphates with amines (2 equiv) was conducted by use of CuCl (1 mol%) in THF at 50°C for 2h. ^bThe reaction of propargyl acetates with amines (2 equiv) was conducted in the presence of CuCl (5 mol%) in THF at reflux for 2h. ^cisolated yield.

The proposed mechanism by Murahashi²⁷⁶ is presented in Scheme 83. For this mechanism, they said that, presence of a terminal acetylenic proton is necessary for this amination reaction with copper as catalyst. Copper acetylide complex **358** that was obtained from the reaction between **357** and cuprous chloride in the presence of a base seemed to be an important intermediate as it was shown for the Glaser-Eglinton coupling reaction.²⁷⁹ By elimination of the ester function from **358**, zwitterion intermediate **359** and/or carbene intermediate **361** could be obtained. It was already reported alcoholysis of propargyl halides in alkaline media was going via such zwitterion intermediates and/or carbene intermediates²⁸⁰ which were obtained from deprotonation followed by elimination of halides. At the end, propargyl amine **360** could be formed from the nucleophilic attack of amines at the C-3 of the intermediate **359** or carbene **361** through which copper(I) could be released to complete catalytic cycle.

²⁷⁹G. Eglinton, W. McCrae, *Adv. Org. Chem.* **1963**, *4*, 225-328. ²⁸⁰V. J. Shiner Jr., J. W. Wilson, *J. Am. Chem. Soc.* **1962**, *84*, 2402-8.



Scheme 83. Proposed copper(I)-catalyzed mechanism of the amination of the propargylic acetate/phosphates by Murahashi.²⁷⁶

III.7.5. S_N1-type nucleophilic substitution of propargylic alcohols or acetates promoted by Lewis or Brønsted acids: Today S_N1-type reactions can be designed easily by use of the Mayr scales (**Fig. 47**).²⁸¹ From this diagram, it is supposed that electrophiles can be reacted with all nucleophiles find below themselves.

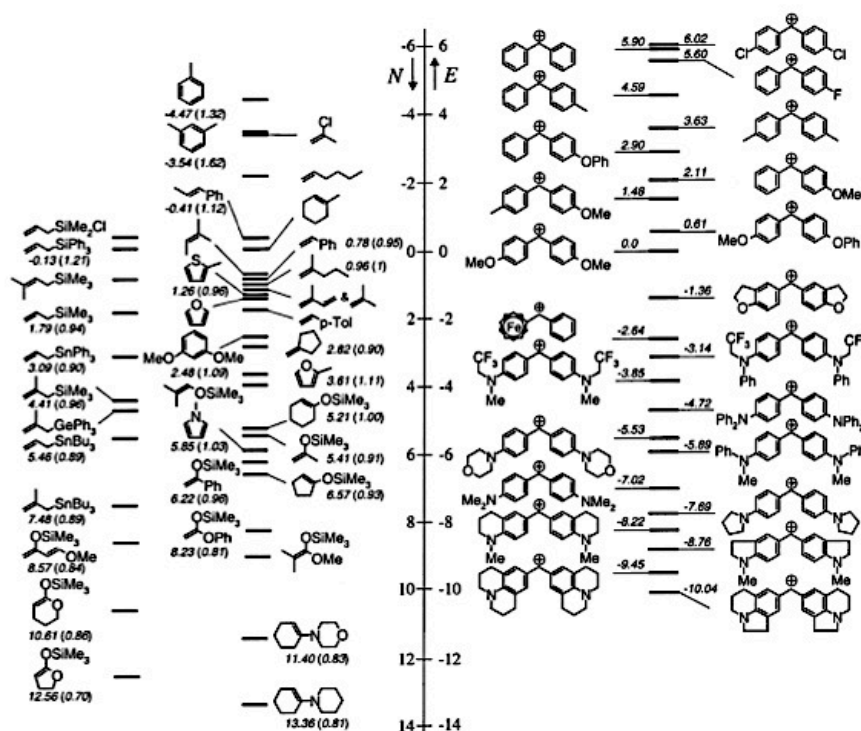
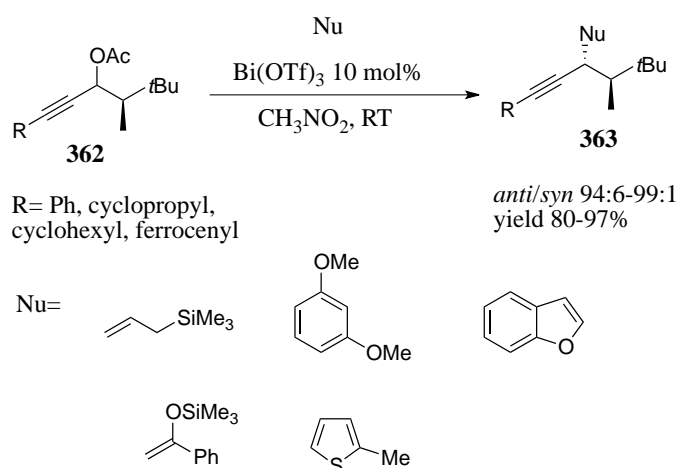


Fig. 47. Collection of all basis set compounds used for the resolution of electro- and nucleophilicity.

²⁸¹H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66-77.

Strong electron-donating functions increase the stability of carbocations. In all reactions illustrated in the literature where Brønsted or Lewis acids are applied, a better understanding of the reactions can come from a careful examination of the concepts demonstrated by the work of Mayr. For example, Bach *et al.*²⁸² presented stereoselective addition of nucleophiles to propargylic cations as the stabilization effect of the propargyl group on the carbocation has been well established (**Scheme 84**).



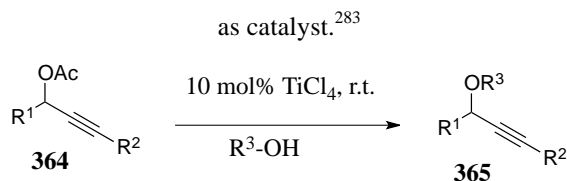
Scheme 84. Diastereoselective substitution of chiral propargylic acetates **362** with nucleophiles proposed by Bach.²⁸²

Under these reaction conditions, propargylic acetates **362** could lead to the corresponding substitution products with high diastereoselectivity under a S_N1 condition.²⁸²

Mahrwald *et al.*²⁸³ have also reported a nucleophilic substitution of propargylic acetate in the presence of TiCl_4 as catalyst. The scope of this reaction was explored by use of different nucleophiles and different substitutions on propargylic core (**Table 24**).²⁸³ In this reaction condition, they found that even alcohols with a less degree of nucleophilicity could give the expected ether in good yields (**Table 24**, entry 5). They also stated that, the yield of the reaction depends mainly on the substituents R^1 and R^2 in the propargyl moiety, because they could have high yields only when they used a diphenylsubstituted propargylic esters (**Table 24**, entries 1-4) and low yields were obtained in the presence of mono-phenyl substituted propargylic ester (**Table 24**, entries 5-8), and no reaction was observed when R^1 was an alkyl substituent. They justified this result by formation of a less stabilized carbocation intermediate during the reaction.

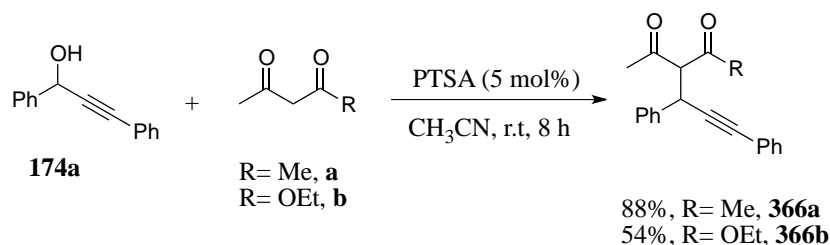
²⁸²P. Rubenbauer, E. Herdtweck, T. Strassner, T. Bach, *Angew. Chem. Int. Ed.* **2008**, *47*, 10106-9. ²⁸³A. Bartels, R. Mahrwald, S. Quint, *Tetrahedron Lett.* **1999**, *40*, 5989-90.

Table 24. Mahrwald's studies on nucleophilic substitution of propargylic ester in the presence of a Lewis acid (TiCl₄) as catalyst.²⁸³



Entry	R ¹	R ²	R ³	Yield (%)
1	Ph	Ph	Me	95
2	Ph	Ph	Et	65
3	Ph	Ph	<i>i</i> Pr	59
4	Ph	Ph	<i>t</i> Bu	55
5	Ph	<i>n</i> Bu	Ph	45
6	Ph	<i>n</i> Bu	Me	76
7	Ph	<i>n</i> Bu	Et	68
8	Ph	<i>n</i> Bu	<i>i</i> Pr	42

In another paper,²⁸⁴ S_N1 nucleophilic substitution of alcohols with Brønsted and Lewis acids was reported by Sanz's group (**Scheme 85**). Using these conditions, activation of the alcohol was not necessary.

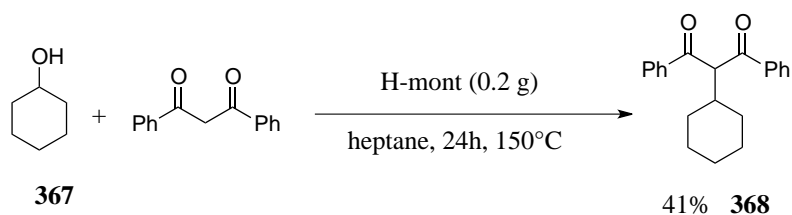


Scheme 85. S_N1 nucleophilic substitution reaction of propargyl alcohol with Brønsted acid.²⁸²

III.7.6. Nucleophilic substitution of alcohols with a solid Brønsted acid :

Kaneda *et al.*²⁸⁵ also reported a S_N1 nucleophilic substitution of propargylic alcohol but by use of a solid Brønsted acid (**Scheme 86**).

²⁸⁴R. Sanz, D. Miguel, A. Martinez, J. M. Avarez-Gutiérrez, F. Rodríguez, *Org. Lett.* **2007**, *9*, 2027-30. ²⁸⁵a) K. Motokura, N. Nakagiri, T. Mizugaki, K. Ebitani, K. Kaneda, *J. Org. Chem.* **2006**, *71*, 5440-7; b) K. Motokura, N. Nakagiri, K. Mori, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda, *Org. Lett.* **2006**, *8*, 4617-20.



Scheme 86. Nucleophilic substitution of cyclohexanol with a solid Lewis acid montmorillonite.²⁸⁵

The reaction is catalyzed by proton- and metal-exchanged montmorillonites (H- and M^{n+} -mont) that reduces the formation of by-products. The catalyst was prepared by treating Na^+ -mont with an aqueous solution of hydrogen chloride or metal salt. The H-mont has shown an excellent catalytic activity for nucleophilic substitution reactions of different alcohols. The catalyst was applied in 10 mol% in heptane at 150°C (**Scheme 86**). The interesting point of this reaction is the use of aliphatic alcohols like cyclohexanol that form less-stabilized carbocations based on Mayr scale.

III.7.7. Metal complexes in the activation of alcohols

III.7.7.1. Ruthenium complexes: The two resonance structures of propargyl cations that have been studied broadly by Olah²⁸⁶ are presented in Figure 48 (A and B).

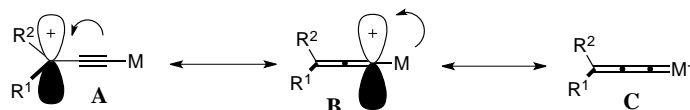
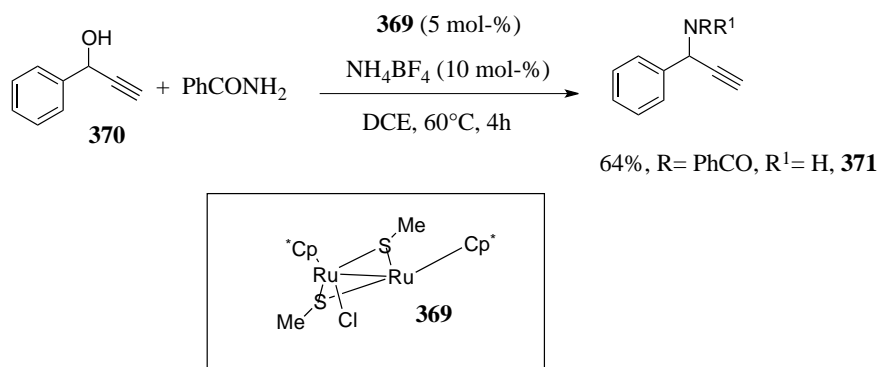


Fig. 48. Stabilization of a propargylic cation.²⁸⁶

Here, stabilization of the positive charge can be increased by insertion of a metal in the γ -position of a propargyl ion (**Fig. 48, C**). From this stabilization result, metal-stabilized propargyl carbocations have been subjected in S_N1 -type reactions.

The first application of the diruthenium complexes in the addition of alcohols, anilines, thiols, and phosphane oxides to propargyl alcohols was proposed by Nishibayashi in 2000 (**Scheme 87**).²⁸⁷ The reaction was carried out with 5 mol% of diruthenium catalyst and 10 mol% of NH_4BF_4 in dichloroethane at 60°C.

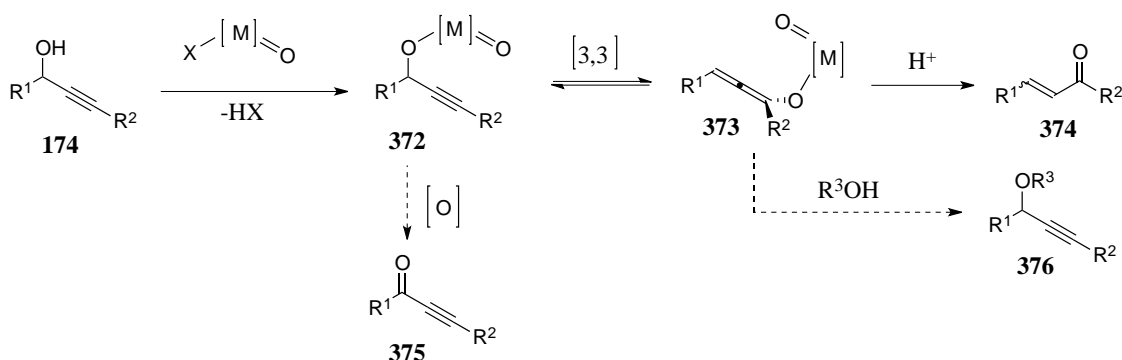
^{286a)} G. A. Olah, R. J. Spear, P. W. Westerman, J.-M. Denis, *J. Am. Chem. Soc.* **1974**, *96*, 5855-59; b) V. V. Krishnamurthy, G. K. S. Prakash, P. S. Iyer, G. A. Olah, *J. Am. Chem. Soc.* **1986**, *108*, 836-8. ²⁸⁷Y. Nishibayashi, I. Wakiji, M. Hidai, *J. Am. Chem. Soc.* **2000**, *122*, 11019-20.



Scheme 87. Propargylic amination conducted by ruthenium catalyst **403**.²⁸⁷

III.7.7.2. Rhenium complexes: Based on reports that metal-oxo complexes result the rearrangement of the propargyl alcohols to enone, Toste investigated metal-oxido complexes for the conversion of propargyl alcohol to propargyl ethers.²⁸⁸

In the course of the study on the rearrangement of propargyl alcohols to enones, Toste had suggested that an allenolate intermediate **373** could undergo S_N2' addition of nucleophile (**Scheme 88**).²⁸⁹



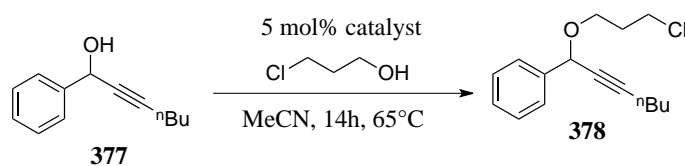
Scheme 88. Toste's suggested S_N2' addition of a nucleophile on intermediate **373**, which undergoes a propargyl ether.²⁸⁹

By keeping in mind this hypothesis, Toste's group tested different metal-oxo complexes including vanadium, rhenium and molybdenum for the selective conversion of propargyl alcohol to propargyl ether. In the presence of vanadium-oxo complex, they observed oxidation of the alcohol to ketone and only a small amount of the expected propargyl ether was obtained (**Table 25**, entry 1);

²⁸⁸B. D. Sherry, A. T. Radosevich, F. D. Toste, *J. Am. Chem. Soc.* **2003**, *125*, 6076-77. ²⁸⁹F. Toda, M. Higashi, K. Akagi, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 829-31; b) T. Kitamura, S. Miyake, S. Kobayashi, H. Taniguchi, *Chem. Lett.* **1985**, *14*, 929-30.

However $\text{MoO}_2(\text{acac})_2$ was found to be an effective catalyst for the substitution reaction with a primary alcohol nucleophile (Table 25, entry 3) but conversion to the enone could also be observed especially when the nucleophile became more hindered (Table 25, entry 3). Among the used catalysts, a rhenium(V)-oxo complex bearing a bidentate phosphine ligand (dppm = diphenylphosphinomethane) was found to be the most effective catalyst for the desired transformation (entry 5). In addition, this catalyst almost completely defeated the competing oxidation and rearrangement reaction in a way that, the calculated conversion by ^1H NMR in other solvents was: benzene **374**(11%):**378**(51%); CH_2Cl_2 **374**(9%):**378**(59%); THF **374**(29%):**378**(71%); acetone **374**(0%):**378**(53%). Another point that they mentioned for these reaction conditions was that, the reaction could be performed without exclusion of air or moisture from the reaction mixture.

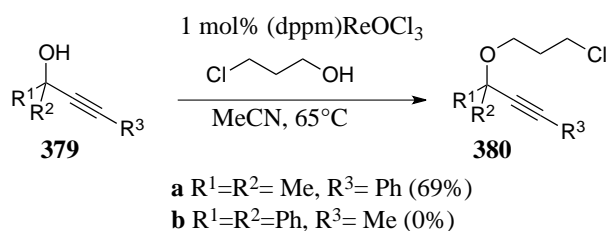
Table 25. Selectivity of Metal-Oxo catalysts for propargyl etherification^a.²⁸⁸



Entry	Catalyst	% 374	% 375	% 378
1	$\text{V}(\text{O})(\text{acac})_2$	0	292	19
2	$[\text{Mo}_2\text{O}_7(\text{BINOL})_2](\text{NBu}_4)_2$	0	10	15
3	$\text{MoO}_2(\text{acac})_2$	20	Trace	77
4	(catechol) ReOCl_3	75	0	25
5	(dppm) ReOCl_3	Trace	Trace	96

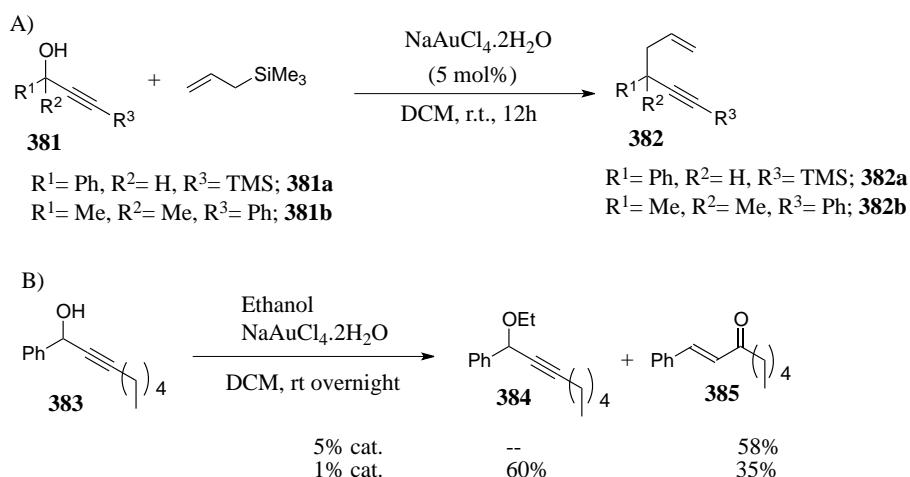
^aThe reaction was performed with 5 mol% catalyst, 3.0 equiv. of alcohol, 1M substrate in MeCN and conversion was determined by ^1H -NMR of the crude reaction mixture.

They could also decrease the amount of catalyst to 1 mol% when (dppm) ReOCl_3 was applied in the reaction (Scheme 89).



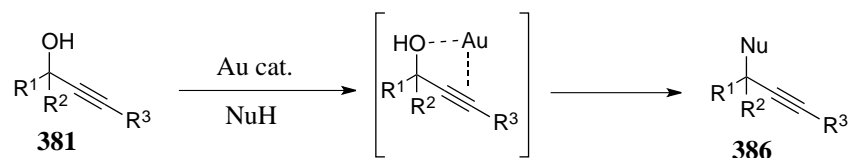
Scheme 89. Decreased amount of rhenium catalyst (1 mol%) could also yielded to the expected propargyl ether.²⁸⁸

III.7.7.3. Gold complexes: The first capability of gold salts in the direct activation of alcohols was reported by Campagne in 2005.²⁹⁰ Different nucleophiles such as allylsilane, alcohols, furan, dimethoxybenzene and thiols were used for the conversion of propargylic alcohols (**Scheme 90**).



Scheme 90. Conversion of propargylic alcohols with gold salts and nucleophiles like allylsilane and ethanol.²⁹⁰

The best results were obtained in the presence of $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ (5 mol%) in dichloromethane. Au^{I} catalysts were less efficient. Campagne and co-workers²⁹⁰ predicted that coordination of gold on π -bond can act as an efficient tool to activate triple bonds for the addition of nucleophiles (**Scheme 91**).

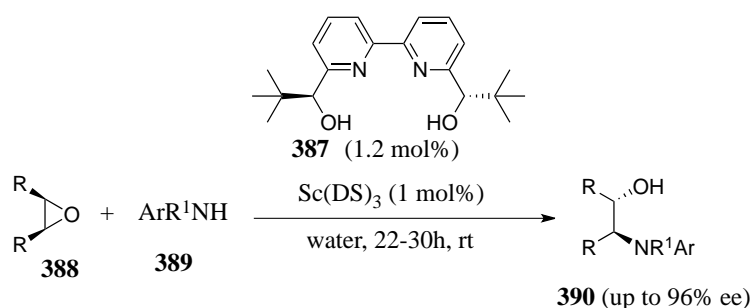


Scheme 91. Coordination of Au(III) on triple bond can activate propargylic alcohol for substitution reaction by a nucleophile.²⁹⁰

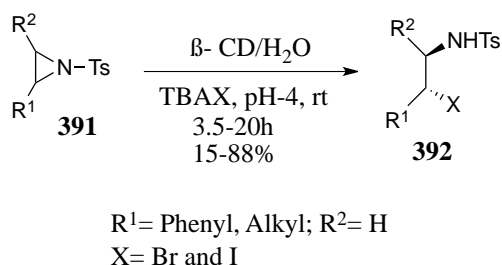
²⁹⁰M. Georgy, V. Boucard, J.-M. Campagne, *J. Am. Chem. Soc.* **2005**, *127*, 14180-1.

III.7.8. Direct nucleophilic substitution of alcohols in water

The interest of using water as catalyst returns to the concept of green chemistry.²⁹¹ Today, many reactions can be performed in water. The “on water concept” was introduced for the first time by Sharpless²⁹² and was reviewed by Fokin.²⁹³ In this reaction, water is the only used solvent without any other co-solvent and insoluble substrates are involved in the reaction medium. Nucleophilic substitutions in water are mostly S_N2-type reactions, for example addition of nucleophiles to epoxides (**Scheme 92**)²⁹⁴ or aziridines (**Scheme 93**).²⁹⁵



Scheme 92. Epoxide opening with scandium tris (dodecyl sulphate) (1 mol%) as a Lewis acid-surfactant combined catalyst and a chiral bipyridine as co-catalyst.^{294b}

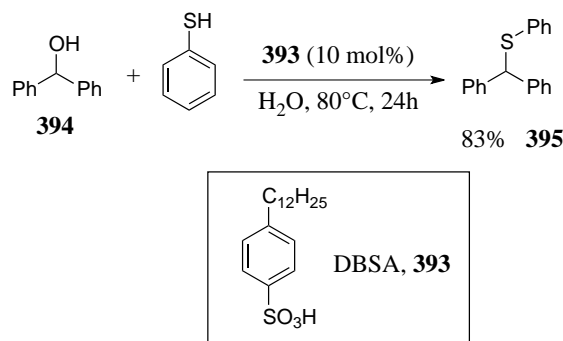


Scheme 93. Regioselective ring-opening of aziridines with tetrabutylammonium halides in the presence of β-cyclodextrin (β-CD) in water.^{295a}

S_N1-type reaction of alcohols is also possible in water. Here formation of the product is controlled by nucleophilicity of the solvent in the reaction mixture. Since water is also a nucleophile, the reaction of a carbocation can be performed in water if the carbocation is stabilized and is not too

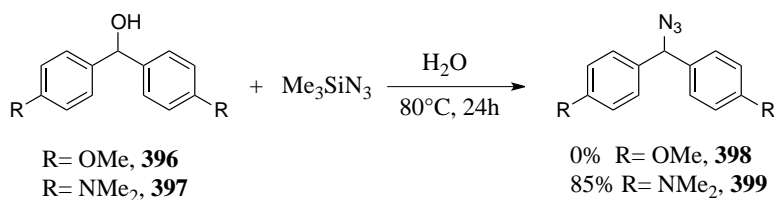
²⁹¹a) U. M. Lindström, *Organic Reactions in Water: Principles, Strategies and Applications*, Wiley-Blackwell, London, **2007**; b) C.-J. Li, L. Chen, *Chem. Soc. Rev.* **2006**, *35*, 68-82. ²⁹²S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem.* **2005**, *117*, 3339-43; *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-79. ²⁹³A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**, *109*, 725-48. ²⁹⁴a) D. Amantini, F. Fringuelli, F. Pizzo, L. A. Vaccaro, *J. Org. Chem.* **2001**, *66*, 4463-67; b) S. Azoulay, K. Manabe, S. Kobayashi, *Org. Lett.* **2005**, *7*, 4593-95. ²⁹⁵a) M. Narender, K. Surendra, N. Srilakshmi Krishnaveni, M. Somi Reddy, K. Rama Rao, *Tetrahedron Lett.* **2004**, *45*, 7995-97; b) S. Minakata, D. Kano, Y. Oderaotoshi, M. *Angew. Chem. Int. Ed.* **2004**, *43*, 79-81.

electrophilic. Kobayashi ²⁹⁶ has reported a nucleophilic displacement in water and in the presence of a surfactant Brønsted acid **393** (Scheme 94).



Scheme 94. Surfactant Brønsted acid in the catalytic addition of PhSH to benzhydric alcohol.²⁹⁶

By use of Mayr's scale, Cozzi and Zoli suggested a direct substitution of alcohols « on water » without use of any Brønsted or Lewis acid as a tool for stabilizing the corresponding carbocation (Scheme 95).²⁹⁷



Scheme 95. Addition of azide nucleophile to benzhydric alcohols using “on water” conditions.²⁹⁷

Such carbocations have a very short lifetime in aqueous solution due to their rapid reactions with water, but their lifetime can be increased by inserting an electron-donating substituents on the aryl ring. Once a less-reactive and more-stabilized carbocation is prompted in water, reaction with the

²⁹⁶S. Shirakawa, S. Kobayashi, *Org. Lett.* **2007**, 9, 311-14. ²⁹⁷P. G. Cozzi, L. Zoli, *Angew. Chem. Int. Ed.* **2008**, 47, 4162-66.

nucleophile can become possible. By considering Mayr scale, this reaction is very limited to carbocations with a certain values of E on the Mayr scale. For example, when this value become near to 0 like in the case of **396** the reaction doesn't occur « on water ».

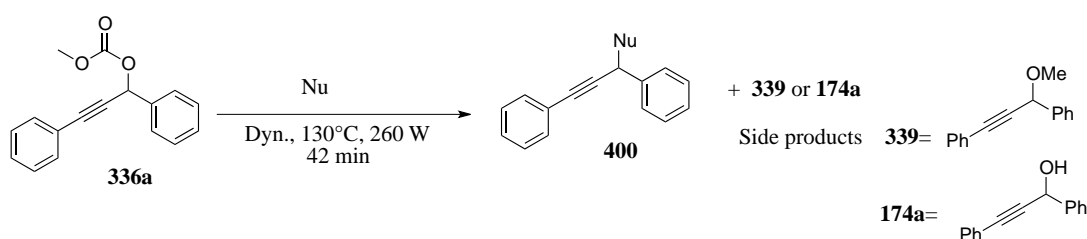
III.7.9. Direct nucleophilic substitution of propargylic ester under microwave irradiations

During our study on 1,3-dipolar Huisgen cycloaddition between internal propargyl ester (**336a**) and benzyl azide under microwave condition, we observed formation of a propargyl ether as a side product in the presence of MeOH as solvent (**Scheme 78**). Since preparation of these kind of propargylic ethers from propargyl esters under microwave condition have not been reported in the literature to the best of our knowledge, and as these products are interesting building blocks in organic synthesis and can be used widely to obtain a variety of structures due to the existing of a triple bond in the structure, we decided to expand the scope of this reaction by using different nucleophiles or alcohols and different propargyl esters. Another point that worth to be mentioned is that, our nucleophilic substitution of propargyl ester is done without use of any catalyst or a toxic metal as catalyst and also without use of any solvent, because the used nucleophile or alcohol has been used as both solvent and nucleophilic source. Furthermore, no special treatment on the medium mixture was necessary at the end of the reaction, and after only a simple evaporation of the solvent *in vacuo* the final product could be obtained enough pure.

This direct nucleophilic substitution of propargyl ester was performed in the presence of different nucleophiles or alcohols such as ethanol, butanol, isopropyl alcohol, propargylic alcohol and allyl alcohol. The results are presented in Table **26**. This reaction was conducted by choosing fixed temperature (Dynamic) method as the method of choice for microwave by which the power of the apparatus could be adjusted on the desired Watt. As is shown in Table **26**, in the presence of alcohols like MeOH and butanol, the conversion of ester to propargyl ether was complete and the expected propargyl ether was found with 100% yield (Table **26**, entries 1 and 2). However, by use of propargyl and allyl alcohols, formation of a side-product, which was a methyl ether could be detected by ^1H NMR (Table **26**, entries 4 and 5). Formation of this methyl ether could be a result from a reaction between the released methalonnate existing on the carbonate function of the starting

propargyl ester and the electrophilic site on the propargyl ester, however in the case of allyl alcohol formation of the starting propargyl alcohol from which the propargyl ester was prepared, could also be detected in the reaction medium with 16% yield. Another remark was when isopropyl alcohol or *tert*-butanol was used as nucleophilic source. In these conditions total conversion of the starting material to the ether compound could not be observed, that could be due to the bulky structure of this alcohol (**Table 26**, entry 3 and 6).

Table 26. Direct nucleophilic substitution of propargylic ester to propargyl ether under microwave irradiations.



Entry	Alcohol ^a	Ester (%) ^b	Ether (%) ^b	Side-product (%) ^b	
				339	174a
1	MeOH	-	100	-	-
			339		
2	BuOH	-	Qtv	-	-
			400a		
3	Isopropyl alcohol	44	56	-	-
			400b		
4	Propargyl alcohol	-	91	9	-
			400c		
5	Allyl alcohol	-	82	16	2
			400d		
6	<i>tert</i> -butyl alcohol	59	35	6	-
			400e		

^aThe alcohol was used in 2 ml and the reaction was conducted at 130°C during 42 min and with an irradiation of 260 W.

^bCompositions were determined by ¹H NMR of the crude reaction mixture.

To optimize the reaction conditions, we chose butanol as a model alcohol and the reaction was performed between propargyl carbonate (**336a**) and butanol in different conditions by examining various parameters like temperature, microwave method (fixed temperature or power) and time of the reaction. First the reaction was carried out by introducing large equivalents of nucleophile (10 to 5 equiv.) into the reaction medium. The best results were obtained where 10 equivalents of alcohol has been used on both fixed temperature and fixed power mode, for which the expected propargyl ether was obtained with 93 to 95% conversions (**Table 27**, entries 2, 3 and 6). However for all of these cases formation of the methyl ether by-product has been also detected (4-5%). When the used equivalents of alcohol (BuOH) was decreased to 5 equivalents conversion of the starting material to the expected product was not total and even by increasing the temperature from 130°C up to 170°C a total conversion could not be obtained and decomposition of the product was observed (**Table 27**, entry 5). In the best case, the ether product was obtained with 73% composition when the reaction was performed on fixed power mode (power= 300 W), at 130°C for 65 min (**Table 27**, entry 7).

Table 27. Direct nucleophilic substitution was performed in fixed temperature and fixed power mode and by use of different reaction conditions and BuOH as nucleophilic source.

	Entry	T(°C)	Power (W)	Equiv.	Time (min)	Starting ^(c) pdct(%) 336a	Pdct(%) ^(c)		
							Pdct 400a	OMe 339	Decomp.
Method A (Fixed temperature)	1	130 ^(a)	260	115	52	-	qtv.	-	-
	2	130 ^(a)	260	10	70	3	93	4	-
	3	170 ^(a)	260	10	30	-	95	5	-
	4	130 ^(a)	260	5	70	75	25	-	-
	5	170 ^(a)	260	5	30	29	71	-	++
	6	127 ^(b)	300	10	35	-	95	5	-
Method B (Fixed power)	7	130 ^(b)	300	5	65	18	73	9	-

^(a)setpoint Temperature. ^(b)reached temperature. ^(c)defined by ¹H NMR of the crude reaction mixture.

In order to see if the reaction could be conducted by use of less butanol but by increasing the time of the reaction, this reaction was repeated at high temperature and on both fixed temperature and power mode. The results are presented in **Table 28**.

Table 28. Nucleophilic substitution of propargyl ester (**336a**) with small amounts of 1-butanol.

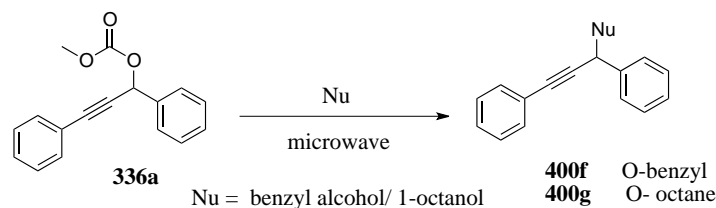
	Entry	T (°C)	Power (W)	Equiv.	Time (min)	Starting ^(c) pdct (%)	Pdct(%) ^(c)		
							Pdct 400a	OMe 339	Decomp.
Method A (Fixed temperature)	1	130 ^(a)	260	3	70	36	61	3	-
	2	130 ^(a)	260	3	52	41	56	3	-
	3	170 ^(a)	260	3	70	22	72	6	++
	4	170 ^(a)	260	3	52	49	51	-	+
	5	170 ^(a)	260	1.1	52	77	7	16	+++
Method B (Fixed power)	6	130 ^(b)	300	3	70	53	47	-	++
	7	153 ^(b)	300	3	25	40	51	9	++
	8	170 ^(b)	300	3	40	15	77	8	>+++
	9	130 ^(b)	300	1.1	40	100	-	-	-
	10	155 ^(b)	300	1.1	70	59	18	23	+++
	11	170 ^(b)	300	1.1	70	52	21	27	>+++

^(a)setpoint temperature. ^(b)reached temperature. ^(c)yield was defined by ¹H NMR of the crude product.

The best result was obtained from the reaction between 3 equivalents of BuOH and propargyl ester on fixed temperature mode and at 130°C for 70 min from which the expected ether was resulted with 61% composition (**Table 28**, entry 1). In the presence of small amounts of butanol decomposition of the product could be observed more especially when the reaction was conducted on fixed power mode and by adjusting the irradiation power at 300 W, where decomposition was the most important (**Table 28**, entry 11).

In order to expand again the feasibility of this nucleophilic substitution, we examined other alcohols like benzyl alcohol and 1-octanol, which are heavier alcohols in comparison with butanol or other used alcohols reported in **Table 26**. The reason for these chosen alcohols was again to examine if the reaction can be conducted with small amounts of nucleophile when a heavier alcohol is used (**Table 29**). All of the reactions were carried out on fixed power mode and by irradiating at 300 W.

Table 29. Nucleophilic substitution between propargylic carbonate **336a** and benzyl alcohol and 1-octanol under microwave irradiations.



Entry	Equiv.	T(°C)	Time (min)	Starting pdct(%) ^(a)	Pdct(%)	OMe 339 (%)	Decomp. (%) ^(a)
Benzyl alcohol							
1	10	170	35	-	91 ^(a)	9	-
2	5	170	35	-	91 ^(a)	9	-
3	2	170	40	-	42 ^(b)	-	-
4	2	127	35	-	96 ^(a)	4	-
5	1.1	170	50	21	66 ^(a)	13	> +++
6	1.1	170	40	10	43 ^(a)	47	++
7	1.1	170	35	22	71 ^(a)	7	++
8	1.1	127	35	62	35 ^(a)	3	+
1-octanol							
9	10	170	20	-	81 ^(b)	-	-
10	5	127	35	8	84 ^(a)	8	-
11	5	127	55	-	91 ^(a)	9	-
12	2	127	35	55	40 ^(a)	5	-
13	2	127	85	39	56 ^(a)	5	A trace
14	1.1	170	35	81	16 ^(a)	3	-
15	1.1	127	40	76	23 ^(a)	1	-
16	1.1	127	81	16	2 ^(a)	1	-

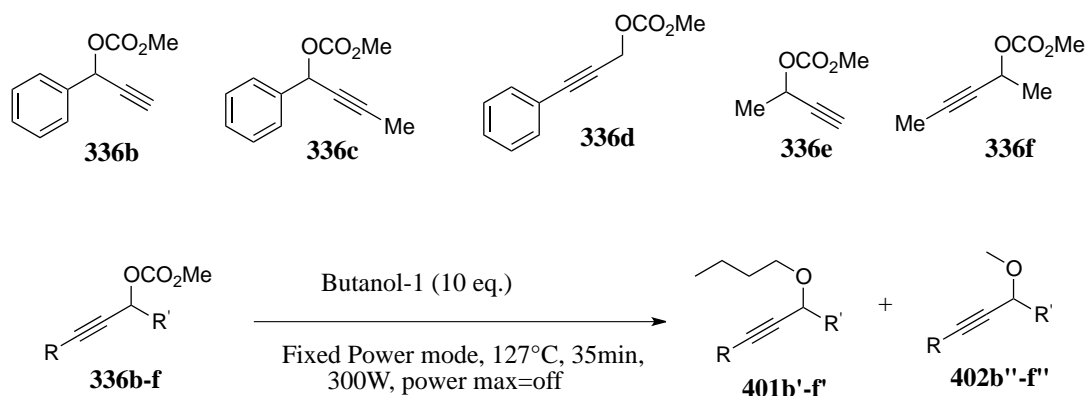
^(a)Composition was determined by ¹HNMR. ^(b)yield of isolated product. In all cases, excess of alcohols remained in medium reaction, which was tried to be eliminated by use of a sulfonyl chloride resin.²⁹⁸

As is shown in Table 29, in the case of benzyl alcohol, the ether product was obtained with the same result (91% composition) when the number of equivalents was decreased from 10 to 5 and by use of the same reaction condition (entry 1 vs 2). With 2 equivalents of benzyl alcohol, the best result was obtained when the reaction was conducted at 127°C for 35 min. This reaction condition gave the ether product with 96% composition. When the reaction was performed with less amount of benzyl alcohol (1.1 equiv.) not even a good yield of the final product was not obtained but more decomposition of the product could be detected. By subjecting 1-octanol in this reaction, the high yields with small amount of this nucleophile could only be observed when 5 equivalents of alcohol were introduced in the reaction (entries 10 and 11). However, use of these heavier alcohols make us capable to perform the reaction with lesser amounts of nucleophile (alcohol), but it

²⁹⁸S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. T. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815-4195.

demands a further treatment of the medium reaction to remove the remained alcohol which is difficult or impossible to be removed in rotary evaporator. The solution here is the treatment of the medium mixture with a solid resin which is a sulfonyl chloride polymer bound ²⁹⁸ following the addition of a small amount of pyridine in dichloromethane. In this condition sulfonyl chloride reacts with the remained alcohols in the medium and at the end, the trapped alcohol on the resin could be separated from the product by a simple filtration.

In the case of butanol, as we could find high yields with 10 equiv. of this alcohol and by doing the reaction on fixed power mode (power= 300 W) at 127°C for 35min, we decided to subjected other synthesized propargyl esters in this reaction condition (**Scheme 96**).



Scheme 96. Other propargylic esters were prepared in order to study the nucleophilic substitution.

These propargyl esters contain either a terminal alkyne or different substituents on propargyl moiety like an aryl or an alkyl group, which let us to study their outcome of nucleophilic substitution on the electrophilic site (**Table 30**).

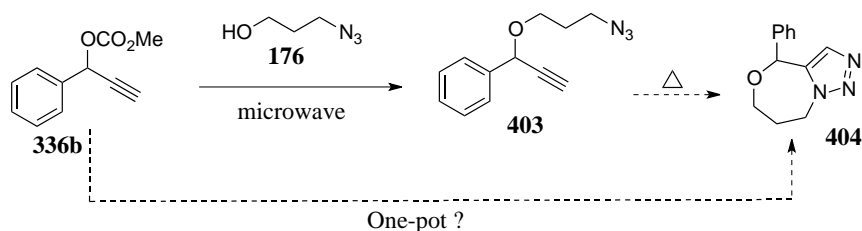
Table 30. Reaction between other synthesized propargylic carbonates and Butanol-1 (10 equiv.) on Fixed Power mode at 127°C for 35min and 300W.

Propargyl carbonate	Starting material*	Butyl ether*		Methyl ether*
	%	%	%	%
336b	29	401b'	71	402b'' -
336c	23	401c'	77	402c'' -
336d	100	401d'	-	402d'' -
336e	100	401e'	-	402e'' -
336f	100	401f'	-	402f'' -

*The compositions were identified by ¹H NMR as the two forms were not separatable on flash chromatography column.

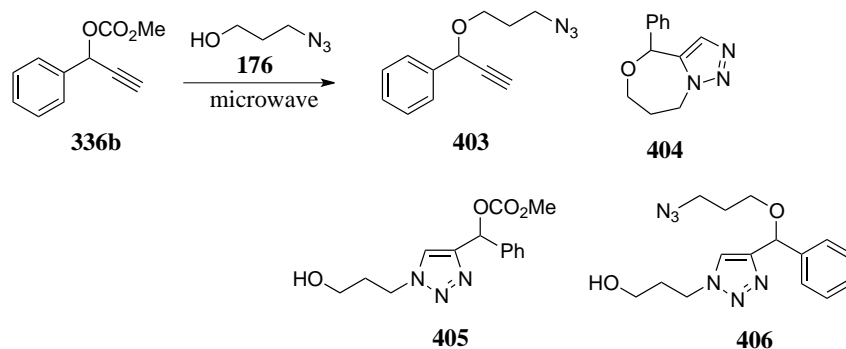
The reaction between propargyl carbonates **336b** and **336c** and butanol-1 (10 eq.) led the expected propargyl ether with 71 and 77% yields respectively. In no cases the methyl ether by-product **402** was formed, but carbonate **336d**, **336e** and **336f** didn't react with butanol and so the starting material was only found at the end of 35min. With carbonate **336c**, we could have better result by increasing the time of the reaction (50 min). In this condition, propargyl carbonate **336c** gave 9% and 91% respectively for the starting material and butyl ether, without formation of the methyl ether. So the reaction with diphenyl substituted propargylic carbonate remains a high yielding reaction. These results are in agreement with the results reported by Mahrwald.²⁸³

In another test, propargyl ester **336b** was subjected to the reaction with 3-azidopropane-1-ol as the nucleophilic source. The existence of a terminal alkyne on the ester structure and azide on the nucleophilic source, may conduct an intramolecular 1,3-dipolar Huisgen cycloaddition following the nucleophilic substitution as it was described previously (**Scheme 97**).



Scheme 97. Intramolecular 1,3-dipolar Huisgen cycloaddition through a nucleophilic substitution of the propargylic carbonate by an azidoalcohol.

In order to study the possibility of doing this reaction in a one-pot manner, different reaction conditions under microwave irradiation were examined. The possible products that can result from this reaction are shown in **Scheme 98**.



Scheme 98. The reaction between propargyl ester **336b** and 3-azidopropanol could yield products **403**, **404**, **405** or **406**.

This experiment was tried using two microwaves modes; fixed temperature (dynamic) and fixed power. The results are shown in Table 31.

Table 31. Nucleophilic substitution and eventual 1,3-dipolar cycloaddition reaction between propargyl carbonate **336b** and azidopropanol.

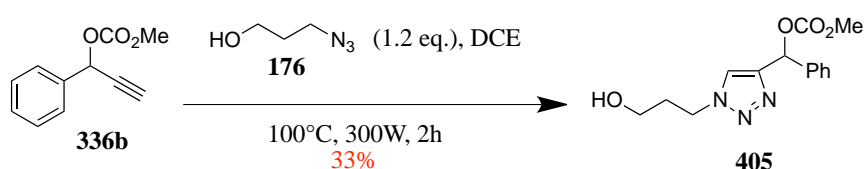
	Entry	Equiv.	Power (W)	Temp. (°C)	Time (min)	Products	Composition% ¹
Fixed temperature (Dynamic)	1	2	260	170	10	403 , 404 , 405	trace
	2	3	260	130	52	403 , 404 , 405 , 406	403 : 4; 404 : 28; 405 : 11; 406 : 37
	3	3	260	130	70	403 , 404 , 405 , 406	403 : 15; 404 : 40; 405 : 14; 406 : 12
Fixed power	4	1.1	300	177	35	Decomp.	-
	5	10	300	139	26	405 , 406	405 : 17; 406 : 6
	6	10	300	100	90	404 , 405 , 406	404 :10; 405 : 6; 406 : 74;

¹Composition was determined by LCMS analysis.

In any case, a total conversion of the starting propargyl carbonate to the expected triazolic bicycle **404** could not be observed, and most of the time a mixture of products was obtained which were difficult or unseperatable by flash column chromatography. The presence of each compound was determined by LCMS analysis. At high temperatures decomposition of the product was observed (entries 1 and 4).

When the reaction was conducted with 10 equivalents of azidoalcohol at 139°C a mixture of products **405** and **406** could be detected on LCMS, formation of another product could be also observed on LCMS which could not be identified, because of an obtained mass of $m/z=375$ that corresponds to non of the possible products (entry 6).

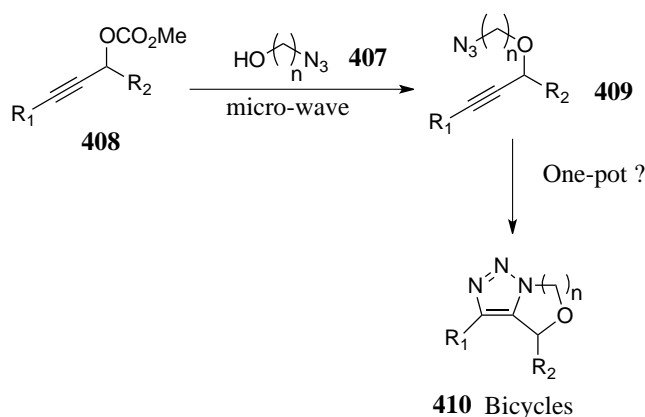
This reaction was also repeated in dichloroethane as solvent and in fixed power mode. After 2h of irradiation at 100°C and with a power of 300W, product **405** was obtained as the only product of the reaction with 33% composition and the starting propargyl carbonate was recovered with 67% composition (Scheme 99).



Scheme 99. Reaction between propargyl carbonate **336b** and azidopropanol in dichloroethane only yielded product **405**.

Since in any conditions we could obtain product **404** as the main product, more studies are needed to find a suitable reaction condition for product **404**.

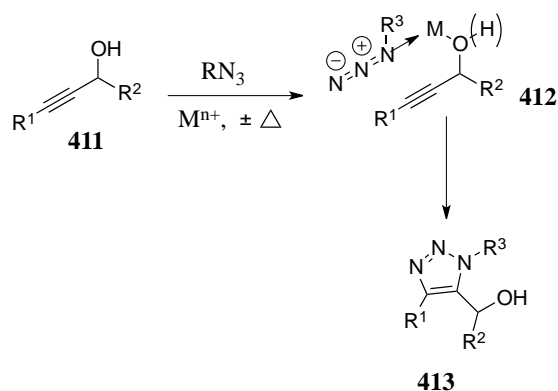
In this part, a direct substitution of propargyl esters under microwave irradiation has been reported, but still further studies are necessary to determine the mechanism of the reaction (S_N1 - or S_N2 -type). Other possible prospect that can be mentioned for this reaction is the use of other propargyl esters and nucleophiles and testing their cycloaddition reaction with azidoalcohol through an intramolecular reaction as is shown in Scheme 100.



Scheme 100. Substitution carbonate function of an internal propargyl carbonate with an azidoalcohol as a nucleophile following by an intramolecular 1,3-dipolar cycloaddition between azide and alkyne.

From the reaction between the internal propargyl ester **408** and azidoalcohol **407** we can first have a simple substitution of the nucleophile on carbonate function and then intramolecular cycloaddition of azide and alkyne can be investigated in order to find bicyclic triazoles. This reaction could be performed in a one-pot manner.

This reaction can be also repeated with a propargyl alcohol and in the presence of a metal as catalyst (**Scheme 101**). For this reaction we suppose chelation of metal on oxygen and addition of azide on metal following by cycloaddition reaction between azide and alkyne.



Scheme 101. Reaction between a propargyl alcohol and an azide in the presence of a metal as catalyst.

This reaction can be conducted without heating or in a thermic condition, then we can study if the reaction is feasible in a one-pot manner or not.

III.8. Conclusion

Some reactions have been reported that were performed under microwave irradiation. Trisubstituted triazoles were tried first to be produced from a reaction between an internal propargylic carbonate or alcohol and an organic azide and without use of any catalyst. Under these conditions, we expected to obtain a mixture of isomers 1,4- and 1,5-trisubstituted triazoles but in any case a total conversion of the starting product could be observed. The best results were obtained when toluene was chosen as solvent. From the reaction in MeOH as solvent we could observe substitution of carbonate by MeOH and formation of a propargyl ether as the main product, we decided to expand the scope of this reaction by use of other alcohols or nucleophilic solvents and other propargyl carbonates. In all cases the expected propargyl ether could be obtained in high yields. The amount of used alcohol could be reduced in the case of heavier alcohols like 1-octanol or benzyl alcohol.

The reaction between non substituted or alkyl propargyl carbonates with an alcohol did not result in the expected propargyl ether, and only the starting products were recovered at the end of the reaction.

At the end, the substitution reaction was run between a true alkyne and an azidoalcohol as nucleophile in order to study first substitution of the carbonate with azidoalcohol followed by an intramolecular cycloaddition reaction between azide and alkyne, but here a mixture of products were obtained, indicating that more studies are needed to optimize the reaction conditions.

Experimental part

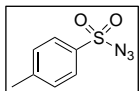
General

All moisture and air-sensitive reactions were carried out under an atmosphere of Argon using oven-dried glassware.

All of the reactions were followed by Thin Layer Chromatography (TLC) which was carried out on silica gel 60 F₂₅₄ (Merck) plates and with visualization by UV-light ($\lambda=254\text{nm}$) and/or by spraying potassium permanganate, anisaldehyde, acid phosphomolybdic and Ceric Ammonium Molybdate (CAM) followed by heating. Flash column chromatography was performed using silica gel 60 (40-63 μm) and the procedure includes the subsequent evaporation of solvents *in vacuo*.

Proton (^1H NMR) and Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Bruker AC300 instrument. Carrier frequencies are respectively 300 MHz for ^1H and 75 MHz for ^{13}C nucleus. The chemical shifts are given in part per million (ppm) on the delta scale. The solvent peak was used as reference values. For ^1H NMR: $\text{CDCl}_3=7.24$ ppm and for ^{13}C NMR: $\text{CDCl}_3=77.16$ ppm. The following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; b, broad. Infrared spectra were recorded neat on a IR affinity-1 equipped by an ATR Gladi Diam for the sample application. Wavelengths of maximum absorbance (ν_{max}) are quoted in wave numbers (cm^{-1}). LC-MS analysis was performed on a Shimadzu LCMS-2010 A device equipped with a UV diode array SPD-M10 A detector (D_2 & W lamp, scanning from 190 to 600 nm), a mass detector LCMS-2010 A (ESI) and a light scattering detector ELSD-LT. The column used is a Waters Sunfire analytical column (C8, reverse phase, $l=53$ mm, d.i.= 7 mm). The used solvents are HPLC grade and degassed with ultrasound for 20 min. The eluents are $\text{H}_2\text{O}/\text{HCOOH}$ 0.1% and $\text{CH}_3\text{CN}/\text{HCOOH}$ 0.1%. The signal is recorded and analysed on a computer equipped with LC-MS Solution® software. The results are reported as a function of m/z . The parent ions $[\text{M}+\text{Na}]^+$ or $[\text{M}-\text{H}]^-$ are quoted.

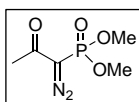
Melting points were measured with Electrothermal IA9000 series digital melting point apparatus. Reagents and solvents were purified using standard means. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 under an argon atmosphere; THF was distilled from sodium metal/benzophenone and stored under an argon atmosphere. Triethylamine (Et_3N) was distilled from CaH_2 . All other chemicals were used as received except when otherwise stated in the experimental text. All other extractive procedures were performed using non-distilled solvents and all aqueous solution used were saturated.

Preparation of alkynes:**4-methylbenzene-1-sulfonyl azide (152):**¹⁶¹

Tosyl chloride (10g, 52.45 mmol, 1 eq.) was dissolved in acetone (148 ml) and water (148 ml). The solution was cooled on ice and sodium azide (3.75g, 57.69 mmol, 1.1 eq.) was added. The reaction was stirred for 2h at room temperature. The acetone was removed under vacuum and the remaining water layer was extracted with EtOAc (130 ml, x2). The organic layer was dried on Na₂SO₄, filtered and evaporated under reduced pressure. The tosylazide was obtained as a colorless liquid (9.69g, 94% yield).

¹H NMR (300MHz, CDCl₃): 2.45 (s, 3H), 7.38 (d, 2H, J= 8.2 Hz), 7.82 (d, 2H, J= 8.2 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): 21.77, 127.55, 130.29, 135.54, 146.21 ppm.

Bestman-Ohira reagent (131):¹⁶¹

Sodium hydride (60% in mineral oil) (1.214g, 50.61 mmol, 1 eq.) was suspended in dry benzene (132 ml) and dry THF (43 ml) under Ar. This mixture was cooled on ice. A solution of dimethyl (2-oxopropyl)-phosphonate (7.651g, 46.06 mmol, 0.91 eq.) in dry benzene (132 ml) was added. A white solid was formed. The reaction mixture was stirred for 1h at room temperature. A solution of 4-methylbenzene-1-sulfonyl azide (9.582g, 48.59 mmol, 0.96 eq.) in dry benzene (23 ml) was added. The mixture was stirred over night at room temperature, then filtered through a celite pad and washed with toluene (100 ml, x3) and EtOAc (132 ml, x14) and concentrated in vacuo. A dark orange oil was obtained. This product was subjected directly into the next reaction without further purification. (11.02 g, Qtv).

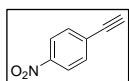
¹H NMR (300 MHz, CDCl₃): 2.22 (s, 3H), 3.81 (d, 6H, J= 11.9 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): 27.08, 53.51, 53.58 (d, J= 5.58 Hz), 16.33, 129.56, 189.85 (d, J= 12.98 Hz) ppm.

General procedure1; preparation of alkynes with Bestman-Ohira reagent: To a solution of alkyne (1 eq.) in anhydrous methanol (0.1 M), were added potassium carbonate (2 eq.) and dimethyl 1-diazo-2-oxopropylphosphonate (1.5 eq.). After 18h of stirring at rt, the reaction was quenched with a half saturated (5%) solution of NaHCO₃ and the aqueous layer was extracted with dichloromethane (x3). The organic extracts were combined and washed with brine, dried over

MgSO₄ and filtered through a small pad of celite and concentrated in vacuo. The resulting residue was purified by flash column chromatography to afford the corresponding alkyne.

1-ethynyl-4-nitrobenzene (**132a**):²⁹⁹



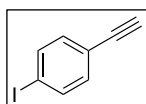
According to the general procedure 1, to a solution of 4-nitrobenzaldehyde (1g, 6.61 mmol) in anhydrous methanol (59 ml) were added potassium carbonate (1.82 g, 13.16 mmol) and dimethyl 1-diazo-2-oxopropylphosphonate (1.904 g, 9.91 mmol). After 18h of stirring at rt, the corresponding alkyne was obtained as a yellow solid (1.078 g, qtv).

¹H NMR (300MHz, CDCl₃): δ 3.33 (s, 1H), 7.62 (d, 2H, J=8.7Hz), 8.18 (d, 2H, J=8.7 Hz) ppm.

¹³C NMR(75 MHz, CDCl₃): δ 81.61, 82.35, 123.57, 128.92, 132.97, 147.54 ppm.

FTIR (ATR): ν (cm⁻¹) 3280, 2917, 2321, 1595, 1510, 1330, 1267, 1035, 1022, 807.

1-ethynyl-4-iodobenzene (**132b**):²⁹⁹

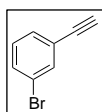


According to the general procedure 1, by using 4-iodobenzaldehyde (0.125 g, 5.38 mmol) this 1-ethynyl-4-iodobenzene (**132b**) was obtained as a yellow solid (0.215 g, Qtv).

¹H NMR (300 MHz, CDCl₃): δ 3.19 (s, 1H), 7.28-7.33 (m, 2H), 7.72-7.74 (m, 2H) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 78.60, 82.70, 94.86, 121.62, 133.60, 137.52 ppm.

1-bromo-3-ethynylbenzene (**132c**):³⁰⁰

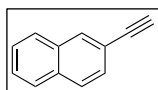


Upon the general procedure 1, using 3-bromobenzaldehyde (200 mg, 1.08 mmol) as the starting product gave the final product (**132c**) as a colorless oil (0.131 g, 67% yield).

¹H NMR (300 MHz, CDCl₃): δ 3.16 (s, 1H), 7.23-7.26 (m, 1H), 7.45-7.54 (m, 2H), 7.68 (t, 1H, J=1.76 Hz) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 78.55, 82.06, 122.11, 124.12, 129.77, 130.70, 132.03, 134.89 ppm.

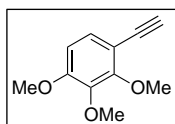
²⁹⁹B. P. Machin, B. L. Pagenkopf, *Synlett* **2011**, 19, 2799-2802. ³⁰⁰L. S. Kallander, Q. Lu, W. Chen, T. Tomaszek, G. Yang, D. Tew, T. D. Mak, G. A. Hofmann, C. K. Schulz-Pritchard, W. W. Smith, C. A. Janson, M. D. Ryan, G. -F. Zhang, K. O. Johanson, R. B. Kirkpatrick, T. F. Ho, P. W. Fisher, M. R. Mattern, R. K. Johnson *et al.*, *J. Med. Chem.* **2005**, 48, 5644-47.

2-ethynynaphthalene (132d):²⁹⁹

The general procedure 1 applied to 2-naphthaldehyde (1.00 g, 6.4 mmol) which gave the product **132d** as a white solid (0.812 g, 83% yield).

¹H NMR (300MHz, CDCl₃): δ 3.15 (s, 1H), 7.46-7.55 (m, 3H), 7.76-7.82 (m, 3H), 8.03 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 76.71, 77.14, 77.57, 84.13, 119.47, 126.69, 126.98, 127.84, 128.62, 132.39, 132.90, 133.11 ppm.

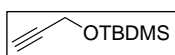
1-ethynyl-2, 3, 4-trimethoxybenzene (132e):

According to the general procedure 1, using 2,3,4-trimethoxybenzaldehyde (2.00 g, 10.2 mmol) as the starting product gave the final product (**132e**) as a colorless oil (0.901g, 45% yield).

¹H NMR (300 MHz, CDCl₃): δ 3.85 (s, 6H), 3.96 (s, 3H), 6.59 (d, 1H, J=8.65Hz), 7.14 (d, 1H, J=8.64 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 56.07, 61.07, 61.32, 79.73, 79.78, 107.30, 109.21, 128.67, 142.12, 154.75, 155.43 ppm.

FTIR (ATR): ν (cm⁻¹)= 3278, 2939, 2839, 1591, 1463, 800, 651.

tert-butyldimethyl(prop-2-yn-1-yloxy)silane (132a):³⁰¹

To a solution of propargyl alcohol (3.00 g, 53.5 mmol) in dry CH₂Cl₂ (150 ml) were added imidazole (5.46 g, 80.3 mmol) and *t*-butyldimethylsilyl chloride (12.1 g, 80.3 mmol) at 0°C. The mixture was stirred at r.t. until disappearance of the starting product, then quenched with saturated NH₄Cl and extracted with Et₂O (x2). The combined organic layers were washed with brine and dried over MgSO₄ and filtered. The filtrate was concentrated under pressure and purified on column chromatography (cyclohexane/EtOAc as eluent). The final product was obtained as a colorless oil (7.57 g, 83% yield).

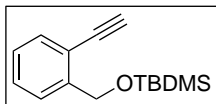
¹H NMR (300 MHz, CDCl₃): δ 0.12 (s, 6H), 0.9 (s, 9H), 2.38 (t, 1H, J= 2.42 Hz), 4.29 (d, 2H, J= 2.42 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 5.20, 25.78, 38.58, 51.51, 72.83, 73.26 ppm.

³⁰¹J. Wang, H.-T. Zhu, Y.-X. Li, L.-J. Wang, Y.-F. Qiu, Z.-H. Qiu, M.-J. Zhong, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2014**, *16*, 2236-9.

FTIR (ATR): ν (cm⁻¹)= 3311, 2859, 2954, 2930, 2182, 1255, 1094, 777.

***tert*-butyl[(2-ethynylphenyl)methoxy]dimethylsilane (132b) :**³⁰²



To a solution of commercial (2-ethynylphenyl)methanol (0.340 g, 2.57 mmol) and imidazole (0.263 g, 3.86 mmol) in anhydrous CH₂Cl₂ (18 ml) was added *t*-butyldimethylsilyl chloride (0.582 g, 3.86 mmol) at 0°C. This reaction mixture was stirred at r.t. until disappearance of the starting product (2h). The reaction mixture was then quenched with NH₄Cl (28 ml) and extracted with Et₂O (15 ml, x2). The combined organic layers were washed with brine (28 ml) and dried over MgSO₄ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography column (pentane/Et₂O as eluent). The final product as a yellow oil (0.489 g, 77% yield).

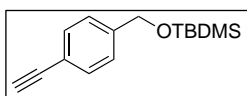
¹H NMR (300 MHz, CDCl₃): δ 0.13 (s, 6H), 0.90 (s, 9H), 3.30 (s, 1H), 4.91 (s, 2H), 7.21 (t, 1H, J= 7.53Hz), 7.38 (t, 1H, J= 7.61Hz), 7.46 (d, 1H, J=7.58Hz), 7.57 (d, 1H, J= 7.76Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 5.29, 25.98, 34.16, 63.12, 81.07, 82.00, 118.78, 125.78, 126.43, 129.00, 132.30, 143.86 ppm.

FTIR (ATR): ν (cm⁻¹)= 3306, 2955, 2929, 2857, 2100, 1076.

LCMS (ESI) : m/z calcd for C₁₅H₂₂OSi 246.42 found [M+NH₄]⁺ 263.950.

***tert*-butyl[(4-ethynylphenyl)methoxy]dimethylsilane (132d):**³⁰³



To a solution of commercial (4-ethynylphenyl)methanol (0.540 g, 4.09 mmol) and imidazole (0.416 g, 6.12 mmol) in anhydrous CH₂Cl₂ (28 ml) was added *t*-butyldimethylsilyl chloride (0.922 g, 6.11 mmol) at 0°C. This reaction mixture was stirred at r.t. until disappearance of the starting material (30 min), then quenched with NH₄Cl (28 ml), and extracted with Et₂O (25 ml, x2). The combined organic layers were washed with brine (28 ml) and dried over MgSO₄, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography column (PE/EA). The final product was obtained as an orange oil (0.910 g, 90% yield).

¹H NMR (300 MHz, CDCl₃): δ 0.09 (s, 3H), 0.10 (s, 3H), 0.94 (s, 9H), 3.04 (s, 1H), 4.73 (s, 2H), 7.26-7.30 (m, 2H), 7.45-7.48 (m, 2H) ppm.

³⁰²K. Shimizu, M. Takimoto, M. Mori, *Org. Lett.* **2003**, *5*, 2323-5. ³⁰³M. Taddei, S. Ferrini, L. Giannotti, M. Corsi, F. Manetti, G. Giannini, L. Versci, F. M. Milazzo, D. Alloatti, M. B. Guglielmi, M. Castorina, M. L. Cervoni, M. Barbarino, R. Federà, V. Carollo, C. Pisano, S. Armaroli, W. Cabri, *J. Med. Chem.* **2014**, *57*, 2258-74.

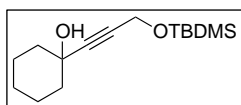
^{13}C NMR (75MHz, CDCl_3): δ 5.26, 25.93, 31.90, 64.60, 82.26, 83.77, 120.52, 125.85, 132.04, 142.36 ppm.

FTIR (ATR): ν (cm^{-1}) = 3300, 2954, 2930, 2857, 2109, 1089.

General procedure 2; coupling between protected propargyl alcohols and cyclohexanone (172a-d):³⁰⁴

To a solution of the protected propargyl alcohol (1 eq.) in dry THF was added *n*-BuLi (1.1 eq.) at -78°C over 5min. This mixture was stirred at this temperature for 2h. Cyclohexanone (1.1 eq.) was then added and the resulting mixture was stirred at -78°C for two more hours. The temperature was then allowed to warm to r.t. and the reaction mixture was quenched with saturated aqueous NH_4Cl . The aqueous phase was extracted with EtOAc (x3). The organic layers were combined and washed with brine, then dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (pentane/EA as eluent).

1-{3-[(*tert*-butyldimethylsilyloxy]prop-1-yn-1-yl)cyclohexan-1-ol (172a):³⁰⁵



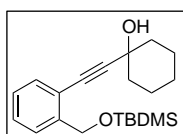
Upon the general procedure 2, this product was obtained from the reaction between **132a** (0.500 g, 2.94 mmol) and cyclohexanone (0.30 ml, 2.94 mmol) in anhydrous THF (2 ml) and in the presence of BuLi (2.5M in hexane, 1.17 ml, 2.94 mmol), as a colorless oil (0.620 g, 78% yield).

^1H NMR (300 MHz, CDCl_3): δ 0.09 (s, 6H), 0.87 (s, 9H), 1.67-1.73 (m, 6H), 1.83 (dt, 4H, $J = 6.14$ and 12.50 Hz), 4.30 (d, 1H, $J = 2.54$ Hz), 4.32 (s, 1H), 5.27 (d, 1H, $J = 2$ Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 5.06, 14.11, 24.98, 25.78, 27.01, 31.28, 51.76, 69.95, 80.73, 91.15 ppm.

LCMS (ESI) : m/z calcd for $\text{C}_{21}\text{H}_{32}\text{O}_2\text{Si}$ 344.56 found $[\text{M}+\text{K}]^+$ 382.750.

1-[2-(2-[(2,3,3-trimethylbutan-2-yl)oxy]methyl)phenyl]ethynyl]cyclohexan-1-ol (172b):



According to the general procedure 2, product **172b** was obtained by departing from **132b** (0.193g, 0.78 mmol) and in the presence of BuLi (2.5M in hexane, 0.31 ml, 0.78 mmol) and

³⁰⁴J. H. Rigby, S. B. Laurent, Z. Kamal, M. J. Heeg, *Org. Lett.* **2008**, *10*, 5609-12. ³⁰⁵Y.-M. Zhao, Y. Tam, Y.-J. Wang, Z. Li, J. sun, *Org. Lett.* **2012**, *14*, 1398-1401.

cyclohexanone (0.081 ml, 0.78 mmol) in dry THF (2 ml) as a yellow oil (0.191 g, 71% yield).

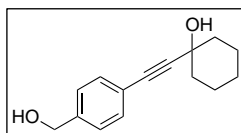
^1H NMR (300 MHz, CDCl_3): δ 0.11 (s, 6H), 0.95 (s, 9H), 1.60-1.78 (m, 8H), 2.01-2.05 (m, 2H), 2.15 (s, 1H), 4.89 (s, 2H), 7.18 (t, 1H, $J=7.51$ Hz), 7.35 (q, 2H, $J=7.75$ Hz), 7.54 (d, 1H, $J=7.77$ Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 5.32, 18.46, 23.60, 25.22, 25.97, 40.16, 63.40, 69.39, 81.82, 119.43, 125.57, 126.38, 128.46, 131.54, 143.21 ppm.

FTIR (ATR): ν (cm^{-1})=3342, 2929, 2856, 835, 756, 667.

LCMS (ESI): m/z calcd for $\text{C}_{21}\text{H}_{32}\text{O}_2\text{Si}$ 344.56 found $[\text{M}+\text{K}]^+$ 382.600.

1-{2-[4-(hydroxymethyl)phenyl]ethynyl}cyclohexan-1-ol (172c):



Upon the general procedure 2, this product was obtained from the reaction between **132c** (0.200g, 1.51 mmol) and cyclohexanone (0.15 ml, 1.51 mmol) in the presence of BuLi (2.5M in hexane, 1.21 ml, 3.03 mmol) in dry THF (2 ml) as a yellow solid (0.082 g, 23% yield).

M.p.: 93.0-94.7°C

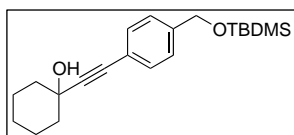
^1H NMR (300 MHz, CDCl_3): δ 1.58-1.76 (m, 8H), 1.98-2.04 (m, 2H), 4.68 (s, 2H), 7.29 (d, 2H, $J=8.01$ Hz), 7.40 (d, 2H, $J=8.16$ Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 23.42, 25.23, 40.07, 62.66, 69.15, 92.87, 107.17, 122.13, 126.72, 131.85, 140.97 ppm.

FTIR (ATR): ν (cm^{-1})= 3300, 2924, 1449, 1060, 800, 669.

LCMS (ESI) : m/z calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$ 230.30 found $[\text{M}+\text{H}]^+$ 231.050.

1-[2-(4-[(*tert*-butyldimethylsilyl)oxy]methyl)phenyl]ethynyl]cyclohexan-1-ol (172d):



According to the general procedure 2, compound **172d** was found from a reaction between **132d** (0.200 g, 0.81 mmol) and cyclohexanone (0.084 ml, 0.81 mmol) and in the presence of BuLi (2.5M in hexane, 0.32 ml, 0.81 mmol) in dry THF (1.30 ml) as a yellow solid (0.140 g, 50% yield).

^1H NMR (300 MHz, CDCl_3): δ 0.08 (d, 6H, $J=0.74$ Hz), 0.93 (d, 9H, $J=0.68$ Hz), 1.59-1.76 (m, 8H), 1.99-2.03 (m, 2H), 4.72 (s, 2H), 7.24 (d, 1H, $J=0.67$ Hz), 7.26 (s, 1H), 7.39 (d, 2H, $J=8.05$ Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 5.24, 18.41, 23.43, 25.24, 25.93, 40.11, 64.67, 69.14, 84.44, 92.36, 121.32, 125.85, 131.57, 141.71 ppm.

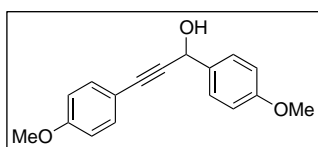
FTIR (ATR): ν (cm^{-1})= 3224, 2927, 2854, 1462, 1380, 1070, 833, 775.

LCMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{28}\text{O}_2\text{Si}$ 268.47 found $[\text{M}+\text{H}]^+$ 270.95.

General procedure 3; preparation of compounds 200:³⁰⁶

To a solution of terminal alkyne (1 eq) in dry THF was added dropwisely BuLi (2.5 M in hexane, 1 eq) at -78°C under argon. After being stirred at the same temperature for 1h, to the reaction mixture was added dropwisely a solution of aldehyde (1 equiv.) in dry THF at -78°C and the reaction was allowed to proceed over night at room temperature. The reaction mixture was then washed with saturated aqueous NH_4Cl and extracted with EtOAc (x2). The organic phase was separated and dried over MgSO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the propargyl alcohol and was purified by silica gel column chromatography using PE/EA as eluent.

1,3-bis (4-methoxyphenyl)prop-2-yn-1-ol (173a):³⁰⁶



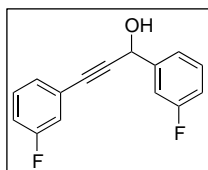
According to the general procedure 3, compound **173a** was obtained from a reaction between 4-ethynylanisole (0.500 g, 3.78 mmol) and *p*-anisaldehyde (0.515 g, 3.78 mmol) in the presence of BuLi (2.5M in hexane, 1.51 ml, 3.78 mmol) in dry THF (4 ml) as a yellow oil (0.673 g, 66% yield).

^1H NMR (300 MHz, CDCl_3): δ 3.47 (s, 1H), 3.81 (d, 6H, $J=3.39$ Hz), 5.62 (s, 1H), 6.83 (d, 2H, $J=8.95$ Hz), 6.92 (d, 2H, $J=8.82$ Hz), 7.40 (d, 2H, $J=8.94$ Hz), 7.53 (d, 2H, $J=8.87$ Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 55.30, 55.35, 64.76, 86.43, 87.62, 113.94, 133.98, 114.61, 128.17, 133.21, 133.26, 133.37, 159.67, 159.79 ppm.

FTIR (ATR): ν (cm^{-1})= 3363, 2933, 2835, 2223, 2191, 1604, 1460, 829, 763.

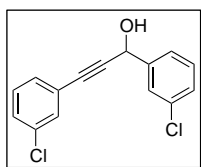
³⁰⁶M. Yoshida, M. Higuchi, K. Shishido, *Org. Lett.* **2009**, *11*, 4752-5.

1,3-bis(3-fluorophenyl)prop-2-yn-1-ol (173b):

Upon the general protocol 3, this product was obtained from the reaction between 1-ethynyl-3,fluoro-benzene (0.500 g, 4.16 mmol) and 3-fluorobenzaldehyde (0.517 g, 4.16 mmol) and in the presence of BuLi (2.5M in hexane, 1.66 ml, 4.16 mmol) in dry THF (4 ml) as an orange oil (0.879 g, 86% yield).

¹H NMR (300 MHz, CDCl₃): δ 2.51 (s, 1H), 5.67 (d, 1H, J= 6.03 Hz), 7.01-7.10 (m, 2H), 7.14-7.18 (m, 1H), 7.28 (dd, 1H, J= 0.44 and 2.34 Hz), 7.30-7.39 (m, 4H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 64.31, 85.80, 88.21, 115.50, 115.61, 118.33, 128.51, 133.60, 136.42, 162.73, 162.80 ppm.

1,3-bis (3-chlorophenyl)prop-2-yn-1-ol (173c):

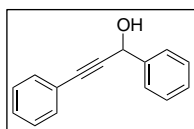
According to the general procedure 3, compound **173c** was found from the reaction between 3-chloro-1-ethynylbenzene (0.500 g, 3.66 mmol) and 3-chlorobenzaldehyde (0.514 g, 3.66 mmol) in the presence of BuLi (2.5M in hexane, 1.75 ml, 4.39 mmol) in dry THF (4 ml) as a white solid (0.670 g, 66% yield).

¹H NMR (300 MHz, CDCl₃): δ 2.43 (d, 1H, 5.87 Hz), 5.66 (d, 1H, J= 5.73 Hz), 7.24-7.31 (m, 5H), 7.45-7.49 (m, 2H), 7.59 (dd, 1H, J= 0.68 and 1.52 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 64.36, 85.62, 89.20, 123.80, 124.78, 126.86, 128.68, 129.14, 129.62, 129.92, 130.00, 131.66, 134.25, 134.63, 142.22 ppm.

General procedure 4; Sonogashira cross-coupling reaction: ³⁰⁶

To a solution of halide (1 eq) in anhydrous Et₃N were added successively the alkyne (1.1 eq), PdCl₂(PPh₃)₂ (0.01 eq) and CuI (0.03 eq) at r.t. and under argon pressure. Stirring continued until disappearance of the starting material at the same temperature, then the reaction mixture was filtered on celite and washed with Et₂O and filtrate was the concentrated *in vacuo*. The crude product was purified by column chromatography (heptane/EtOAc).

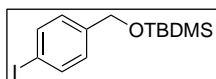
1,3-diphenylprop-2-yn-1-ol (174a):³⁰⁶

Upon the general procedure 4, iodobenzene (2.73 g, 13.4 mmol) and 1-phenyl-2-propyn-1-ol (0.500 g, 3.80 mmol) in the presence of PdCl₂(PPh₃)₂ (0.095 g, 0.13 mmol) and CuI (0.077 g, 0.40 mmol) in dry Et₃N (20 ml) gave product **174a** as a brown oil (0.867 g, Qtv).

¹H NMR (300 MHz, CDCl₃): δ 2.37 (s, 1H), 5.70 (s, 1H), 7.31-7.51 (m, 8H), 7.63 (d, 2H, J= 7.27 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 65.14, 86.70, 88.78, 122.45, 126.78, 128.34, 128.71, 131.79, 137.51, 140.69 ppm.

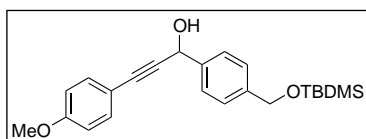
FTIR (ATR): ν (cm⁻¹)= 3352, 1750, 1440, 1258, 756, 692.

1-(tert-butyl-dimethyl-silyloxymethyl)-4-iodobenzen:³⁰⁷

To a solution of 4-iodobenzyl alcohol (1.00 g, 4.27 mmol) in dry THF (11 ml) were added imidazole (0.436 g, 6.40 mmol) and *tert*-butyldimethylsilyl chloride (0.96 g, 6.40 mmol) at 0°C. The resulting mixture was slowly warmed to room temperature over 2h and poured into a mixture of 1M HCl (11 ml) and Et₂O (11 ml). The organic layer was separated, and the aqueous layer was extracted with ether (7ml, x3). The combined organic layers were washed with brine (11 ml), dried over MgSO₄, filtered and concentrated under vacuum. The crude residue was purified on silica gel (eluent PE/EtOAc) to give the protected alcohol as a colorless oil (1.252 g, 84% yield).

¹H NMR (300 MHz, CDCl₃): δ 0.09 (s, 6H), 0.93 (s, 9H), 4.67 (s, 2H), 7.07 (d, 2H, J= 8.53 Hz), 7.64 (d, 2H, J= 8.29 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 5.25, 25.93, 31.90, 64.39, 92.04, 128.00, 137.24, 141.17 ppm.

1-(4-[[*tert*-butyldimethylsilyloxy]methyl]phenyl)-3-(4-methoxyphenyl)prop-2-yn-1-ol (174b):

According to the general procedure 4, compound **202** was found by departing from 1-(*tert*-butyl-dimethyl-silyloxymethyl)-4-iodobenzene³⁰⁷ (0.500 g, 1.43 mmol) and

³⁰⁷E. Yashima, S. Huang, T. Matsushima, Y. Okamoto, *Macromolecules* **1995**, 28, 4184-93.

the commercial available 1-(4-methoxyphenyl)prop-2-yn-1-ol (0.254 g, 1.57 mmol) in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.010 g, 0.014 mmol) and CuI (0.008 g, 0.043 mmol) in dry Et_3N (4 ml) as a brown oil (0.474 g, 78% yield).

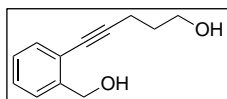
$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 0.09 (d, 6H, $J= 1.02$ Hz), 0.94 (d, 9H, $J= 1$ Hz), 3.46 (br, 1H), 3.82 (d, 3H, $J= 0.88$ Hz), 4.73 (s, 2H), 5.26 (s, 1H), 6.92 (d, 2H, $J= 8.50$ Hz), 7.42-7.52 (m, 4H), 8.03 (dd, 2H, $J= 8.58$ and 23.17 Hz) ppm.

$^{13}\text{C NMR}$ (75MHz, CDCl_3): δ 5.24, 25.94, 29.72, 55.34, 55.67, 64.65, 73.10, 73.89, 113.62, 113.88, 125.87, 128.94, 131.60, 131.69, 142.02, 159.75 ppm.

FTIR (ATR): ν (cm^{-1}) 3253, 2927, 2856, 1608, 1510, 1462, 1253, 835, 777.

LCMS (ESI): m/z calcd for $\text{C}_{23}\text{H}_{30}\text{O}_3\text{Si}$ 382.57 found $[\text{M}+\text{K}]^+$ 419.250.

5-[2-(hydroxymethyl)phenyl]pent-4-yn-1-ol (174c):³⁰⁸



Upon the Sonogashira general procedure 4, this product was found from commercial available starting materials 2-iodobenzyl alcohol (1.00 g, 4.27 mmol) and 4-pentyn-1-ol (0.400 g, 4.7 mmol) in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.030 g, 0.04 mmol), CuI (0.016 g, 0.09 mmol) and Et_3N (1.2 ml, 8.54 mmol) in dry THF (12 ml) as a yellow oil (0.532 g, 65% yield).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.81 (quintet, 2H, $J= 6.46$ Hz), 2.03 (d, 2H), 2.54 (t, 2H, $J= 6.83$ Hz), 3.76 (t, 2H, $J= 6.03$ Hz), 4.74 (s, 2H), 7.17-7.28 (m, 2H), 7.36-7.39 (m, 2H) ppm.

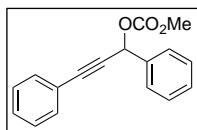
$^{13}\text{C NMR}$ (75MHz, CDCl_3): δ 21.03, 30.94, 31.15, 61.39, 63.88, 78.69, 94.43, 122.14, 127.38, 127.43, 128.02, 132.11, 142.36 ppm.

FTIR (ATR): ν (cm^{-1})= 3336, 2937, 2882, 1718, 1245, 1044, 759.

Preparation of propargyl carbonates:³⁰⁶

General procedure 5: To a stirred solution of propargyl alcohols (1 equiv.) in dry CH_2Cl_2 were added pyridine (3 equiv.) and methylchloroformate (1.2 equiv.) at 0°C , and stirring was continued for 1h at the same temperature. The reaction mixture was diluted with aqueous NH_4Cl and extracted with EtOAc . The combined extracts were washed with brine. The residue was purified on silica gel (heptane/ EtOAc as eluent).

³⁰⁸M. C. B. Jaimes, F. Rominger, M. M. Pereira, R. M. B. Carrilho, S. A. C. Carabineiro, A. S. K. Hashmi, *Chem. Commun.* **2014**, 50, 4937-40.

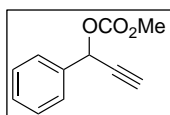
1,3-diphenylprop-2-yn-1-yl methyl carbonate (336a):³⁰⁶

Upon the general procedure 5, this compound was obtained from **174a** (0.841 g, 4.03 mmol) in the presence of pyridine (0.970 ml, 12.1 mmol) and methyl chloroformate (0.370 ml, 4.79 mmol) in dry CH_2Cl_2 (22 ml) as a pale yellow oil (2.625 g, Qtv).

^1H NMR (300 MHz, CDCl_3): δ 3.83 (s, 3H), 6.54 (s, 1H), 7.31-7.36 (m, 3H), 7.41 (dd, 3H, $J = 0.97$ and 6.87 Hz), 7.47-7.51 (m, 2H), 7.61-7.65 (m, 2H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 55.10, 70.26, 84.87, 88.08, 121.99, 127.84, 128.30, 128.74, 128.91, 129.24, 131.93, 136.58, 154.95 ppm.

FTIR (ATR): ν (cm^{-1}) = 2954, 2227, 1745, 1440, 1246, 754, 690.

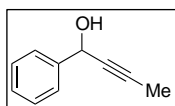
Methyl 1-phenylprop-2-yn-1-yl carbonate (336b):³⁰⁶

According to the general procedure 5, this product was found from 1-phenyl-2-propyn-1-ol (1.00 g, 7.56 mmol) and methylchloroformate (0.70 ml, 9.07 mmol) in the presence of pyridine (1.83 ml, 22.70 mmol) in dry CH_2Cl_2 (33 ml) as a yellow oil (1.302 g, 90% yield).

^1H NMR (300 MHz, CDCl_3): δ 2.73 (d, 1H, $J = 2.28$ Hz), 3.81 (s, 3H), 6.30 (d, 1H, $J = 2.28$ Hz), 7.38-7.44 (m, 3H), 7.55-7.58 (m, 2H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 55.15, 69.34, 76.49, 79.61, 127.72, 128.76, 129.37, 135.85, 154.84 ppm.

FTIR (ATR): ν (cm^{-1}) = 3286, 2958, 1745, 1441, 1252, 788, 695.

1-phenylbut-2-yn-1-ol:³⁰⁹

To a stirred solution of benzaldehyde (1.00 g, 9.42 mmol) in dry diethyl ether (15 ml) was added 1-propynylmagnesium bromide (0.5M in THF, 23.54 ml, 11.77 mmol) at 0°C . The resulting solution was allowed to warm to room temperature and was kept overnight whilst stirring at the same temperature. After treatment with saturated aqueous NH_4Cl and extraction with Et_2O , the organic layers were combined, washed with brine, and dried with MgSO_4 , and the solvents were evaporated in vacuo. Filtration through a small pad of silica gel (EA/heptane) gave the final product

³⁰⁹V. Maraval, C. Duhayon, Y. Coppel, R. Chauvin, *Eur. J. Org. Chem.* **2008**, (30), 5144-56.

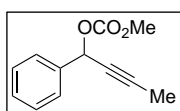
as a yellow oil (1.184 g, 88% yield).

^1H NMR (300 MHz, CDCl_3): δ 1.91 (d, 3H, J = 2.21 Hz), 2.12 (br, 1H), 5.42 (d, 1H, J = 2.07 Hz), 7.36 (dt, 3H, J = 6.38 and 12.28 Hz), 7.53-7.56 (m, 2H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 3.75, 64.85, 79.18, 83.14, 126.59, 128.26, 128.58, 141.23 ppm.

FTIR (ATR): ν (cm^{-1})= 3342, 3030, 2918, 1635, 1450, 1271, 727, 696.

Methyl 1-phenylbut-2-yn-1-yl carbonate (336c):



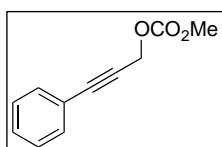
Upon the general procedure 5, this compounds was obtained from a reaction between 1-phenylbut-2-yn-1-ol (1.14 g, 7.82 mmol) and methylchloroformate (0.720 ml, 9.38 mmol) and pyridine (1.89 ml, 23.46 mmol) in anhydrous dichloromethane (42 ml) as a pale yellow oil (1.498 g, 94% yield).

^1H NMR (300 MHz, CDCl_3): δ 1.91 (d, 3H, J = 2.24 Hz), 3.79 (s, 3H), 6.25 (q, 1H, J = 2.20 Hz), 7.36-7.39 (m, 3H), 7.53 (dd, 2H, J = 1.88 and 7.46 Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 3.83, 54.98, 70.18, 75.36, 85.01, 127.66, 128.62, 129.03, 136.98, 154.99 ppm.

FTIR (ATR): ν (cm^{-1})= 2956, 2241, 2206, 1745, 1645, 1440, 1247, 759, 694.

Methyl 3-phenylprop-2-yn-1-yl carbonate (336d):³¹⁰



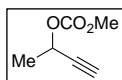
According the general procedure 5, this compound was obtained from 3-phenyl-2-propyn-1-ol (1.00 g, 7.56 mmol), methylchloroformate (0.700 ml, 9.07 mmol) and pyridine (1.83 ml, 22.7 mmol) in dry dichloromethane (40 ml) as a white solid (1.239 g, 86% yield).

^1H NMR (300 MHz, CDCl_3): δ 3.83 (s, 3H), 4.96 (s, 2H), 7.31 (dt, 3H, J = 1.03 and 5.19 Hz), 7.44-7.47 (m, 2H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 55.16, 56.24, 82.28, 87.19, 122.00, 128.32, 128.88, 131.91, 155.30 ppm.

FTIR (ATR): ν (cm^{-1})= 2956, 2924, 2856, 2187, 1751, 1660, 1442, 1375, 756, 690.

³¹⁰C. K. Hazra, M. Oestreich, *Org. Lett.* **2012**, *14*, 4010-3.

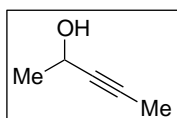
But-3-yn-2-yl methyl carbonate (336e):³¹¹

Upon the general procedure 5 this product was obtained from 3-butyn-2-ol (1.00 g, 14.1 mmol) and methylchloroformate (1.30 ml, 16.92 mmol) and pyridine (3.34 ml, 42.3 mmol) in dry CH_2Cl_2 (75 ml) as a colorless oil (0.914 g, 50% yield).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.54 (d, 3H, $J = 6.74$ Hz), 2.50 (dd, 1H, $J = 0.32$ and 2.13 Hz), 3.79 (s, 3H), 5.28 (qd, 1H, $J = 2.12$ and 6.74 Hz) ppm.

$^{13}\text{C NMR}$ (75MHz, CDCl_3): δ 21.19, 54.93, 64, 73.77, 81.37, 154.78 ppm.

FTIR (ATR): ν (cm^{-1})= 3292, 1745, 1442, 1251, 1024.

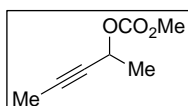
Pent-3-yn-2-ol:³¹²

To a solution of 1-propynylmagnesium bromide (0.5 M in THF, 60.0 ml, 30 mmol) was added slowly a solution of acetaldehyde (2.51 ml, 45.0 mmol) in anhydrous diethyl ether (4 ml) at 0°C . Then the reaction was allowed to warm to room temperature and stirred over 16h, then cooled to 10°C and ice-cold saturated NH_4Cl was added. The organic layer was separated and washed with brine, dried over MgSO_4 and concentrated in vacuo. The crude was purified by fraction distillation (20 mm Hg, 55°C) to afford final product as colorless oil (2.027 g, 53% yield).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.39 (d, 3H, $J = 0.42$ Hz), 1.82 (d, 3H, $J = 2.11$ Hz), 4.48 (br, 1H), 4.78 (s, 1H) ppm.

$^{13}\text{C NMR}$ (75MHz, CDCl_3): δ 3.48, 24.64, 58.56, 80.13, 81.40 ppm.

FTIR (ATR): ν (cm^{-1})= 3278, 3000, 1086.

Methyl pent-3-yn-2-yl carbonate (336f):³¹³

According to the general procedure 5, product **336f** was found from pent-3-yn-1-ol (1.723 g, 20.48 mmol), methylchloroformate (1.90 ml, 24.57 mmol) and pyridine (5 ml, 62.0 mmol) in dry dichloromethane (126 ml) as a colorless oil (1.455 g, 50% yield).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 3.82 (s, 3H), 6.53 (s, 1H), 7.32 (dd, 3H, $J = 1.55$ and 5.75 Hz), 7.41 (dd, 3H, $J = 0.95$ and 6.82 Hz), 7.48 (dd, 2H, $J = 2.46$ and 7.22 Hz), 7.62 (dd, 2H, $J = 1.84$ and 7.41 Hz) ppm.

³¹¹J. -R. Labrosse, P. Lhoste, D. Sinou, *J. Org. Chem.* **2001**, *66*, 6634-42. ³¹²Z. Li, B. T. Parr, H. M. L. Davies, *J. Am. Chem. Soc.* **2012**, *134*, 10942-6.

³¹³T. Minami, M. Yuhara, H. Watanabe, J. Tsuji, *J. Organometallic Chem.* **1987**, *334*, 225-42.

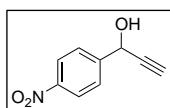
^{13}C NMR (75MHz, CDCl_3): δ 55.11, 70.26, 84.85, 88.08, 121.97, 127.84, 128.30, 128.74, 128.92, 129.25, 136.55, 154.95 ppm.

FTIR (ATR): ν (cm^{-1})= 2228, 1748, 1440, 1257.

General procedure 6; preparation of propargylic alcohols: ³¹⁴

To a solution of aldehyde (1 eq) in anhydrous THF was added a solution of Ethynylmagnesium bromide (0.5M in THF, 1.3 eq) at 0°C. The mixture had been stirred at room temperature until disappearance the starting aldehyde (monitored by TLC), then a saturated solution of NH_4Cl was added to the solution and the aqueous phase was extracted with EA (x3) and the organic layers were washed with water and brine and then dried over Na_2SO_4 . The resulting crude product was purified on silica gel (heptane/EtOAc as eluent).

1-(4-nitrophenyl)prop-2-yn-1-ol (171a): ³¹⁵



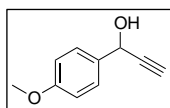
Upon the general procedure 6, the reaction between 4-nitrobenzaldehyde (1.00 g, 6.61 mmol) and ethynylmagnesium bromide (0.5M in THF, 16 ml, 8.0 mmol) in dry THF (13 ml) gave product **171a** as an orange solid (0.478 g, 40% yield).

^1H NMR (300 MHz, CDCl_3): δ 2.64 (d, 1H, J = 5.8 Hz), 2.71 (d, 1H, J = 2.3 Hz), 5.55 (dd, 1H, J = 5.6 Hz, 2.3 Hz), 7.71 (d, 2H, J = 8.7 Hz), 8.21 (d, 2H, J = 8.7 Hz) ppm.

^{13}C NMR (75 MHz, CDCl_3): δ 63.34, 75.97, 82.33, 123.84, 127.38, 146.73, 147.87 ppm.

FTIR (ATR): ν (cm^{-1}) 3261, 3001, 2956, 2920, 1516, 1342, 1261, 800, 702.

1-(4-methoxyphenyl)prop-2-yn-1-ol (171b): ³¹⁴

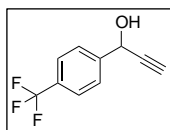


Upon the general procedure 6, this product was prepared from a reaction between the commercial available *p*-anisaldehyde (2.00 g, 14.68 mmol) and ethynylmagnesium bromide (0.5M in THF, 38.2 ml, 19.1 mmol) in dry THF (30 ml) as a yellow oil (1.865 g, 78% yield).

^1H NMR (300 MHz, CDCl_3): δ 2.63 (s, 1H), 3.78 (s, 3H), 6.88 (d, 2H, J = 8.7 Hz), 7.44 (d, 2H, J = 8.7 Hz) ppm,

^{13}C NMR (75 MHz, CDCl_3): δ 55.34, 63.99, 74.59, 83.78, 114.02, 128.07, 132.46, 159.77 ppm.

³¹⁴S. Chassaing, M. Kueny-Stotz, G. Isorez, R. Brouillard, *Eur. J. Org. Chem.* **2007**, (15), 2438-48. ³¹⁵H.-S. M. Siah, M. Kaur, N. Iqbal, A. Fiksdahl, *Eur. J. Org. Chem.* **2014**, 2014, 1727-40.

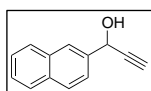
1-[4-(trifluoromethyl)phenyl]prop-2-yn-1-ol (171c): ³¹⁶

Upon the general procedure 6, this product was obtained from a reaction between 4-(trifluoromethyl)benzaldehyde (2.00 g, 11.48 mmol) and ethynylmagnesium bromide (0.5M in THF, 27.54 ml, 13.77 mmol) in dry THF (23 ml) as an orange oil (1.846 g, 80% yield).

¹H NMR (300 MHz, CDCl₃): δ 2.68 (d, 1H, J= 2.2 Hz), 5.49 (dd, 1H, J= 5.6 Hz, 2.3 Hz), 7.59-7.66 (m, 4H) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 63.69, 75.49, 122.19, 125.58, 125.63, 130.45, 130.88, 143.69 ppm.

FTIR (ATR): ν (cm⁻¹)= 3400, 3305, 2930, 2887, 1620, 1413, 1321, 1109, 1064, 1016, 846, 765, 642.

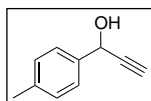
1-(naphthalene-2-yl)prop-2-yn-1-ol (171d): ³¹⁶

Upon the general procedure 6, 2-naphthaldehyde (1.00 g, 6.40 mmol) and ethynylmagnesium bromide (0.5M in THF, 15.36 ml, 7.68 mmol) in dry THF (13 ml) gave this propargylic alcohol as a yellow solid (0.874g, 74% yield).

¹H NMR (300 MHz, CDCl₃): δ 2.51 (d, 1H, J= 6.2 Hz), 2.71 (d, 1H, J= 2.3 Hz), 5.61 (dd, 1H, J= 6.7 Hz, 2.3 Hz), 7.49 (dd, 2H, J= 6.3 Hz, 3.3 Hz), 7.63 (dd, 1H, J= 8.8 Hz, 1.8 Hz), 7.84 (tt, 3H, J= 7.0 Hz, 2.7 Hz), 7.97 (s, 1H) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 64.59, 75.17, 83.25, 124.48, 125.53, 126-40-126.45 (d), 127.74, 128.26, 128.67, 133.17, 133.34, 137.36 ppm.

FTIR (ATR): ν (cm⁻¹)= 3338, 3277, 2987, 2900, 1640, 1510, 1020, 823, 740, 644.

1-(4-methylphenyl)prop-2-yn-1-ol (171e): ³¹⁷

According to the general procedure 6, this propargylic alcohol was obtained from a reaction between the commercial available *p*-toulaldehyde (0.700 g, 5.82 mmol) and ethynylmagnesium bromide (0.5M in THF, 15.12 ml, 7.56 mmol) in dry THF (12 ml) as a yellow oil (0.832g, 97% yield).

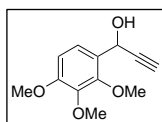
¹H NMR (300 MHz, CDCl₃): δ 2.01 (s, 1H), 2.34 (s, 3H), 2.63 (d, 1H, J= 2.2 Hz), 5.4 (dd, 1H, J= 6.2 Hz, 2.3 Hz), 7.17 (d, 2H, J= 8.2 Hz), 7.42 (d, 2H, J= 8.2 Hz) ppm.

³¹⁶A. S. El Douhaibi, Z. M. A. Judeh, H. Basri, Z. Moussa, M. Messali, G. Qi, *Synth. Commun.* **2011**, *41*, 533-40. ³¹⁷M. Chiarucci, E. Matteucci, G. Cera, G. Fabrizi, M. Bandini, *Chem. Asian. J.* **2013**, *8*, 1176-9.

^{13}C NMR (75 MHz, CDCl_3): δ 21.21, 64.26, 74.67, 83.72, 126.62, 129.37, 137.24, 138.43 ppm.

FTIR (ATR): ν (cm^{-1})= 3381, 3001, 2918, 1653, 1436, 1315, 1012, 950, 524.

1-(2,3,4-trimethoxyphenyl)prop-2-yn-1-ol (171f): ³¹⁴



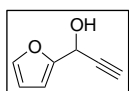
According to the general procedure 6, this propargylic alcohol was found from a reaction between 2,3,4-trimethylbenzaldehyde (1.00 g, 5.1 mmol) and ethynylmagnesium bromide (0.5M in THF, 15.26 ml, 7.63 mmol) in dry THF (10 ml) as a yellow oil (0.649 g, 57% yield).

^1H NMR (300 MHz, CDCl_3): δ 2.61 (d, 1H, J = 2.16 Hz), 2.99 (br, 1H), 3.86 (s, 6H), 4.00 (s, 3H), 5.53 (s, 1H), 6.65 (d, 1H, J = 8.60 Hz), 7.19 (d, 1H, J = 8.59 Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 56.05, 60.77, 61.04, 61.36, 73.84, 84.03, 107.07, 122.18, 126.51, 142.14, 151.44, 154.25 ppm.

FTIR (ATR): ν (cm^{-1}) 3419, 3280, 2941, 2837, 1417, 1276, 808, 650.

1-(furan-2-yl)prop-2-yn-1-ol (171g): ³¹⁸



Upon the general procedure 6, the reaction between the commercial available 2-fluraldehyde (1.00 g, 10.40 mmol) and ethynylmagnesium bromide (0.5M in THF, 31.2 ml, 15.6 mmol) in dry THF (21 ml) gave this propargylic alcohol as an orange oil (0.978g, 76% yield).

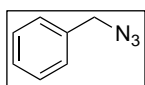
^1H NMR (300 MHz, CDCl_3): δ 1.24 (td, 1H, J = 7.15, 1.08 Hz), 2.02 (d, 1H, J = 1.08 Hz), 2.61 (dd, 1H, J = 2.3, 1.07 Hz), 2.77 (s, 1H), 4.10 (qd, 1H, J = 7.15, 1 Hz), 5.45 (s, 1H), 6.34-6.36 (m, 1H), 6.45-6.47 (m, 1H), 7.40 (dt, 1H, J = 1.8, 0.96 Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 57.87, 74.14, 81.06, 108.04, 110.48, 143.16, 152.40 ppm.

FTIR (ATR): ν (cm^{-1})= 3387, 3290, 1625, 1143, 1004.

Preparation of azides:

Benzylazide (77): ³¹⁹



To a mixture of benzyl bromide (4.27g, 25.0 mmol) and sodium iodide (7.495g, 50 mmol) in acetonitrile (42 ml) was added sodium azide (5.688g, 87.5 mmol). This mixture was

³¹⁸V. Singh, V. Singh, *Synth. Commun.* **2010**, *40*, 1280-91. ³¹⁹A. W. Gann, J. W. Amoroso, V. J. Einck, W. P. Rice, J. J. Chambers, N. A. Schnarr, *Org. Lett.* **2014**, *16*, 2003-5.

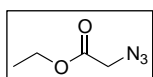
heated at 60°C and stirring continued over night, then the solvent was evaporated in vacuo and the residue was diluted in CH₂Cl₂ and washed two times with a sat. solution of NaCl and also a sat. solution of Na₂SO₃ (10%). The organic layers were combined and dried over Na₂SO₄. The solvent was evaporated under reduced pressure to afford benzylazide as a pale yellow liquid. No further purification was done on the crude. (3.06 g, 91% yield).

¹H NMR (300MHz, CDCl₃): δ 4.33 (s, 2H), 7.24-7.41 (m, 5H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 54.84, 128.25, 128.34, 128.87, 135.40 ppm.

FTIR (ATR): ν (cm⁻¹)= 3042, 2986, 2869, 2093, 1633, 1581, 887, 693.

Ethyl 2-azidoacetate (175): ³¹⁹



To a solution of ethyl bromoacetate (2.00 g, 12 mmol) in acetone (12 ml) was added at 0°C, a solution of sodium azide (2.730 g, 42 mmol) in water (12 ml) under vigorous agitation. Then this reaction mixture was warmed to room temperature and heated at 60°C over night, then the aqueous phase was washed with CH₂Cl₂ (14, x3). The organic layers were combined and washed with a solution (10%) of sodium bicarbonate (20 ml) and water (20 ml). Then the organic layer was dried on MgSO₄ and the solvent was evaporated in vacuo to afford ethyl 2-azidoacetate as a pale yellow liquid. No further purification was done on the crude (2.077 g, Qtv).

¹H NMR (300MHz, CDCl₃): δ 1.28 (t, 3H, J= 7.1Hz), 3.83 (s, 3H), 4.22 (q, 2H, J= 7.2Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.12, 50.36, 61.86, 168.28 ppm.

FTIR (ATR): ν (cm⁻¹) 2992, 2866, 2100, 1739, 1433, 1382, 1100, 1043.

3-azidopropan-1-ol (176): ³¹⁹

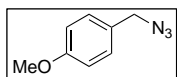


To a solution of sodium azide (11.63 g, 179 mmol) in water (70 mL) was added portionwise chloropropanol (4,23 g, 44,76 mmol). The mixture was refluxed for 16h then allowed to reach to rt and extracted with CH₂Cl₂ (70 ml, x3). The combined organic layers were dried over Na₂SO₄, filtered and the solvent rotary evaporated to afford azide as a yellow liquid. (4.512 g, 99% yield).

¹H NMR (300MHz, CDCl₃): δ 1.77 (m, 2H, J= 6.3Hz), 2.13 (b, 1H), 3.41 (t, 2H, J= 6.6Hz), 3.7 (t, 2H, J= 6Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 31.44, 48.42, 59.68 ppm.

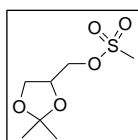
FTIR (ATR): ν (cm⁻¹) 3468, 2988, 2089, 1446, 1297, 678.

1-(azidomethyl)-4-methoxybenzene (177): ³²⁰

To a solution of 4-methoxybenzyl chloride (2.39 g, 15.26 mmol) in acetone (15 ml) was added slowly a solution of sodium azide (2.48 g, 38.15 mmol) in water (15 ml). This mixture was stirred at 60°C over night, then the resulting solution was extracted with DCM (x3). The organic phase was then washed with a 10% solution of sodium bicarbonate and water, then dried over MgSO₄ and filtered and concentrated in vacuo to afford the expected azide as a colorless liquid. (2.017 g, 81% yield).

¹H NMR (300 MHz, CDCl₃): δ 3.80 (s, 3H), 4.25 (s, 2H), 6.89 (d, 2H, J= 8.7 Hz), 7.23 (d, 2H, J= 8.3 Hz) ppm.

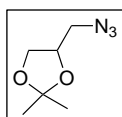
¹³C NMR (75MHz, CDCl₃): δ 54.42, 55.30, 114.23, 127.44, 129.79, 159.67 ppm.

Mesylated solketal (178a and b): ³²¹

To a solution of solketal (1.00 g, 7.56 mmol) in dichloromethane (20 ml) was added methane sulfonyl chloride (1.71 ml, 21.7 mmol) and triethylamine (13.28 ml, 95.2 mmol) at 0°C. After 2.5h the solution was diluted with 5 volume of DCM, washed twice with brine (50 ml), dried over MgSO₄. The solvent was removed under vacuum and the product was obtained as a dark red liquid, no further purification was done on the crude. (2.269 g, Qtv)

¹H NMR (300MHz, CDCl₃): δ 1.32 (s, 3H), 1.39 (s, 3H), 3.02 (s, 3H), 3.78 (dd, 1H, J= 8.6Hz, 5.4Hz), 4.06 (dd, 1H, J= 8.7Hz, 6.5Hz), 4.18 (d, 2H, J= 5Hz), 4.34 (m, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.19, 26.69, 37.67, 65.81, 69.26, 73.24, 110.25 ppm.

4-azidomethyl-2,2-dimethyl-1,3-dioxalane (179a and b): ³²²

Mesylated solketal (2,078 g, 9.88 mmol) was dissolved in dimethylformamide (3 mL), followed by the addition of sodium azide (0.770 g, 11.85 mmol) in water (3mL) and the resulting mixture was heated at 110°C until disappearance of the starting product. The reaction mixture was then cooled to rt, and was quenched with brine (3 ml), and the solution was extracted with Et₂O (3, x5), after which the extracts were combined and concentrated. The resulting organic solution

³²⁰S. Bai, S. Li, J. Xu, X. Peng, K. Sai, W. Chu, Z. Tu, C. Zeng, R. H. Mach, *J. Med. Chem.* **2014**, *57*, 4239-51. ³²¹H. S. Kim, D. Barak, T. K. Harden, J. L. Boyer, K. A. Jacobson, *J. Med. Chem.* **2001**, *44*, 3092-3108. ³²²F. S. Gibson, M. S. Park, H. Rapoport, *J. Org. Chem.* **1994**, *59*, 7503-7.

was washed with water (2ml, x2), dried and then evaporated. The resulting crude was purified by flash chromatography column which gave the expected azide as a colorless liquid. (1.131 g, 99% yield).

¹H NMR (300 MHz, CDCl₃) : δ 1,34 (s, 3H), 1.44 (s, 3H), 3,28 (dd, 1H, J= 14 Hz, 5.1 Hz), 3.38 (dd, 1H, J= 14 Hz, 5.2 Hz), 3.75 (dd, 1H, J= 8.5 Hz, 5.8 Hz), 4.03 (dd, 1H, J= 8.5 Hz, 6.4 Hz), 4.25 (qd, 1H, J= 5.8 Hz) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 22.6, 25.25, 26.63, 52.85, 65.86, 66.62, 74.59, 109.97 ppm.

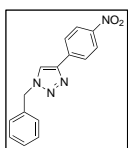
FTIR (ATR): ν (cm⁻¹) 840.81, 969.05, 1052.94, 1077.05, 1156.12, 1218.79, 1267.97, 1375.96, 2099.14.

Synthesis of triazolic derivatives from terminal alkynes:

- General procedure 7: preparation of triazoles:

A-21+CuI (0.04 mmol) was suspended in dichloromethane (2 ml). To this mixture were added alkyne (0.5 mmol) and azide (0.55 mmol) at room temperature, and this reaction mixture was stirred at the same temperature for 16 hours, then the mixture was filtered and the filtrate was evaporated in vacuo to afford the corresponding triazole. The final obtained product was enough pure and no further purification was done.

1-benzyl-4-(4-nitrophenyl)-1H-1,2,3-triazole (180): ³²³



Upon the general procedure 7, the reaction between 1-ethynyl-4-nitrobenzene (**132a**) (0.074 g, 0.50 mmol), A-21.CuI (0.033 g, 0.04 mmol) and benzylazide (**77**) (0.073 g, 0.55 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a yellow solid. (0.131g, 93% yield).

M.p.: 166.1-168.3°C

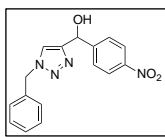
¹H NMR (300 MHz, CDCl₃): δ 5.58 (s, 2H), 7.29-7.34 (m, 2H), 7.36-7.40 (m, 3H), 7.78 (s, 1H), 7.95 (d, 2H, J= 8.8 Hz), 8.24 (d, 2H, J= 8.9 Hz) ppm.

¹³C NMR (75 MHz, CDCl₃): δ 54.51, 121.00, 124.28, 126.15, 128.22, 129.08, 129.32, 134.19, 136.82, 146.04, 147.33 ppm.

FTIR (ATR): ν (cm⁻¹) 2920, 2852, 1602, 1506, 1456, 1330, 1228, 1107, 866, 777.

LCMS (ESI): ELSD 100%, R_t= 5.38 min, m/z calcd for C₁₅H₁₂N₄O₂ 280.28 found [M+H]⁺ 281.05.

³²³R. B. Nasir Baig, R. S. Varma, *Green Chem.* **2013**, *15*, 1839-43.

(1-benzyl-1H-1, 2, 3-triazol-4-yl)(4-nitrophenyl)methanol (210):

According to the general procedure 7, This triazole was obtained from a reaction between 1-(4-nitrophenyl)prop-2-yn-1-ol (**171a**) (0.089 g, 0.50 mmol) and benzylazide (**77**) (0.073 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a dark orange solid (0.140g, 90% yield).

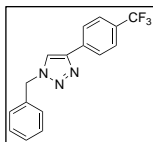
M.p.: 138.1-139.2°C

¹H NMR (300 MHz, CDCl₃): δ 5.45 (s, 2H), 5.61 (s, 1H), 6.17 (br, 1H), 7.33-7.41 (m, 5H), 7.60-7.67 (m, 2H), 8.17-8.24 (m, 2H), 8.22 (d, 1H, J= 4.05Hz), 8.34 (d, 0.5H, J= 8.62Hz), 8.61 (d, 0.5H, J= 8.64Hz) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 54.67, 71.95, 123.45, 123.83, 128.32, 128.46, 128.71, 129.17, 129.38, 129.45, 131.67, 133.35, 141.05, 147.71, 150.28 ppm.

FTIR (ATR): ν (cm⁻¹) 3220, 3180, 2976, 2900, 1506, 1338, 1224, 1055, 729, 694.

LCMS (ESI): ELSD 100%, R_t= 4.72 min, *m/z* calcd for C₁₆H₁₄N₄O₃ 310.11 found [M+H]⁺ 311.05.

1-benzyl-4-[4-(trifluoromethyl)phenyl]-1H-1,2,3-triazole (185):³²⁴

Upon the general procedure 7, the commercial available 4-ethynyl- α,α,α -trifluorotoluene (0.085 g, 0.50 mmol), benzylazide (0.073 g, 0.55 mmol) and A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a white solid (0.147 g, 97% yield).

M.p.: 135.6-137.1°C

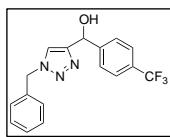
¹H NMR (300MHz, CDCl₃): δ 5.56 (d, 2H, J= 1.32Hz), 7.34 (m, 5H), 7.62 (d, 2H, J= 7.49), 7.76 (s, 1H), 7.89 (d, 2H, J= 7.67Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 54.35, 120.39, 122.32, 125.72, 125.77, 125.82, 125.92, 128.12, 128.94, 129.24, 129.73, 130.16, 134.04, 134.44 ppm.

FTIR (ATR): ν (cm⁻¹) 3021, 2918, 2852, 1458, 1327, 1226, 1153, 1105, 1062, 975, 844, 825, 700.

LCMS (ESI): ELSD 100%, R_t= 5.85 min, *m/z* calcd for C₁₆H₁₂F₃N₃ 303.10 found [M+H]⁺ 304.100.

³²⁴H. Hiroki, K. Ogata, S. -i. Fukuzawa, *synlett* **2013**, 24, 843-6.

(1-benzyl-1H-1,2,3-triazol-4-yl)[4-(trifluoromethyl)phenyl]methanol (215):

According to the general procedure 7, this product was obtained from a reaction between the propargyl alcohol (**171c**) (0.100 g, 0.50 mmol) and benzylazide (0.073 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a yellow solid (0.154 g, 92% yield).

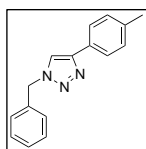
M.p.: 127.7-128.7°C

¹H NMR (300MHz, CDCl₃): δ 5.45 (s, 2H), 7.22 (dd, 2H, J= 2.81Hz, 0.34Hz), 7.35 (dd, 4H, J= 4.86Hz, 1.12Hz), 7.54-7.59 (m, 5H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 29.72, 54.59, 122.27, 125.43, 125.48, 125.88, 126.75, 128.12, 128.45, 128.90, 129.15, 129.42, 129.78, 130.21, 130.93, 134.16 ppm.

FTIR (ATR): ν (cm⁻¹) 3298, 3122, 3068, 1618, 1423, 1332, 1066, 1016, 717, 603.

LCMS (ESI): ELSD 100%, R_t= 5.19 min, *m/z* calcd for C₁₇H₁₄F₃N₃O 333.11 found [M+H]⁺ 334.05.

1-benzyl-4-(4-methylphenyl)-1H-1, 2, 3-triazole (190): ³²³

Upon the general procedure 7, the reaction between the commercial available 4-ethynyltoluene (0.058 g, 0.50 mmol) and benzylazide (0.073 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a white solid (0.154g, Qtv).

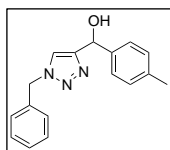
M.p.: 152.6-154.3°C

¹H NMR (300MHz, CDCl₃): δ 2.36 (d, 3H, J= 3.12 Hz), 5.57 (d, 2H, J= 3.27 Hz), 7.22-7.19 (m, 2H), 7.41-7.29 (m, 5H), 7.62 (d, 1H, J= 3.67 Hz), 7.71-7.67 (m, 2H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 21.29, 54.22, 119.13, 125.62, 127.75, 128.07, 128.76, 129.07, 129.15, 129.48, 132.02, 134.77, 138.01 ppm.

FTIR (ATR): ν (cm⁻¹) 3021, 2920, 2852, 1541, 1489, 1456, 1338, 1220, 1045, 790, 717.

LCMS (ESI): ELSD 100%, R_t= 5.45 min, *m/z* calcd for C₁₆H₁₅N₃ 249.13 found [M+H]⁺ 250.100.

(1-benzyl-1H-1,2,3-triazol-4-yl)(4-methylphenyl)methanol (220):

According to the general procedure 7, this product was obtained from a reaction between the propargyl alcohol (**171e**) (0.073 g, 0.50 mmol) and benzylazide (0.073 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.124g, 80% yield).

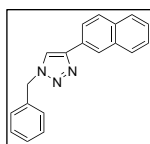
M.p.: 147.1-148.2°C

¹H NMR (300MHz, CDCl₃): δ 2.33 (s, 3H), 3.14 (s, 1H), 5.45 (s, 2H), 5.97 (s, 1H), 7.14-7.24 (m, 5H), 7.29-7.36 (m, 5H) ppm.

¹³C NMR (100MHz, CDCl₃): δ 21.15, 54.49, 71.30, 121.82, 126.50, 128.16, 128.83, 129.12, 129.26, 130.80, 134.42, 137.81, 139.05 ppm.

FTIR (ATR): ν (cm⁻¹) 3651, 3021, 2857, 2368, 2318, 1600, 1480, 1390, 1300, 1282, 1250, 790, 690.

LCMS(ESI): ELSD 100%, R_t= 4.84 min, *m/z* calcd for C₁₇H₁₇N₃O 279.14 found [M+H]⁺ 280.100.

1-benzyl-4-(naphthalen-2-yl)-1H-1,2,3-triazole (195):³²⁵

Upon the general procedure 7, this product was obtained by treating the alkyne (**162**) (0.076 g, 0.50 mmol) with benzylazide (0.073 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.130g, 91% yield).

M.p. : 184.7-185.2°C

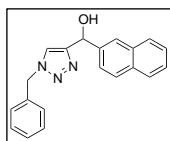
¹H NMR (300MHz, CDCl₃): δ 5.61 (s, 2H), 7.33-7.42 (m, 5H), 7.44-7.52 (m, 2H), 7.77 (s, 1H), 7.81-7.89 (m, 4H), 8.31 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 54.34, 119.78, 123.85, 124.42, 126.16, 126.45, 127.78, 127.89, 128.15, 128.19, 128.56, 128.86, 129.22, 133.17, 133.53, 134.67, 148.3 ppm.

FTIR (ATR): ν (cm⁻¹) 3021, 2950, 2857, 2372, 1600, 1480, 1047, 798, 721.

LCMS(ESI): ELSD 100%, R_t= 5.69 min, *m/z* calcd for C₁₉H₁₅N₃ 285.13 found [M+H]⁺ 286.100.

³²⁵I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem., Int. Ed.* **2009**, *48*, 4017-21.

(1-benzyl-1H-1,2,3-triazol-4-yl)(naphthalen-2-yl)methanol (225):

Upon the general procedure 7, propargyl alcohol (**171d**) (0.091 g, 0.50 mmol), benzylazide (0.073 g, 0.55 mmol) and A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) gave this triazole as a green solid (0.145 g, 92% yield).

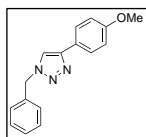
M.p.: 128.6-129.7°C

^1H NMR (300MHz, CDCl_3): δ 4.06 (br, 1H), 5.37 (s, 2H), 7.16 (s, 2H), 7.30 (d, 3H, $J= 4.67\text{Hz}$), 7.46-7.47 (m, 4H), 7.74-7.80 (m, 4H), 7.87 (s, 1H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 54.49, 71.27, 124.58, 125.23, 126.16, 126.62, 127.61, 128.15, 128.36, 128.80, 129.05, 129.36, 133.11, 133.21, 134.26 ppm.

FTIR (ATR): ν (cm^{-1}) 3232, 3120, 2920, 2852, 1541, 1496, 1456, 1053, 761, 715.

LCMS(ESI): ELSD 97%, $R_t= 5.14$ min, m/z calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}$ 315.14 found $[\text{M}+\text{H}]^+$ 316.100.

1-benzyl-4-(4-methoxyphenyl)-1H-1,2,3-triazole (200): ³²³

According the general procedure 7, this product was obtained from a reaction between the commercial available 4-ethynylanisole (0.066 mg, 0.50 mmol) and benzylazide (0.073 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) as a yellow solid (0.147 g, Qtv).

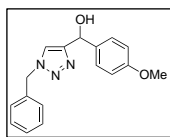
M.p.: 142.0-144.5°C

^1H NMR (300MHz, CDCl_3): δ 3.81 (d, 3H, $J= 5.14\text{Hz}$), 5.54 (d, 2H, $J= 4.88\text{Hz}$), 6.90-6.95 (m, 2H), 7.25-7.30 (m, 2H), 7.32-7.37 (m, 3H), 7.58 (d, 1H, $J= 4.77\text{Hz}$), 7.70-7.74 (m, 2H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 54.14, 55.32, 114.24, 118.85, 123.32, 127.02, 128.03, 128.71, 129.12, 134.85, 148.06, 159.61 ppm.

FTIR (ATR): ν (cm^{-1}) 3100, 2998, 2980, 1496, 1456, 1348, 1247, 1026, 794, 717.

LCMS(ESI): ELSD 100%, $R_t= 5.14$ min, m/z calcd for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}$ 265.12 found $[\text{M}+\text{H}]^+$ 266.00.

(1-benzyl-1H-1,2,3-triazol-4-yl)(4-methoxyphenyl)methanol (230):

Upon the general procedure 7, this triazole was obtained by departing from propargyl alcohol (**171b**) (0.081 g, 0.50 mmol) and benzylazide (0.073 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a green solid (0.171 g, Qtv).

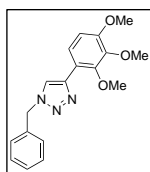
M.p.: 102.1-104.4°C

¹H NMR (300MHz, CDCl₃): δ 1.68 (s, 1H), 3.79 (d, 3H, J= 6.81), 5.42 (d, 1H, J= 2.47Hz), 5.47 (s, 2H), 6.81-6.89 (m, 2H), 7.21-7.26 (m, 3H), 7.27-7.39 (m, 5H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 54.05, 55.29, 73.47, 113.87, 113.94, 114.12, 128.01, 128.06, 128.14, 128.25, 128.33, 128.60, 128.64, 128.75, 128.86, 129.03, 131.55, 132.06, 134.64, 134.68, 159.36, 159.46 ppm.

FTIR (ATR): ν (cm⁻¹) 3307, 3116, 2918, 2848, 1608, 1510, 1456, 1300, 1236, 1028, 804, 709.

LCMS(ESI): ELSD 100%, R_t= 4.40 min, *m/z* calcd for C₁₇H₁₇N₃O₂ 295.13 found [M+H]⁺ 296.100.

1-benzyl-4-(2,3,4-trimethoxyphenyl)-1H-1,2,3-triazole (205):

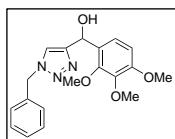
According to the general procedure 7, the reaction between the alkyne (**132e**) (0.096 g, 0.50 mmol) and benzylazide (0.073 g, 0.55 mmol) and A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ gave this triazole as a brown oil (0.162 g, 100% yield).

¹H NMR (300MHz, CDCl₃): δ 3.80 (d, 3H, J= 2.29Hz), 3.87 (d, 3H, J= 2.33Hz), 3.88 (d, 3H, J= 2.14Hz), 5.57 (s, 2H), 6.78 (dd, 1H, J= 8.85Hz, 2.18Hz), 7.33 (m, 5H), 7.88 (s, 1H), 7.94 (dd, 1H, J= 8.82Hz, 2.30Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 54.02, 56.05, 60.25, 60.87, 107.98, 117.56, 121.85, 122.16, 127.85, 128.21, 128.55, 128.82, 129.02, 135.10, 142.33, 150.55, 153.59 ppm.

FTIR (ATR): ν (cm⁻¹) 3199, 2935, 2837, 1604, 1469, 1344, 1280, 1230, 1083, 798, 719.

LCMS(ESI): ELSD 100%, R_t= 5.36 min, *m/z* calcd for C₁₈H₁₉N₃O₃ 325.14 found [M+H]⁺ 326.00.

(1-benzyl-1H-1,2,3-triazol-4-yl)(2,3,4-trimethoxyphenyl) methanol (235):

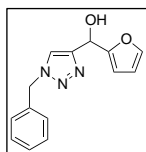
Upon the general procedure 7, this product was obtained from a reaction between propargyl alcohol (**171f**) (0.111 g, 0.50 mmol) and benzylazide (0.073 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a green oil (0.161 g, 90% yield).

¹H NMR (300MHz, CDCl₃): δ 3.68 (s, 3H), 3.79 (s, 6H), 5.24 (s, 1H), 5.43 (s, 2H), 6.62 (s, 1H), 7.07 (s, 1H), 7.19 (s, 2H), 7.25-7.36 (m, 5H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 53.56, 54.79, 55.99, 60.71, 61.06, 107.28, 122.13, 128.09, 128.22, 128.30, 128.70, 128.83, 129, 134.68, 135.37, 142.05, 151.24, 153.57 ppm.

FTIR (ATR): ν (cm⁻¹) 3348, 3100, 2933, 2848, 1598, 1492, 1462, 1415, 1278, 1091, 1008, 798, 719.

LCMS(ESI): ELSD 100%, R_t=4.36 min, *m/z* calcd for C₁₉H₂₁N₃O₄ 355.15 found [M+H]⁺ 356.050.

(1-benzyl-1H-1,2,3-triazol-4-yl)(furan-2-yl)methanol (240):

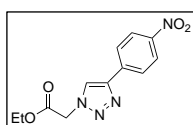
According to the general procedure 7, the reaction between propargyl alcohol (**171g**) (0.061 g, 0.50 mmol) and benzylazide (0.073 g, 0.55 mmol) and A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a green oil (0.132 g, Qtv).

¹H NMR (300MHz, CDCl₃): δ 5.48 (s, 2H), 6.02 (s, 1H), 6.28 (d, 2H, J= 8.74Hz), 7.25 (dd, 2H, J= 6.09Hz, 0.92Hz), 7.34-7.36 (m, 5H), 7.50 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 54.37, 63.14, 107.83, 110.39, 128.14, 128.82, 129.14, 134.37, 142.64, 153.96 ppm.

FTIR (ATR): ν (cm⁻¹) 3339, 3132, 2920, 2852, 1703, 1496, 1456, 1222, 1047, 715, 610.

LCMS(ESI): ELSD 100%, R_t= 4.26 min, *m/z* calcd for C₁₄H₁₃N₃O₂ 255.10 found [M+H]⁺ 256.100.

Ethyl 2-[4-(4-nitrophenyl)-1H-1,2,3-triazol-1-yl]acetate (181):³²⁶

Upon the general procedure 7, this triazole was obtained from a reaction between the alkyne (**132a**) (0.074 g, 0.50 mmol) and ethyl 2-azidoacetate (**175**) (0.071 g, 0.55 mmol) and A-

³²⁶K. Odlo, E. A. Hoydahl, T. V. Hansen, *Tetrahedron Lett.* **2007**, 48, 2097-9.

21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.126 g, 91% yield).

M.p.: 154.1-157.6°C

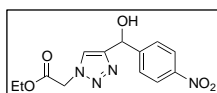
¹H NMR (300MHz, CDCl₃): δ 1.33 (t, 3H, J= 7.15Hz), 4.31 (q, 2H, J= 7.15Hz), 5.25 (s, 2H), 7.28 (s, 1H), 8.04 (t, 2H, J= 9.54), 8.30 (d, 2H, J= 8.97) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.10, 51.05, 62.73, 122.43, 124.34, 126.29, 136.61, 146.11, 166.03 ppm.

FTIR (ATR): ν (cm⁻¹) 3150, 2920, 2852, 1749, 1602, 1508, 1458, 1334, 1219, 1018, 819, 758.

LCMS(ESI): ELSD 100%, R_t= 5.02 min, *m/z* calcd for C₁₂H₁₂N₄O₄ 276.09 found [M+H]⁺ 277.100.

Ethyl 2-{4-[hydroxy(4-nitrophenyl)methyl]-1H-1,2,3-triazol-1-yl}acetate (211):



According to the general procedure 7, the reaction between the propargyl alcohol (**171a**) (0.089 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2ml) gave this product as a dark orange oil (0.150 g, 98% yield).

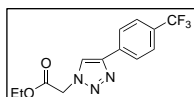
¹H NMR (300MHz, CDCl₃): δ 1.32 (t, 3H, J= 7.15), 2.71 (s; 1H), 4.24 (q, 2H, J= 7.15), 5.12 (s, 2H), 6.19 (s, 1H), 7.49 (s, 1H), 7.66 (d, 2H, J= 8.27), 8.21 (d, 2H, J= 8.09) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.05, 14.09, 51.10, 62.67, 62.96, 123.49, 123.79, 130.41, 130.16, 141.055, 150.35, 165.55 ppm.

FTIR (ATR): ν (cm⁻¹) 736, 824, 1015, 1222, 1339, 1458, 1521, 1750, 2318, 2372, 2958, 3651.

LCMS(ESI): ELSD 100%, R_t= 4.30 min, *m/z* calcd for C₁₃H₁₄N₄O₅ 306.1 found [M+H]⁺ 307.50.

Ethyl 2-{4-[4-(trifluoromethyl)phenyl]-1H-1,2,3-triazol-1-yl}acetate (186):



From the general procedure 7, This triazole was obtained by treating the commercial available 4-ethynyl- α,α,α -trifluorotoluene (0.085 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.138 g, 92% yield).

M.p.: 141.8-143.7°C

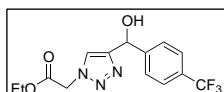
¹H NMR (300MHz, CDCl₃): δ 1.27 (t, 3H, J= 7.12Hz), 4.24 (q, 2H, J= 7.10Hz), 5.20 (s, 2H), 7.62 (d, 2H, J= 8.02Hz), 7.90 (d, 2H, J= 7.81Hz), 8.01 (s, 1H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 14, 50.96, 62.55, 121.98, 122.29, 125.72, 125.77, 125.82, 125.89, 129.78, 130.22, 133.85, 146.76, 166.24 ppm.

FTIR (ATR): ν (cm^{-1}) 3110, 2998, 1737, 1622, 1456, 1430, 1381, 1330, 1228, 1103, 835, 769.

LCMS(ESI): ELSD 100%, $R_t=5.36$ min, m/z calcd for $\text{C}_{13}\text{H}_{12}\text{F}_3\text{N}_3\text{O}_2$ 299.09 found $[\text{M}+\text{H}]^+$ 300.050.

Ethyl 2-(4-{hydroxy[4-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazol-1-yl)acetate (216):



Upon the general procedure 7, the reaction between the propargyl alcohol (**171c**) (0.100 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) gave this triazole as a yellow solid (0.154 g, 93% yield).

M.p.: 104.6-105°C

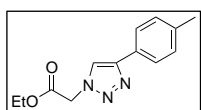
^1H NMR (300MHz, CDCl_3): δ 1.22 (t, 3H, $J=6.94\text{Hz}$), 4.16 (q, 2H, $J=6.75\text{Hz}$), 5.04 (s, 3H), 6.06 (s, 1H), 7.53 (m, 5H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 13.91, 51.09, 62.49, 89.84, 122.29, 125.29, 125.33, 125.38, 125.53, 125.90, 126.82, 126.95, 129.66, 130.07, 166.24 ppm.

FTIR (ATR): ν (cm^{-1}) 680, 820, 1114, 1231, 1380, 1455, 1480, 1505, 1559, 1645, 1750, 2326, 2376, 3646.

LCMS(ESI): ELSD 100%, $R_t=5.25$ min, m/z calcd for $\text{C}_{14}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_3$ 329.10 found $[\text{M}+\text{H}]^+$ 330.050.

Ethyl 2-[4-(4-methylphenyl)-1H-1,2,3-triazol-1-yl]acetate (191):³²⁷



According to the general procedure 7, this product was obtained by departing from a commercial available 4-ethynyltoluene (0.058 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) as a white solid (0.113 g, 92% yield).

M.p.: 98.5-99.1°C

^1H NMR (300MHz, CDCl_3): δ 1.25 (t, 3H, $J=7.07\text{Hz}$), 2.34 (s, 3H), 4.21 (q, 2H, $J=7.06\text{Hz}$), 5.14 (s, 2H), 7.21 (t, 2H, $J=10.71\text{Hz}$), 7.69 (d, 2H, $J=7.84\text{Hz}$), 7.86 (s, 1H) ppm.

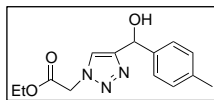
^{13}C NMR (75MHz, CDCl_3): δ 14.05, 21.28, 50.91, 62.37, 120.83, 125.69, 127.61, 129.51, 138.07, 148.19, 166.39 ppm.

³²⁷A. Coelho, P. Diz, O. Cammano, E. Sotelo, *Adv. Synth. Catal.* **2010**, 352, 1179-92.

FTIR (ATR): ν (cm⁻¹) 3123, 2916, 2852, 1741, 1456, 1379, 1215, 1022, 800, 705.

LCMS(ESI): ELSD 100%, R_t = 5.04 min, m/z calcd for C₁₃H₁₅N₃O₂ 245.12 found [M+H]⁺ 246.100.

Ethyl 2-[4-[hydroxy(4-methylphenyl)methyl]-1H-1,2,3-triazol-1-yl]acetate (221):



From the general procedure 7, the reaction between the propargyl alcohol (**171e**) (0.073 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI(0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a green solid (0.148 g, Qtv).

M.p.: 94.0-96.0°C

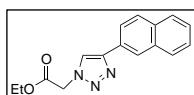
¹H NMR (300MHz, CDCl₃): δ 1.27 (t, 3H, J= 7.15Hz), 2.34 (s, 3H), 3.29 (s, 1H), 4.22 (q, 2H, J=7.15Hz), 5.08 (d, 2H, J= 2.75Hz), 6.00 (s, 1H), 7.16 (d, 2H, J= 7.05Hz), 7.32 (d, 2H, J= 6.89Hz), 7.43 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.03, 21.13, 50.94, 53.53, 62.39, 126.50, 129.18, 137.57, 141.94, 166.30 ppm.

FTIR (ATR): ν (cm⁻¹) 3650, 3021, 2920, 2857, 2372, 2314, 1753, 1375, 1218, 1019, 795, 728.

LCMS(ESI): ELSD 100%, R_t = 4.30 min, m/z calcd for C₁₄H₁₇N₃O₃ 275.13 found [M+H]⁺ 276.50.

Ethyl 2-[4-(naphthalen-2-yl)-1H-1,2,3-triazol-1-yl]acetate (196):



From the general procedure 7, this triazole was obtained by treating the alkyne (**132d**) (0.076 g, 0.50 mmol) with ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.130 g, 92% yield).

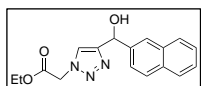
M.p.: 119.9-121.0°C

¹H NMR (300MHz, DMSO): δ 1.24 (t, 3H, J= 7.11Hz), 4.21 (q, 2H, J= 7.11Hz), 5.51 (d, 2H, J= 3.60Hz), 7.49-7.57 (m, 2H), 7.92-7.95 (m, 1H), 7.98-8.02 (m, 3H), 8.44 (s, 1H), 8.70 (d, 1H, J= 3.63Hz) ppm.

¹³C NMR (75MHz, DMSO): δ 14.47, 51.11, 62.09, 123.64, 124.02, 124.10, 126.65, 127.08, 128.17, 128.48, 128.50, 129.07, 133.07, 133.65, 146.91, 167.72 ppm.

FTIR (ATR): ν (cm⁻¹) 3150, 2983, 2880, 1747, 1488, 1417, 1375, 1220, 1151, 1026, 804, 750.

LCMS(ESI): ELSD 100%, R_t = 5.33 min, m/z calcd for C₁₆H₁₅N₃O₂ 281.12 found [M+H]⁺ 282.100.

Ethyl 2-{4-[hydroxy(naphthalen-2-yl)methyl]-1H-1,2,3-triazol-1-yl}acetate (226):

Upon the general procedure 7, the reaction between propargyl alcohol (**171d**) (0.091 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) gave this triazole as a green solid (0.154 g, 99% yield).

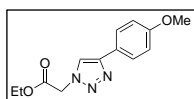
M.p.: 96.0-98.0°C

¹H NMR (300MHz, CDCl₃): δ 1.23 (t, 3H, J= 7.17Hz), 4.18 (q, 2H, J= 6.87Hz), 5.02 (s, 2H), 5.28 (d, 1H, J= 1.23Hz), 6.19 (br, 1H), 7.45-7.52 (m, 4H), 7.80 (d, 3H, J= 6.32Hz), 7.91 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.03, 50.96, 62.45, 72.89, 124.53, 125.26, 126.13, 126.24, 127.68, 128.17, 128.42, 128.43, 133.11, 133.24, 166.17 ppm.

FTIR (ATR): ν (cm⁻¹) 3651, 3057, 2924, 2850, 2372, 2314, 1746, 1732, 1508, 1455, 1375, 1267, 1213, 1019, 862, 736.

LCMS(ESI): ELSD 98%, R_t= 4.71 min, *m/z* calcd for C₁₇H₁₇N₃O₃ 311.13 found [M+H]⁺ 312.100.

Ethyl 2-[4-(4-methoxyphenyl)-1H-1,2,3-triazol-1-yl]acetate (201):

From the general procedure 7, this product was obtained from a reaction between the commercial available 4-ethynylanisole (0.066 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a yellow solid (0.137 g, Qtv).

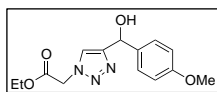
M.p.: 115.0-117.0°C

¹H NMR (300MHz, CDCl₃): δ 1.29 (t, 3H, J= 7.15Hz), 3.82 (d, 3H, J= 1.65Hz), 4.26 (q, 2H, J= 7.14Hz), 5.17 (d, 2H, J= 1.44Hz), 6.94 (dd, 2H, J= 8.69Hz, 1.49Hz), 7.75 (dd, 2H, J= 8.68Hz, 1.53Hz), 7.81 (d, 1H, J= 1.31Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.06, 50.90, 55.31, 62.38, 113.96, 114.25, 120.32, 123.13, 127.10, 133.57, 148.01, 159.67, 166.41 ppm.

FTIR (ATR): ν (cm⁻¹) 3099, 2987, 2933, 1745, 1456, 1370, 1201, 1024, 769, 698.

LCMS(ESI): ELSD 100%, R_t= 4.59 min, *m/z* calcd for C₁₃H₁₅N₃O₃ 261.11 found [M+H]⁺ 261.950.

Ethyl 2-{4-[hydroxy(4-methoxyphenyl)methyl]-1H-1,2,3-triazol-1-yl}acetate (231):

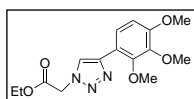
From the general procedure 7, the reaction between the propargyl alcohol (**171b**) (0.081 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) and A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a green oil (0.144 g, 99% yield).

¹H NMR (300MHz, CDCl₃): δ 1.31 (t, 3H, J= 7.15Hz), 1.76 (br, 1H), 3.83 (d, 3H, J= 4.75Hz), 4.27 (q, 2H, J= 7.12Hz), 5.12 (d, 2H, J= 10.55Hz), 5.33 (s, 1H), 6.91-6.95 (m, 2H), 7.38 (dd, 2H, J= 18.28Hz, 8.68Hz), 7.62 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.04, 53.46, 55.31, 62.43, 73.22, 113.96, 127.94, 128.81, 131.43, 131.99, 159.54, 166.22 ppm.

FTIR (ATR): ν (cm⁻¹) 3180, 3336, 2924, 2852, 1745, 1610, 1458, 1375, 1211, 1172, 800.

LCMS(ESI): ELSD 100%, R_t= 5.36 min, *m/z* calcd for C₁₄H₁₇N₃O₄ 291.12 found [M+H]⁺ 292.100.

Ethyl 2-[4-(2,3,4-trimethoxyphenyl)-1H-1,2,3-triazol-1-yl]acetate (206):

According to the general procedure 7, this product was obtained by treating the alkyne (**132e**) (0.096 g, 0.50 mmol) with ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as green crystals (0.154 g, 96% yield).

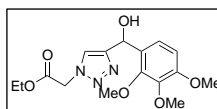
M.p.: 110.1-112.8°C

¹H NMR (300MHz, CDCl₃): δ 1.29 (t, 3H, J= 7.15Hz), 3.89 (s, 9H), 4.27 (q, 2H, J= 7.15Hz), 5.19 (s, 2H), 6.79 (d, 1H, J= 8.86Hz), 7.94 (d, 1H, J= 8.81Hz), 8.08 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.05, 50.87, 56.04, 60.29, 60.87, 62.27, 107.92, 117.38, 122.17, 123.21, 142.31, 143.53, 143.56, 150.63, 153.63, 166.41 ppm.

FTIR (ATR): ν (cm⁻¹) 3142, 2941, 2839, 1749, 1604, 1454, 1338, 1280, 1087, 817, 688.

LCMS(ESI): ELSD 100%, R_t= 4.80 min, *m/z* calcd for C₁₅H₁₉N₃O₅ 321.13 found [M+H]⁺ 322.00.

Ethyl 2-{4-[hydroxy(2,3,4-trimethoxyphenyl)methyl]-1H-1,2,3-triazol-1-yl}acetate (236):

Upon the general procedure 7, the reaction between the propargyl alcohol (**171f**) (0.11 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) and A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a green oil (0.172 g, 98% yield).

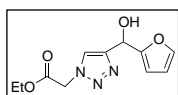
¹H NMR (300MHz, CDCl₃): δ 1.27 (t, 3H, J= 8.12Hz), 3.82(d, 9H, J= 16.48Hz), 4.24 (quintet, 2H, J= 6.77Hz), 5.12 (d, 2H, J= 5.07Hz), 5.28 (s, 1H), 6.13 (s, 1H), 6.66 (d, 1H, J= 8.34Hz), 7.06 (d, 1H, J= 8.46Hz), 7.56 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14, 50.31, 53.54, 55.97, 60.68, 61.11, 61.84, 62.30, 62.42, 107.29, 122.13, 124.01, 151.21, 153.57, 166.33, 168.33 ppm.

FTIR (ATR): ν (cm⁻¹) 3390, 3180, 2939, 2839, 2106, 1745, 1598, 1492, 1462, 1415, 1276, 1209, 1091, 1008, 796, 688.

LCMS(ESI): ELSD 100%, R_t= 3.98 min, m/z calcd for C₁₆H₂₁N₃O₆ 351.14 found [M+H]⁺ 352.050.

Ethyl 2-{4-[furan-2-yl(hydroxy)methyl]-1H-1,2,3-triazol-1-yl}acetate (**241**):



From the general procedure 7, this triazole was found from a reaction between the propargyl alcohol (**171g**) (0.061 g, 0.50 mmol) and ethyl 2-azidoacetate (0.071 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ as a brown oil (0.123 g, 98% yield).

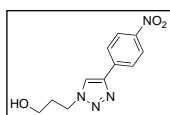
¹H NMR (300MHz, CDCl₃): δ 1.25 (t, 3H, J= 6.26Hz), 3.65 (br, 1H), 4.21 (q, 2H, J= 6.63Hz), 5.12 (s, 2H), 6.01 (s, 1H), 6.27 (d, 2H, J= 11.41), 7.36 (d, 1H, J= 3.87Hz), 7.70 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 14.02, 50.95, 62.45, 85.98, 107.88, 110.40, 139.77, 142.64, 154.02, 162.76, 166.33 ppm.

FTIR (ATR): ν (cm⁻¹) 3400, 3147, 2922, 2850, 1743, 1458, 1375, 1211, 1016.

LCMS(ESI): ELSD 100%, R_t= 3.41 min, m/z calcd for C₁₁H₁₃N₃O₄ 251.09 found [M+H]⁺ 252.100.

3-[4-(4-nitrophenyl)-1H-1, 2, 3-triazol-1-yl]propan-1-ol (**182**):



Upon the general procedure 7, this product was obtained by treating the terminal alkyne (**159**) (0.074 g, 0.50 mmol) with 3-azidopropan-1-ol (**176**) (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a yellow solid (0.048 g, 38% yield).

M.p.: 135.0-139.4°C

¹H NMR (300MHz, Acetone D₆): δ 1.34 (quintet, 2H, J= 6.50Hz), 2.80 (t, 2H, J= 5.32Hz), 3.05 (br, 1H), 3.79 (t, 2H, J= 7.05Hz), 7.35 (dd, 2H, J= 9.17Hz, 2.18Hz), 7.49 (dd, 2H, J= 9.12Hz,

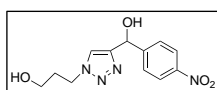
2.22Hz), 7.80 (d, 1H, J= 2.81Hz) ppm.

¹³C NMR (75MHz, Acetone D₆): δ 33, 47.19, 58.05, 122.78, 124.13, 125.92, 137.83, 144.84, 147.09 ppm.

FTIR (ATR): ν (cm⁻¹) 3523, 3120, 2920, 2852, 1600, 1498, 1456, 1338, 1041, 852, 756.

LCMS(ESI): ELSD 100%, R_t= 3.93 min, m/z. calcd for C₁₁H₁₂N₄O₃ 248.09 found [M+H]⁺ 249.100.

3-{4-[hydroxy(4-nitrophenyl)methyl]-1H-1,2,3-triazol-1-yl}propan-1-ol (212):



From the general procedure 7, the reaction between the propargyl alcohol (**171a**) (0.089 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ gave this triazole as an orange solid (0.115 g, 82% yield).

M.p.: 88.3-90.5°C

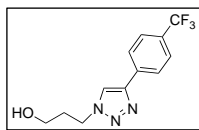
¹H NMR (300MHz, CDCl₃): δ 2.04 (q, 2H, J= 5.97Hz), 2.55 (br, 1H), 3.52 (t, 2H, J= 5.78Hz), 4.39-4.44 (m, 2H), 5.51 (br, 1H), 6.05 (s, 1H), 7.43 (s, 1H), 7.60 (d, 2H, J= 8.70Hz), 8.15 (d, 2H, J= 8.70Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 32.41, 50.37, 58.21, 58.36, 67.78, 67.81, 123.69, 127.10, 131.63, 147.37, 149.50 ppm.

FTIR (ATR): ν (cm⁻¹) 3356, 3112, 2920, 2852, 1521, 1456, 1348, 1056, 719.

LCMS(ESI): ELSD 100%, R_t= 2.89 min, m/z. calcd for C₁₂H₁₄N₄O₄ 278.10 found [M+H]⁺ 279.050.

3-{4-[4-(trifluoromethyl)phenyl]-1H-1,2,3-triazol-1-yl}propan-1-ol (187):



According to the general procedure, the reaction between the commercial available 4-ethynyl-α,α,α-trifluorotoluene (0.085 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a white solid (0.147 g, Qtv).

M.p.: 105.3-106.9°C

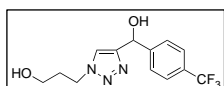
¹H NMR (300MHz, CDCl₃): δ 2.16 (quintet, 2H, J= 6.18Hz), 3.13 (br, 1H), 3.68 (t, 2H, J= 5.69Hz), 4.56 (t, 2H, J= 6.77Hz), 7.62 (d, 2H, J= 7.84Hz), 7.88 (d, 2H, J= 8.12Hz), 7.93 (s, 1H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 32.61, 47.25, 58.54, 121.15, 122.26, (125.79, 125.82, 125.88), 129.79, 130.22, 133.88, 146.32 ppm.

FTIR (ATR): ν (cm^{-1}) 3273, 3099, 2939, 2891, 1622, 1458, 1336, 1118, 1066, 1047, 837, 599.

LCMS(ESI): ELSD 100%, R_t = 4.60 min, m/z calcd for $\text{C}_{12}\text{H}_{12}\text{F}_3\text{N}_3\text{O}$ 271.09 found 271.24.

3-(4-{hydroxy[4-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazol-1-yl)propan-1-ol (217):



Upon the general procedure 7, this triazole was obtained by treating the propargyl alcohol (**171c**) (0.100 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) as a green solid (0.093 g, 62% yield).

M.p.: 87.4-88.0°C

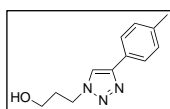
^1H NMR (300MHz, CDCl_3): δ 2.21 (dt, 2H, J = 6.25 and 12.25 Hz), 3.72 (t, 2H, J = 5.79 Hz), 4.61 (t, 2H, J = 6.72 Hz), 5.30 (d, 1H, J = 4.35), 7.49 (dt, 2H, J = 2.84 and 6.58 Hz), 7.83-7.93 (m, 2H), 8.33 (s, 1H) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 32.30, 47.40, 58.33, 58.56, 117.95, 125.55, 126.98, 130.90, 135.14, 142.03 ppm.

FTIR (ATR): ν (cm^{-1}) 3381, 3101, 2990, 2926, 1480, 1321, 1122, 858, 773.

LCMS(ESI): ELSD 100%, R_t = 4.10 min, m/z calcd for $\text{C}_{13}\text{H}_{14}\text{F}_3\text{N}_3\text{O}_2$ 301.10 found $[\text{M}+\text{H}]^+$ 302.100.

3-[4-(4-methylphenyl)-1H-1,2,3-triazol-1-yl]propan-1-ol (192):



From the general procedure 7, the reaction between the commercial available 4-ethynyltoluene (0.058 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) gave this triazole as a white solid (0.113 g, Qtv).

M.p.: 110.3-111.2°C

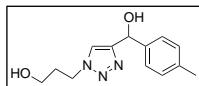
^1H NMR (300MHz, CDCl_3): δ 2.164 (quintet, 2H, J = 6.16Hz), 2.37 (s, 3H), 2.44 (br, 1H), 3.67 (t, 2H, J = 5.69Hz), 4.55 (t, 2H, J = 6.73Hz), 7.22 (dt, 2H, J = 7.79Hz, 0.61Hz), 7.69 (dd, 2H, J = 8.09Hz, 1.55Hz), 7.63 (d, 1H, J = 1.58Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 21.27, 32.75, 47.14, 58.51, 120.11, 125.60, 127.62, 129.56, 138.07, 147.70 ppm.

FTIR (ATR): ν (cm^{-1}) 3257, 3150, 2916, 2856, 1456, 1348, 1045, 810, 725.

LCMS(ESI): ELSD 100%, $R_t = 4.00$ min, m/z calcd for $C_{12}H_{15}N_3O$ 217.12 found $[M+H]^+$ 218.100.

3-{4-[hydroxy(4-methylphenyl)methyl]-1H-1,2,3-triazol-1-yl}propan-1-ol (222):



According to the general procedure 7, this product was obtained from a reaction between the propargyl alcohol (**171e**) (0.073 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) as a green oil (0.123 g, 95% yield).

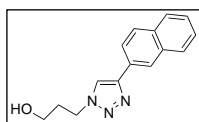
1H NMR (300MHz, DMSO- d_6): δ 1.91 (dt, 2H, $J = 6.26, 12.70$ Hz), 2.26 (s, 3H), 4.34 (t, 2H, $J = 6.99$ Hz), 4.52 (t, 1H, $J = 6.98$ Hz), 4.65 (t, 1H, $J = 4.51$ Hz), 5.75 (s, 1H), 5.89 (s, 1H), 7.12 (d, 2H, $J = 7.48$ Hz), 7.26 (d, 2H, $J = 7.35$ Hz), 7.39 (d, 1H, $J = 7.72$ Hz), 7.85 (s, 1H) ppm.

^{13}C NMR (75MHz, DMSO- d_6): δ 21.15, 21.70, 33.11, 33.40, 47.61, 57.87, 57.95, 68.36, 126.79, 129.05, 129.58, 130.39, 130.58, 134.50, 136.50, 144.21 ppm.

FTIR (ATR): ν (cm^{-1}) 3340, 3120, 2924, 2879, 1604, 1436, 1346, 1045, 906, 759.

LCMS(ESI): ELSD 98%, $R_t = 3.04$ min, m/z calcd for $C_{13}H_{17}N_3O_2$ 247.13 found $[M+H]^+$ 248.150.

3-[4-(naphthalen-2-yl)-1H-1,2,3-triazol-1-yl]propan-1-ol (197):



From the general procedure 7, the reaction between the alkyne (**132d**) (0.076 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) gave this product as a white solid (0.120 g, 95% yield).

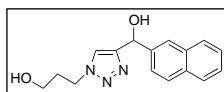
M.p.: 166.8-167.9°C

1H NMR (300MHz, $CDCl_3$): δ 2.20 (quintet, 2H, $J = 5.89$ Hz), 3.71 (t, 2H, $J = 5.51$ Hz), 4.61 (t, 2H, $J = 6.73$ Hz), 7.48-7.53 (m, 2H), 7.83-7.92 (m, 6H), 8.33 (s, 1H) ppm.

^{13}C NMR (75MHz, $CDCl_3$): δ 32.61, 47.02, 58.83, 120.39, 123.84, 124.41, 126.17, 126.47, 126.48, 127.79, 128.20, 128.61, 133.18, 133.19, 133.57, 151.07 ppm.

FTIR (ATR): ν (cm^{-1}) 3738, 3110, 2978, 2924, 1750, 1537, 1045, 808, 742.

LCMS(ESI): ELSD 100%, $R_t = 4.42$ min, m/z calcd for $C_{15}H_{15}N_3O$ 253.12 found $[M+H]^+$ 354.150.

3-[4-[hydroxy(naphthalen-2-yl)methyl]-1H-1, 2, 3-triazol-1-yl]propan-1-ol (227):

According to the general procedure 7, the reaction between the propargyl alcohol (**171d**) (0.091 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a green solid (0.114 g, 81% yield).

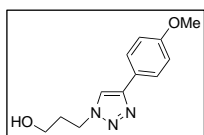
M.p.: 86.5-87.2°C

¹H NMR (300MHz, CDCl₃): δ 2.01-2.04 (m, 2H), 2.65 (br, 1H), 3.43-3.55 (m, 2H), 4.38-4.41 (m, 2H), 5.30 (d, 1H, J= 3.79Hz), 6.16 (br, 1H), 7.45-7.49 (m, 4H), 7.79-7.82 (m, 3H), 7.92 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 29.71, 31.47, 32.30, 48.51, 58.70, 59.93, 124.48, 126.19, 126.26, 127.65, 128.16, 128.18, 128.44, 133.14, 133.25 ppm.

FTIR (ATR): ν (cm⁻¹) 3246, 3101, 2910, 2852, 1449, 1037, 785, 744.

LCMS(ESI): ELSD 100%, R_t= 3.91 min, *m/z* calcd for C₁₆H₁₇N₃O₂ 283.13 found [M+H]⁺ 284.100.

3-[4-(4-methoxyphenyl)-1H-1, 2, 3-triazol-1-yl]propan-1-ol (202):

According to the general procedure 7, This triazole was obtained by treating the commercial available 4-ethynylanisole (0.066 g, 0.50 mmol) with 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.115 g, 99% yield).

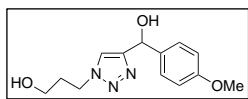
M.p.: 119.2-120.0°C

¹H NMR (300MHz, CDCl₃): δ 2.15 (t, 2H, J= 6.12Hz), 2.43 (br, 1H), 3.67 (t, 2H, J= 5.64Hz), 3.83 (s, 3H), 4.54 (t, 2H, J= 6.71Hz), 6.94 (d, 2H, J= 8.61), 7.72 (d, 3H, J= 8.51Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 32.68, 47.01, 55.34, 58.70, 113.95(d), 119.46, 123.22, 127.02, 127.09, 133.59(d), 147.60, 159.63 ppm.

FTIR (ATR): ν (cm⁻¹) 3307, 3100, 2929, 2840, 1556, 1456, 1340, 1028, 819.

LCMS(ESI): ELSD 100%, R_t= 3.42 min, *m/z* calcd for C₁₂H₁₅N₃O₂ 233.12 found [M+H]⁺ 234.00.

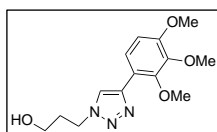
3-{4-[hydroxy(4-methoxyphenyl)methyl]-1H-1, 2, 3-triazol-1-yl}propan-1-ol (232):

From the general procedure 7, the reaction between the propargyl alcohol (**171b**) (0.081 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a green oil (0.113 g, 87% yield). ¹H NMR (300MHz, CDCl₃): δ 1.89-1.96 (m, 2H), 3.36-3.44 (m, 2H), 3.70 (d, 3H, J= 3.01Hz), 4.27-4.31 (m, 2H), 5.32 (d, 1H, J= 7.2), 6.78-6.83 (m, 5H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 31.47, 47.18, 48.38, 55.29, 58.22, 58.32, 113.85, 114, 114.18, 127.89, 128.56, 128.77, 131.30, 131.81, 159.452 ppm.

FTIR (ATR): ν (cm⁻¹) 612, 799, 940,1023, 1177, 1243, 1301, 1458, 1512, 2102, 2318, 2372, 2850, 2920, 3381.

LCMS(ESI): ELSD 100%, R_t= 4.01 min, m/z calcd for C₁₃H₁₇N₃O₃ 263.13 found [M+H]⁺ 264.100.

3-[4-(2,3,4-trimethoxyphenyl)-1H-1, 2, 3-triazol-1-yl]propan-1-ol (207):

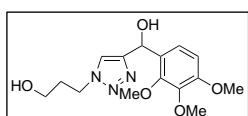
According to the general procedure 7, this triazole was found from a reaction between the alkyne (**132e**) (0.096 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.4 mmol) in CH₂Cl₂ (2 ml) as a brown oil (0.150 g, Qtv).

¹H NMR (300MHz, CDCl₃): δ 2.15 (quintet, 2H, J= 6.20Hz), 2.64 (br, 1H), 3.67 (t, 2H, J= 5.75Hz), 3.87 (d, 9H, J= 4.53Hz), 4.55 (t, 2H, J= 6.77Hz), 6.77 (d, 1H, J= 8.82Hz), 7.89 (d, 1H, J= 8.81Hz), 7.98 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 32.86, 47.04, 56.03, 58.58, 60.33, 60.87,107.25, 107.99, 117.34, 122.03, 122.37, 142.29, 150.53, 153.59 ppm.

FTIR (ATR): ν (cm⁻¹) 3365, 3190, 2935, 2839, 1606, 1469, 1346, 1085, 854, 800.

LCMS(ESI): ELSD 98%, R_t= 3.72 min, m/z calcd for C₁₄H₁₉N₃O₄ 293.14 found [M+H]⁺ 293.950.

3-{4-[hydroxy(2,3,4-trimethoxyphenyl)methyl]-1H-1, 2, 3-triazol-1-yl}propan-1-ol (237):

From the general procedure 7, this product was obtained by treating the propargyl alcohol (**171f**) (0.111 g, 0.50 mmol) with 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the

presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as green crystals (0.173 g, Qtv).

M.p.: 110.2-112.7°C

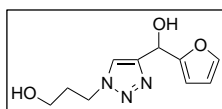
¹H NMR (300MHz, DMSO-d₆): δ 1.94 (t, 2H, J= 5.97Hz), 3.36-3.40 (m, 3H), 3.67 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H), 4.37 (t, 2H, J= 6.91Hz), 5.75 (s, 1H), 6.00 (s, 1H), 6.83 (d, 1H, J=8.40Hz), 7.15 (d, 1H, J= 8.66Hz), 7.87 (s, 1H) ppm.

¹³C NMR (75MHz, DMSO-d₆): δ 33.42, 47.06, 56.28, 57.97, 60.72, 61.29, 62.69, 108.26, 122.28, 122.30, 130.40, 132.68, 135.17, 141.84, 141.85, 150.76, 152.97 ppm.

FTIR (ATR): ν (cm⁻¹) 3292, 3132, 2972, 2900, 1463, 1282, 1066, 1053, 804, 688.

LCMS(ESI): ELSD 100%, R_t= 2.59 min, *m/z* calcd for C₁₅H₂₁N₃O₅ 323.15 found [M+H]⁺ 324.00.

3-{4-[furan-2-yl(hydroxy)methyl]-1H-1, 2, 3-triazol-1-yl}propan-1-ol (242):



According to the general procedure 7, the reaction between the propargyl alcohol

(**171g**) (0.061 g, 0.50 mmol) and 3-azidopropan-1-ol (0.056 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a brown oil (0.116 g, Qtv).

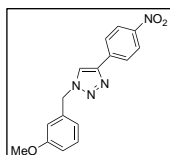
¹H NMR (300MHz, CDCl₃): δ 1.67 (br, 1H), 2.12-2.18 (m, 2H), 3.65 (t, 2H, J= 5.79 Hz), 4.52 (t, 2H, J= 6.75), 6.03 (s, 1H), 6.31-6.37 (m, 3H), 7.41 (dd, 1H), 7.60 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 32.48, 47.10, 58.61, 63.09, 107.79, 110.42, 122.32, 142.67, 154.02, 155.83 ppm.

FTIR (ATR): ν (cm⁻¹) 3329, 3160, 2924, 1458, 1224, 1139, 1049.

LCMS(ESI): ELSD 100%, R_t= 2.28 min, *m/z* calcd for C₁₀H₁₃N₃O₃ 223.10 found [M+H]⁺ 224.100.

1-[(3-methoxyphenyl)methyl]-4-(4-nitrophenyl)-1H-1,2,3-triazole (183):



Upon the general procedure 7, this product was obtained by treating the alkyne (**132a**) (0.074 g, 0.50 mmol) with 1-(azidomethyl)-4-methoxybenzene (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a yellow solid (0.158 g, Qtv).

M.p.: 138.7-140.4°C

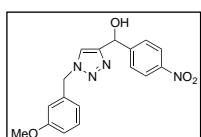
¹H NMR (300MHz, CDCl₃): δ 3.84 (s, 3H), 5.56 (s, 2H), 6.95 (d, 2H, J= 8.26Hz), 7.32 (d, 2H, J= 8.39Hz), 7.81 (s, 1H), 7.98 (d, 2H, J= 8.38Hz), 8.27 (d, 2H, J= 8.74Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 54.02, 54.39, 55.37 (d), 114.64, 120.95, 124.24, 126.09 (d), 127.39, 129.82 (d), 136.93, 145.87, 147.22, 159.62, 160.13 ppm.

FTIR (ATR): ν (cm^{-1}) 3180, 2933, 2837, 1510, 1456, 1328, 1028, 813, 756.

LCMS(ESI): ELSD 100%, R_t = 5.32 min, m/z calcd for $\text{C}_{16}\text{H}_{14}\text{N}_4\text{O}_3$ 310.11 found $[\text{M}+\text{H}]^+$ 311.250.

{1-[(3-methoxyphenyl)methyl]-1H-1, 2, 3-triazol-4-yl}(4-nitrophenyl)methanol (213):



From the general procedure 7, the reaction between the propargyl alcohol (**171a**) (0.089 g, 0.50 mmol) and the azide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2ml) gave this triazole as an orange solid (0.168 g, 98% yield).

M.p.: 155.4-156.6°C

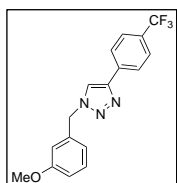
^1H NMR (300MHz, CDCl_3): δ 3.85 (s, 3H), 5.59 (s, 2H), 6.94 (d, 2H, J = 8.77Hz), 7.29 (d, 2H, J = 8.74Hz), 7.68 (br, 1H), 8.23 (d, 1H, J = 4.49Hz), 8.38 (d, 2H, J = 8.91Hz), 8.64 (d, 2H, J = 9.09Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 47.62, 55.36, 59.27, 114.21, 114.56, 123.45, 123.80, 125.98, 127.17, 129.76, 129.79, 131.68, 139.83, 147.59, 160.10 ppm.

FTIR (ATR): ν (cm^{-1}) 3050, 2972, 2900, 2360, 2336, 2095, 1515, 1348, 1250, 670, 612.

LCMS(ESI): ELSD 100%, R_t = 4.65 min, m/z calcd for $\text{C}_{17}\text{H}_{16}\text{N}_4\text{O}_4$ 340.12 found $[\text{M}+\text{H}]^+$ 341.00.

1-[(3-methoxyphenyl)methyl]-4-[4-(trifluoromethyl)phenyl]-1H-1, 2, 3-triazole (188):



According to the general procedure, this product was obtained from a reaction between the commercial available 4-ethynyl- α,α,α -trifluorotoluene (0.085 g, 0.50 mmol) and the azide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) as a white solid (0.211 g, Qtv).

M.p.: 144.2-146.0°C

^1H NMR (300MHz, CDCl_3): δ 3.81 (s, 3H), 5.52 (s, 2H), 6.92 (d, 2H, J = 8.63Hz), 7.28 (d, 2H, J = 8.69Hz), 7.64 (d, 2H, J = 7.97Hz), 7.69 (s, 1H), 7.90 (d, 2H, J = 7.88Hz) ppm.

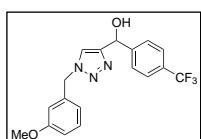
^{13}C NMR (75MHz, CDCl_3): δ 53.94, 55.37, 104.78, 114.61, 120.07, 125.70, 125.72, 125.77,

125.80, 126.32, 129.71, 129/72, 129.78, 130.14, 134.06, 144.29, 146.73, 160.03 ppm.

FTIR (ATR): ν (cm⁻¹) 3089, 1622, 1456, 1321, 1126, 840, 769.

LCMS(ESI): ELSD 100%, R_t = 5.72 min, m/z calcd for C₁₇H₁₄F₃N₃O 333.11 found [M+H]⁺ 334.050.

{1-[(3-methoxyphenyl)methyl]-1H-1,2,3-triazol-4-yl}[4-(trifluoromethyl)phenyl]methanol (218):



Upon the general procedure 7, this product was obtained by treating the propargyl alcohol (**171c**) (0.100 g, 0.50 mmol) with the azide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a pale green solid (0.188 g, Qtv).

M.p.: 134.6-136.9°C

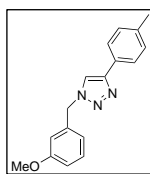
¹H NMR (300MHz, CDCl₃): δ 3.76 (s, 3H), 5.36 (s, 2H), 6.86 (d, 2H, J= 8.25Hz), 7.17 (d, 2H, J= 8.13Hz), 7.24 (s, 1H), 7.51-7.58 (m, 5H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 54.38, 55.31, 114.19, 114.45, 122.220 125.45, 126.05, 126.77, 129.76, 160.01 ppm.

FTIR (ATR): ν (cm⁻¹) 3651, 3120, 2974, 2900, 1613, 1458, 1323, 1251, 1051, 840, 669.

LCMS(ESI): ELSD 100%, R_t = 5.12 min, m/z calcd for C₁₈H₁₆F₃N₃O₂ 363.12 found [M+H]⁺ 364.00.

1-[(3-methoxyphenyl)methyl]-4-(4-methylphenyl)-1H-1,2,3-triazole (193):



According to the general procedure 7, the reaction between the commercial available 4-ethynyltoluene (0.058 g, 0.50 mmol) and the methoxyazide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a white solid (0.152 g, Qtv).

M.p.: 155.6-156.7°C

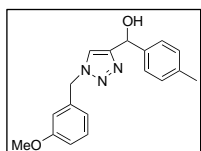
¹H NMR (300MHz, CDCl₃): δ 2.35 (s, 3H), 3.80 (s, 3H), 5.49 (s, 2H), 6.90 (d, 2H, J= 8.74Hz), 7.19 (d, 2H, J= 7.90Hz), 7.26 (d, 2H, J= 8.80Hz), 7.57 (s, 1H), 7.67 (d, 2H, J= 8.12Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 21.30, 53.71, 55.35, 114.49, 119.05, 125.59, 126.76, 127.83, 129.48, 129.66, 137.93, 148.16, 159.91 ppm.

FTIR (ATR): ν (cm⁻¹) 3130, 1610, 1514, 1454, 1433, 1340, 1244, 1024, 812, 765.

LCMS(ESI): ELSD 100%, R_t = 5.41 min, m/z calcd for C₁₇H₁₇N₃O 279.14 found [M+H]⁺ 280.200.

{1-[(3-methoxyphenyl)methyl]-1H-1, 2, 3-triazol-4-yl}(4-methylphenyl)methanol (223):



From the general procedure 7, this triazole was obtained from a reaction between the propargyl alcohol (**171e**) (0.073 g, 0.50 mmol) and the methoxyazide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ as a green solid (0.153 g, 99% yield).

M.p.: 107.0-108.1°C

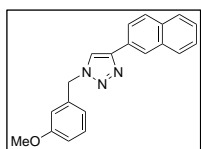
¹H NMR (300MHz, CDCl₃): δ 2.34 (s, 3H), 3.78 (s, 3H), 5.36 (s, 2H), 5.94 (s, 1H), 6.88 (d, 2H, J= 8.47Hz), 7.15 (m, 5H), 7.29 (d, 2H, J= 7.25Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 21.10, 54.35, 55.31, 114.21, 114.35, 126.43, 126.48, 129.12, 129.72, 137.46, 159.82 ppm.

FTIR (ATR): ν (cm⁻¹) 3588, 3110, 2987, 2900, 1508, 1458, 1380, 1055.

LCMS(ESI): ELSD 100%, R_t =4.68 min, m/z calcd for C₁₈H₁₉N₃O₂ 309.15 found [M+H]⁺ 310.150.

4-(6-ethynynaphthalen-2-yl)-1-[(3-methoxyphenyl)methyl]-1H-1, 2, 3-triazole (198):



Upon the general procedure 7, the reaction between the alkyne (**132d**) (0.076 g, 0.50 mmol) and the azide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a white solid (0.156 g, 99% yield).

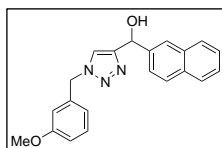
M.p.: 169.9-172.4°C

¹H NMR (300MHz, CDCl₃): δ 3.82 (d, 3H, J= 2.40Hz), 5.53 (s, 2H), 6.93 (dd, 2H, J= 2.30Hz, 8.74Hz), 7.30 (dd, 2H, J= 2.15Hz, 7.47 (dd, 2H, J= 2.70Hz, 6.50Hz), 7.73 (d, 1H, J= 2.33Hz), 7.81-7.88 (m, 4H), 8.30 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 53.87, 55.38, 114.56, 119.58, 123.86, 124.37, 126.13, 126.44, 126.61, 127.77, 127.97, 128.18, 128.54, 129.76, 133.14, 133.53, 160 ppm.

FTIR (ATR): ν (cm⁻¹) 3030, 2920, 2850, 1610, 1510, 1456, 1246, 1029, 815, 742.

LCMS(ESI): ELSD 100%, R_t = 5.68 min, m/z calcd for C₂₀H₁₇N₃O 315.14 found [M+H]⁺ 316.050.

{1-[(3-methoxyphenyl)methyl]-1H-1,2,3-triazol-4-yl}(naphthalen-2-yl)methanol (228):

From the general procedure 7, the reaction between the propargyl alcohol (**171d**) (0.091 g, 0.50 mmol) and the azide **177** (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a green solid (0.179 g, Qtv).

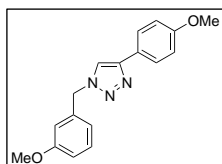
M.p.: 141.1-142.1°C

¹H NMR (300MHz, CDCl₃): δ 1.69 (br, 1H), 3.77 (s, 3H), 5.29 (s, 1H), 5.36 (s, 2H), 6.84 (d, 2H, J= 8.40Hz), 7.15 (d, 2H, J= 7.41Hz), 7.48 (dd, 3H, J= 4.45Hz, 7.44Hz), 7.82 (m, 4H), 7.90 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 54.20, 55.33, 91.53, 114.46, 124.51, 125.19, 126.17, 126.21, 127.64, 128.17, 128.19, 128.43, 129.66, 129.74, 133.14, 133.24, 159.97 ppm.

FTIR (ATR): ν (cm⁻¹) 3257, 3130, 2972, 2900, 1512, 1053, 794, 742.

LCMS(ESI): ELSD 100%, R_t= 4.99 min, m/z calcd for C₂₁H₁₉N₃O₂ 345.15 found [M+H]⁺ 346.00.

4-(4-methoxyphenyl)-1-[(3-methoxyphenyl)methyl]-1H-1, 2, 3-triazole (203):³²⁸

According to the general procedure 7, this triazole was found from a reaction between the commercial available 4-ethynylanisole (0.066 g, 0.50 mmol) and the methoxyazide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.151g, Qtv).

M.p.: 165.9-168.1°C

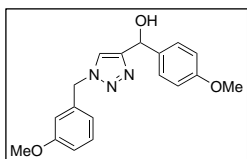
¹H NMR (300MHz, CDCl₃): δ 3.82 (t, 6H, J= 4.34 Hz), 5.49 (d, 2H, J= 3.52 Hz), 6.89-6.95 (m, 5H), 7.54 (d, 2H, J= 3.60 Hz), 7.71 (dd, 2H, J= 3.84 and 8.79 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 53.74, 55.32, 55.36, 114.20, 114.50, 118.52, 123.37, 126.75, 127, 128.80, 129.65, 134.05, 147.99, 159.58, 159.93 ppm.

FTIR (ATR): ν (cm⁻¹) 3150, 2929, 2850, 1610, 1496, 1456, 1350, 1024, 815, 765.

LCMS(ESI): ELSD 100%, R_t= 5.09 min, m/z calcd for C₁₇H₁₇N₃O₂ 295.34 found [M+H]⁺ 296.050.

³²⁸D. Linares, O. Bottzcek, O. Pereira, A. Praud-Tabaries, Y. Blache, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6751-55.

(4-methoxyphenyl)({1-[(3-methoxyphenyl)methyl]-1H-1, 2, 3-triazol-4-yl})methanol (233):

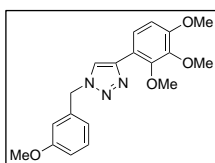
Upon the general procedure 7, the reaction between the propargyl alcohol (**171b**) (0.081 g, 0.50 mmol) and the azide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a green oil (0.179 g, Qtv).

¹H NMR (300MHz, CDCl₃): δ 3.77 (s, 6H), 5.36 (s, 1H), 6.83-6.86 (m, 4H), 7.13-7.23 (m, 4H), 7.29 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 53.57, 55.25, 73.42, 113.80, 113.88, 114.06, 114.19, 114.35, 126.44, 126.58, 127.90, 128.60, 128.72, 129.65, 129.73, 131.53, 159.29, 159.39, 159.77, 159.84 ppm.

FTIR (ATR): ν (cm⁻¹) 3273, 3150, 2931, 2837, 1610, 1510, 1458, 1301, 1242, 1172, 1026, 804.

LCMS(ESI): ELSD 99%, R_t= 5.73 min, *m/z* calcd for C₁₈H₁₉N₃O₃ 325.36 found [M+H]⁺ 326.200.

1-[(3-methoxyphenyl)methyl]-4-(2,3,4-trimethoxyphenyl)-1H-1,2,3-triazole (208):

According to the general procedure 7, this triazole was obtained from a reaction between the alkyne (**132e**) (0.096 g, 0.50 mmol) and the methoxy azide (**177**) (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a green solid (0.177 g, 100% yield).

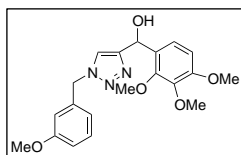
M.p.: 108.0-110.0°C

¹H NMR (300MHz, CDCl₃): δ 3.78 (d, 6H, J= 2.59 Hz), 3.87 (dd, 6H, J= 2.96 and 3.80 Hz), 5.49 (s, 2H), 6.77 (dd, 1H, J= 2.69 and 8.84 Hz), 6.88 (dd, 3H, J= 2.46 and 8.72 Hz), 7.23 (d, 1H, J= 2.27 Hz), 7.85 (d, 1H, J= 3.01 Hz), 7.93 (dd, 1H, J= 2.96 and 8.82 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 55.29, 56.03, 60.24, 60.85, 107.95, 114.18, 114.37, 117.62, 121.61, 122.13, 127.09, 129.42, 142.31, 143.48, 150.53, 153.54, 159.78 ppm.

FTIR (ATR): ν (cm⁻¹) 3190, 2935, 2837, 1610, 1463, 1292, 1246, 777, 812.

LCMS(ESI): ELSD 100%, R_t= 5.31 min, *m/z* calcd for C₁₉H₂₁N₃O₄ 355.39 found [M+H]⁺ 356.00.

{1-[(3-methoxyphenyl)methyl]-1H-1,2,3-triazol-4-yl}(2,3,4-trimethoxyphenyl)methanol (238):

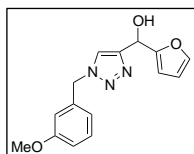
From the general procedure 7, the reaction between the propargyl alcohol (**171f**) (0.111 g, 0.50 mmol) and the azide **177** (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a green solid (0.186g, 96% yield).

¹H NMR (300MHz, DMSO d₆): δ 3.62 (s, 2H), 3.74 (d, 10H, J= 13.75 Hz), 5.45 (s, 2H), 5.75 (s, 1H), 5.97 (s, 1H), 6.80 (d, 1H, J= 6.87 Hz), 6.90-6.97 (m, 2H), 7.13 (d, 1H, J= 7.03 Hz), 7.27-7.30 (m, 2H), 7.87 (s, 1H) ppm.

¹³C NMR (75MHz, DMSO d₆): δ 52.79, 53.70, 55.59, 56.28, 60.70, 61.22, 108.26, 114.50, 114.54, 122.22, 127.86, 128.59, 130.10, 130.53, 141.84, 150.74, 152.97, 159.60, 159.66 ppm.

FTIR (ATR): ν (cm⁻¹) 3327, 3120, 2935, 2837, 1610, 1512, 1462, 1415, 1093, 1029, 798, 720.

LCMS(ESI): ELSD 100%, R_t= 4.46 min, *m/z* calcd for C₂₀H₂₃N₃O₅ 385.41 found [M+H]⁺ 386.050.

Furan-2-yl({1-[(3-methoxyphenyl)methyl]-1H-1,2,3-triazol-4-yl})methanol (243):

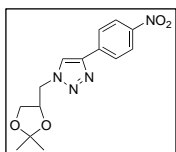
Upon the general procedure 7, this product was obtained by treating the propargyl alcohol (**171g**) (0.061 g, 0.50 mmol) with the methoxyazide (0.090 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a brown oil (0.190 g, Qtv).

¹H NMR (300MHz, CDCl₃): δ 3.79 (s, 3H), 5.29 (s, 1H), 5.43 (s, 2H), 6 (br, 1H), 6.27-6.32 (m, 2H), 6.88 (d, 2H, J= 8.51 Hz), 7.21 (d, 2H, J= 8.42 Hz), 7.37 (s, 1H), 7.46 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 53.81, 54.34, 62.96, 107.68, 110.33, 114.18, 114.42, 126.41, 127.60, 129.72, 142.51, 154.18, 159.84 ppm.

FTIR (ATR): ν (cm⁻¹) 3367, 3136, 2933, 2837, 1610, 1512, 1458, 1438, 1359, 1246, 1176, 1028, 817, 767.

LCMS(ESI): ELSD 100%, R_t= 4.21 min, *m/z* calcd for C₁₅H₁₅N₃O₃ 285.30 found [M+H]⁺ 286.00.

(R,S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(4-nitrophenyl)-1H-1,2,3-triazole (184a):

According to the general procedure 7, this product was obtained from a reaction between the alkyne (**132a**) (0.074 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) and A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a yellow solid (0.120 g, 79% yield).

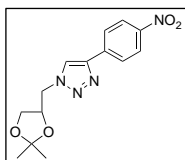
M.p.: 131.2-134.5°C

¹H NMR (300MHz, CDCl₃): δ 1.31 (s, 3H), 1.36 (s, 3H), 3.78 (dd, 1H, J= 8.77Hz, 5.55Hz), 4.15 (dd, 1H, J= 8.68Hz, 6.26Hz), 4.42-4.50 (m, 2H), 4.64 (q, 1H, J= 8.54Hz), 7.98 (d, 2H, J= 8.62Hz), 8.08 (s, 1H), 8.25 (d, 2H, J= 8.66) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.14, 26.74, 52.66, 66.35, 73.98, 110.40, 122.58, 124.31, 126.18, 136.87, 145.58, 147.30 ppm.

FTIR (ATR): ν (cm⁻¹) 3132, 2978, 2887, 1541, 1458, 1375, 1056, 879, 669.

LCMS(ESI): ELSD 100%, R_t= 4.99 min, *m/z* calcd for C₁₄H₁₆N₄O₄ 304.12 found [M+H]⁺ 305.10.

(S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(4-nitrophenyl)-1H-1,2,3-triazole (184b):

Upon the general procedure 7, the reaction between the alkyne (**132a**) (0.074 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a yellow solid (131.41 g, 86% yield).

M.p.: 132.2-134.2°C

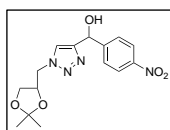
¹H NMR (300MHz, CDCl₃): δ 1.34 (s, 3H), 1.39 (s, 3H), 3.77 (dd, 1H, J= 8.9, 5.6Hz), 4.16 (dd, 1H, J= 8.9, 6.3Hz), 4.43-4.54 (m, 2H), 4.64 (d, 1H, J= 10.7Hz), 8.0 (dd, 2H, J= 8.6, 1.8Hz), 8.04 (s, 1H), 8.27 (d, 2H, J= 8.8Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.14, 26.74, 52.66, 66.34, 73.98, 81.60, 82.42, 110.41, 122.57, 123.54, 124.32, 126.16, 128.94, 129.70, 132.06, 132.96, 136.85, 147.27 ppm.

FTIR (ATR): ν (cm⁻¹) 3120, 2978, 2887, 1541, 1458, 1375, 1056, 879, 669.

LCMS(ESI): ELSD 63%, R_t= 5.06 min, *m/z* calcd for C₁₄H₁₆N₄O₄ 304.12 found [M+H]⁺ 304.95.

(R,S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(4-nitrophenyl) methanol (213a):



Upon the general procedure 7, this product was obtained from a reaction between the propargyl alcohol (**171a**) (0.089 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as an orange solid (0.141 g, 84% yield).

M.p.: 98.0-99.7°C

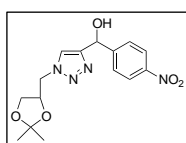
¹H NMR (300MHz, CDCl₃): δ 1.19 (s, 2H), 1.26 (s, 4H), 3.61-3.67 (m, 1H), 4.0-4.07 (m, 1H), 4.32-4.48(m, 4H), 6.11 (d, 1H, J= 6.5Hz), 7.42 (s, 1H), 7.62 (d, 2H, J= 8.6Hz), 8.16 (d, 2H, J= 8.6Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.01, 25.04, 26.47, 26.57, 52.31, 52.40, 66.04, 66.16, 73.76, 110.19, 110.22, 122.95, 123.08, 123.65, 123.74, 127.13, 127.20, 127.24, 147.33, 147.35, 147.48, 149.19, 149.47, 150.29, 150.35 ppm.

FTIR (ATR): ν (cm⁻¹) 3192, 3050, 2922, 2852, 1510, 1456, 1380, 1342, 1222, 1128, 1039, 821, 742.

LCMS(ESI): ELSD 100%, R_t= 4.17 min, *m/z* calcd for C₁₅H₁₈N₄O₅ 334.13 found [M+H]⁺ 335.15.

(S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(4-nitrophenyl)methanol (214b):



According to the general procedure 7, the reaction between the propargyl alcohol (**171a**) (0.089 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) gave this triazole as an orange solid (0.123 g, 74% yield).

M.p.: 103.0-104.6°C

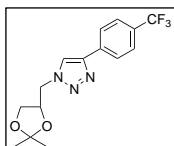
¹H NMR (300MHz, CDCl₃): δ 1.18 (s, 3H), 1.26 (s, 3H), 3.63 (m, 1H), 4.04 (m, 1H), 4.34-4.47 (m, 3H), 5 (br, 1H), 5.05 (d, 1H, J= 4.99Hz), 7.45 (s, 1H), 7.61 (d, 2H, J= 8.70Hz), 8.13 (d, 2H, J= 8.61Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.02, 25.04, 26.47, 26.54, 52.32, 52.41, 66.10, 66.17, 67.78, 67.81, 73.76, 110.20, 110.26, 122.95, 123.08, 123.66, 127.14, 127.21, 147.35, 147.37, 149.33, 150.25, 150.33 ppm.

FTIR (ATR): ν (cm^{-1}) 3278, 3050, 2978, 2906, 1650, 1521, 1450, 1375, 1249, 1224, 1066, 821, 669.

LCMS(ESI): ELSD 95%, $R_t = 4.27$ min, m/z calcd for $\text{C}_{15}\text{H}_{18}\text{N}_4\text{O}_5$ 334.13 found $[\text{M}+\text{H}]^+$ 335.00.

(R,S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-[4-(trifluoromethyl)phenyl]-1H-1,2,3-triazole (189a):



Upon the general procedure 7, the reaction between the commercial available 4-ethynyl- α,α,α -trifluorotoluene (0.085 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) gave this product as a white solid (0.140 g, 86% yield).

M.p.: 132.4-133.7°C

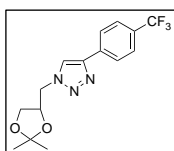
^1H NMR (300MHz, CDCl_3): δ 1.35 (s, 3H), 1.39 (s, 3H), 3.78 (dd, 1H, $J = 8.74\text{Hz}, 5.76\text{Hz}$), 4.15 (dd, 1H, $J = 8.73\text{Hz}, 6.26\text{Hz}$), 4.04-4.64 (m, 3H), 7.61 (d, 2H, $J = 7.84\text{Hz}$), 7.95 (d, 2H, $J = 7.8\text{Hz}$), 8.07 (dd, 1H, $J = 0.02\text{Hz}$) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 25.18, 26.72, 52.52, 66.38, 74.04, 110.35, 118.71, 122.05, 125.84, 125.88, 129.30, 129.33, 130.59, 130.60, 134.09, 146.5 ppm.

FTIR (ATR): ν (cm^{-1}) 3142, 2987, 2900, 1630, 1460, 1325, 1066, 891, 669.

LCMS(ESI): ELSD 100%, $R_t = 5.51$ min, m/z calcd for $\text{C}_{15}\text{H}_{16}\text{F}_3\text{N}_3\text{O}_2$ 327.12 found $[\text{M}+\text{H}]^+$ 328.10.

(S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-[4-(trifluoromethyl)phenyl]-1H-1,2,3-triazole (189b):



From the general procedure 7, the reaction between the commercial available 4-ethynyl- α,α,α -trifluorotoluene (0.085 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH_2Cl_2 (2 ml) gave this triazole as a white solid (0.121 g, 74% yield).

M.p.: 128.1-129.8°C

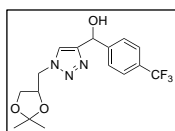
¹H NMR (300MHz, CDCl₃): δ 1.39 (s, 3H), 1.43 (s, 3H), 3.81 (dd, 1H, J= 8.80Hz, 5.77Hz), 4.18 (dd, 1H, J= 8.76Hz, 6.27Hz), 4.50-4.68 (m, 3H), 7.70 (d, 2H, J= 8.16 Hz), 7.97 (d, 2H, J= 8.23 Hz), 8.03 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.17, 26.72, 52.50, 66.36, 74.03, 110.35, 121.83, 125.87, 127.06, 129.75, 130.18, 134.02, 146.40 ppm.

FTIR (ATR): ν (cm⁻¹) 3089, 2966, 2902, 1650, 1458, 1325, 1064, 827, 669.

LCMS(ESI): ELSD 95%, R_t= 5.75 min, m/z calcd for C₁₅H₁₆F₃N₃O₂ 327.12 found [M+H]⁺ 328.00.

(R,S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}[4-(trifluoromethyl)phenyl]methanol (219a**):**



Upon the general procedure 7, this product was found from a reaction between the propargyl alcohol (**171c**) (0.100 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a yellow solid (0.153 g, 86% yield).

M.p.: 131.2-132.9°C

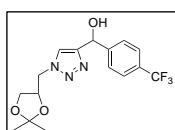
¹H NMR (300MHz, CDCl₃): δ 1.17 (s, 2H), 1.26 (dd, 4H, J= 4.4, 2.3Hz), 3.59-3.66 (m, 1H), 4.00-4.05 (dd, 1H, J= 8.6, 4.9Hz), 4.30-4.45 (m, 4H), 6.06 (d, 1H, J= 8.2Hz), 7.38 (s, 1H), 7.53-7.59 (m, 4H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.06, 26.41, 26.51, 52.18, 52.20, 66.11, 66.20, 68.17, 68.18, 68.21, 73.78, 110.19, 110.25, 125.43, 125.48, 125.49, 125.54, 126.59, 126.70, 122.3, 125.9, 129.7, 130.1, 146.04, 146.06 ppm.

FTIR (ATR): ν (cm⁻¹) 3261, 3120, 2987, 2899, 1620, 1420, 1350, 1323, 1047, 821, 792.

LCMS(ESI): ELSD 100%, R_t= 4.69 min, m/z calcd for C₁₆H₁₈F₃N₃O₃ 357.13 found [M+H]⁺ 358.10.

(S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}[4-(trifluoromethyl)phenyl]methanol (219b**):**



From the general procedure 7, the reaction between the propargyl alcohol (**171c**) (0.100 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033

g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a yellow solid (0.100 g, 65% yield).

M.p.: 116.2-118.5°C

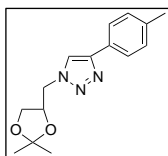
¹H NMR (300MHz, CDCl₃): δ 1.14 (s, 3H), 1.24 (s, 3H), 3.56-3.64 (m, 1H), 3.97-4.03 (m, 1H), 4.32-4.45 (m, 3H), 6.04 (d, 1H, J=7.8Hz), 7.39 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.04, 26.37, 26.49, 52.11, 52.28, 66.07, 66.19, 68.05, 73.75, 73.77, 110.17, 110.23, 122.29, 122.86, 123.05, 125.33, 125.90, 126.52, 126.70, 129.66, 130.12, 146.09, 146.11, 150.79, 150.80, 150.90 ppm.

FTIR (ATR): ν (cm⁻¹) 3299, 3120, 2987, 2900, 1620, 1480, 1323, 1251, 1224, 1111, 1064, 819, 792.

LCMS(ESI): ELSD 95%, R_t= 5.75 min, *m/z* calcd for C₁₆H₁₈F₃N₃O₃ 357.13 found [M+H]⁺ 358.00.

(R,S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(3-methylphenyl)-1H-1,2,3-triazole (194a):



According to the general procedure 7, this triazole was obtained by treating the commercial available 4-ethynyltoluene (0.058 g, 0.50 mmol) with the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.112 g, 82% yield).

M.p.: 126.8-128.1°C

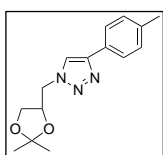
¹H NMR (300MHz, CDCl₃): δ 1.33 (s, 3H), 1.37 (s, 3H), 2.35 (s, 3H), 3.75 (dd, 1H, J= 8.8Hz, 4.8Hz), 4.11 (dd, 1H, J= 8.8, 6.1Hz), 4.40-4.58 (m, 3H), 7.21 (d, 2H, J= 7.74Hz), 7.7 (d, 2H, J= 7.8Hz), 7.83 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 21.31, 25.28, 26.74, 52.27, 66.47, 74.16, 110.24, 120.64, 125.65, 127.75, 129.54, 138.02, 147.88 ppm.

FTIR (ATR): ν (cm⁻¹) 3142, 2978, 2900, 1600, 1480, 1373, 1250, 1066, 827, 802.

LCMS(ESI): ELSD 100%, R_t= 5.12 min, *m/z* calcd for C₁₅H₁₉N₃O₂ 273.15 found [M+H]⁺ 274.10.

(S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(3-methylphenyl)-1H-1,2,3-triazole (194b) :



Upon the general procedure 7, the reaction between the commercial available

4-ethynyltoluene (0.058 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a white solid (0.077 g, 57% yield).

M.p.: 139.1-141.6°C

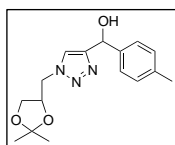
¹H NMR (300MHz, CDCl₃): δ 1.35 (s, 3H), 1.39 (s, 3H), 2.37 (s, 3H), 3.76 (dd, 1H, J= 8.76Hz, 5.86Hz), 4.12 (dd, 1H, J= 8.77Hz, 6.18Hz), 4.42-4.60 (m, 3H), 7.22 (d, 2H, J= 7.86Hz), 7.71 (d, 2H, J= 8.13Hz), 7.86 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 21.32, 25.28, 26.74, 52.27, 66.46, 74.15, 110.85, 120.65, 125.65, 127.74, 129.54, 138.64, 147.87 ppm.

FTIR (ATR): ν (cm⁻¹) 3142, 2970, 2900, 1630, 1400, 1394, 1251, 1228, 1056, 893, 867.

LCMS(ESI): ELSD 100%, R_t= 5.30 min, *m/z* calcd for C₁₅H₁₉N₃O₂ 273.15 found [M+H]⁺ 273.95.

(R,S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(4-methylphenyl)methanol (224a**):**



According to the general procedure 7, the reaction between the propargyl alcohol (**171e**) (0.073 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a yellow solid (0.131 g, 87% yield).

M.p.: 89.0-90.0°C

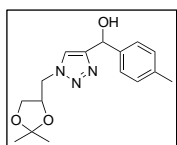
¹H NMR (300MHz, CDCl₃): δ 1.32 (s, 3H), 1.36 (s, 3H), 2.34 (s, 3H), 3.71-3.76 (m, 1H), 4.07-4.12 (m, 1H), 4.26-4.45 (m, 4H), 5.97 (br, 1H), 7.15 (d, 2H, J= 7.79Hz), 7.32 (d, 2H, J= 7.70Hz), 7.43 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 21.15, 25.17, 26.50, 26.58, 52, 66.24, 66.33, 68.61, 110, 110.13, 122.74, 122.90, 126.30, 126.43, 129.15, 129.16, 137.44, 137.50, 139.98, 151.65, 151.75 ppm.

FTIR (ATR): ν (cm⁻¹) 3319, 3118, 2983, 2922, 1620, 1456, 1375, 1219, 1043, 833, 786.

LCMS(ESI): ELSD 100%, R_t= 4.23 min, *m/z* calcd for C₁₆H₂₁N₃O₃ 303.16 found [M+H]⁺ 304.10.

(S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(4-methylphenyl)methanol (224b):



From the general procedure 7, the reaction between the propargyl alcohol (**171e**) (0.073 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a yellow solid (0.097 g, 64% yield).

M.p.: 76.9-78.9°C

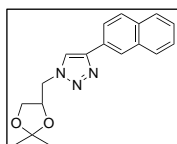
¹H NMR (300MHz, CDCl₃): δ 1.20 (s, 3H), 1.28 (s, 3H), 2.31 (s, 3H), 3.58-3.65 (m, 1H), 3.96-4.02 (m, 1H), 4.32-4.40 (m, 3H), 5.91 (d, 1H, J= 5.9Hz), 7.11 (d, 2H, J= 7.8Hz), 7.27 (d, 2H, J= 8.1Hz), 7.36 (d, 1H, J= 2.8Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 21.16, 25.17, 25.19, 26.51, 26.59, 52.02, 52.11, 66.25, 66.31, 68.71, 68.76, 73.89, 110.12, 110.16, 122.71, 122.86, 126.30, 126.48, 129.17, 137.09, 137.55, 139.24, 151.58, 151.68 ppm.

FTIR (ATR): ν (cm⁻¹) 3319, 3118, 2987, 2902, 1650, 1541, 1460, 1420, 1066, 891, 669.

LCMS(ESI): ELSD 100%, R_t= 4.30 min, *m/z* calcd for C₁₆H₂₁N₃O₃ 303.16 found [M+H]⁺ 304.00.

(R,S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(naphthalen-2-yl)-1H-1,2,3-triazole (199a):



From the general procedure 7, this triazole was obtained by treating the alkyne (**132d**) (0.090 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a white solid (0.127 g, 82% yield).

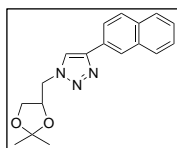
M.p.: 184.2-185.6°C

¹H NMR (300MHz, CDCl₃): δ 1.35 (s, 3H), 1.40 (s, 3H), 3.75-3.80 (m, 1H), 4.10-4.16 (m, 1H), 4.47-4.64 (m, 3H), 7.43-7.50 (m, 2H), 7.80-7.93 (m, 4H), 7.99 (s, 1H), 8.33 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.29, 26.75, 52.43, 66.50, 74.17, 110.33, 123.88, 124.43, 126.18, 126.48, 127.80, 128.22, 128.61, 133.18, 133.57 ppm.

FTIR (ATR): ν (cm⁻¹) 3110, 2978, 2908, 1690, 1541, 1430, 1226, 1051, 806, 669.

LCMS(ESI): ELSD 100%, R_t= 5.38 min, *m/z* calcd for C₁₈H₁₉N₃O₂ 309.15 found [M+H]⁺ 310.15.

(S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(naphthalen-2-yl)-1H-1,2,3-triazole (199b):

Upon the general procedure 7, the reaction between the alkyne (**132d**) (0.090 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a white solid (0.130 g, 85% yield).

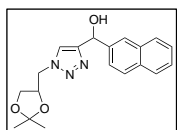
M.p.: 187.7-189.4°C

¹H NMR (300MHz, CDCl₃): δ 1.36 (s, 3H), 1.40 (s, 3H), 3.74-3.79 (m, 1H), 4.10-4.14 (m, 1H), 4.45-4.63 (m, 3H), 7.46-7.49 (m, 2H), 7.85-7.92 (m, 4H), 8.00 (s, 1H), 8.34 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.28, 26.78, 52.43, 66.49, 74.17, 110.32, 121.26, 121.27, 123.88, 124.43, 126.17, 126.48, 127.79, 127.91, 128.21, 128.60, 133.18, 133.56, 147.87 ppm.

FTIR (ATR): ν (cm⁻¹) 3149, 2987, 2900, 1670, 1460, 1373, 1224, 1051, 837, 759.

LCMS(ESI): ELSD 100%, R_t= 5.71 min, *m/z* calcd for C₁₈H₁₉N₃O₂ 309.15 found [M+H]⁺ 310.00.

(R,S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(naphthalen-2-yl)methanol (229a):

According to the general procedure 7, this triazole was found from a reaction between the propargylic alcohol (**171d**) (0.091 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) and A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a yellow solid (0.143 g, 85% yield).

M.p.: 109.6-111.5°C

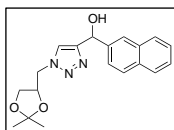
¹H NMR (300MHz, CDCl₃): δ 1.14 (s, 2H), 1.23 (d, 4H, J=4Hz), 3.54-3.62 (m, 1H), 3.92-3.98 (m, 1H), 4.23-4.34 (m, 3H), 6.14 (d, 1H, J=8.4Hz), 7.34 (d, 1H, J=4.3Hz), 7.41-7.49 (m, 3H), 7.73-7.78 (m, 3H), 7.88 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.14, 25.149, 26.47, 26.56, 25.01, 25.14, 66.18, 66.27, 68.85, 68.93, 73.83, 110.11, 110.14, 110.16, 122.89, 123.06, 124.52, 124.60, 124.93, 125.16, 126.04, 126.07, 126.22, 127.68, 128.19, 128.29, 128.32, 133, 133.02, 133.23, 139.60, 151.37, 151.48 ppm.

FTIR (ATR): ν (cm⁻¹) 3207, 3064, 2924, 2852, 1650, 1541, 1440, 1253, 1222, 1045, 794, 669.

LCMS(ESI): ELSD 100%, R_t= 4.53 min, *m/z* calcd for C₁₉H₂₁N₃O₃ 339.16 found [M+H]⁺ 340.15.

(S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(naphthalen-2-yl)methanol (229b):



Upon the general procedure 7, the reaction between the propargyl alcohol (**171d**) (0.091 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.55 mmol) in CH₂Cl₂ (2 ml) gave this product as a white solid (0.124 g, 75% yield).

M.p.: 108.7-109.9°C

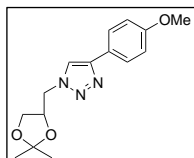
¹H NMR (300MHz, CDCl₃): δ 1.15 (s, 3H), 1.21 (s, 3H), 3.52-3.60 (m, 1H), 3.91-3.95 (m, 1H), 4.23-4.34 (m, 3H), 4.78 (br, 1H), 6.15 (d, 1H, J= 7.81Hz), 7.36 (s, 1H), 7.42-7.46 (m, 3H), 7.75-7.77 (m, 3H), 7.89 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.13, 26.47, 26.56, 52, 52.14, 62.27, 66.17, 68.81, 73.81, 73.83, 110.09, 110.15, 124.55, 124.63, 124.99, 125.16, 126.04, 126.06, 126.21, 132.99, 133.24, 139.64 ppm.

FTIR (ATR): ν (cm⁻¹) 3207, 3064, 2985, 2900, 1630, 1420, 1350, 1228, 1066, 792, 669.

LCMS(ESI): ELSD 100%, R_t= 4.66 min, m/z calcd for C₁₉H₂₁N₃O₃ 339.16 found [M+H]⁺ 340.00.

(R,S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(4-methoxyphenyl)-1H-1,2,3-triazole (204a):



Upon the general procedure 7, this triazole was found from a reaction between the commercial available 4-ethynylanisole (0.066 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.55 mmol) in CH₂Cl₂ (2 ml) as a yellow solid (0.102 g, 71% yield).

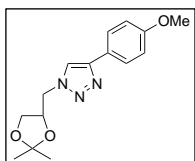
M.p.: 143.1-147.1°C

¹H NMR (300MHz, CDCl₃): δ 1.33 (s, 3H), 1.37 (s, 3H), 3.72-3.79 (m, 1H), 3.83 (d, 3H, J= 5Hz), 4.08-4.13 (m, 1H), 4.40-4.59 (m, 3H), 6.92-6.96 (m, 2H), 7.72-7.76 (m, 2H), 7.79 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.27, 26.74, 52.27, 55.33, 66.48, 110.21, 114.26, 120.20, 123.31, 127.03, 147.64, 159.61 ppm.

FTIR (ATR): ν (cm⁻¹) 3138, 2980, 2933, 1500, 1458, 1375, 1249, 1066, 837, 806.

LCMS(ESI): ELSD 100%, R_t= 4.64 min, m/z calcd for C₁₅H₁₉N₃O₃ 289.14 found [M+H]⁺ 290.150.

(S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(4-methoxyphenyl)-1H-1,2,3-triazole (204b):

According to the general procedure 7, the reaction between the commercial available 4-ethynylanisole (0.066 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a white solid (0.148 g, Qtv).

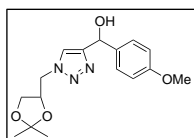
M.p.: 152.5-154.1°C

¹H NMR (300MHz, CDCl₃): δ 1.33 (s, 3H), 1.37 (s, 3H), 3.72-3.79 (m, 1H), 3.83 (d, 3H, J= 5Hz), 4.08-4.13 (m, 1H), 4.40-4.59 (m, 3H), 6.92-6.96 (m, 2H), 7.72-7.76 (m, 2H), 7.79 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.27, 26.74, 52.27, 55.33, 66.48, 110.21, 114.26, 120.20, 123.31, 127.03, 147.64, 159.61 ppm.

FTIR (ATR): ν (cm⁻¹) 3138, 2956, 2840, 1616, 1458, 1375, 1249, 1170, 1066, 1028, 806, 713.

LCMS(ESI): ELSD 100%, R_t= 4.62 min, *m/z* calcd for C₁₅H₁₉N₃O₃ 289.14 found [M+H]⁺ 290.00.

(R,S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(4-methoxyphenyl)methanol (234a):

From the general procedure 7, the reaction between the propargyl alcohol (**171b**) (0.081 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a yellow solid (0.066 g, 42% yield).

M.p.: 108.4-109.6°C

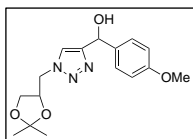
¹H NMR (300MHz, CDCl₃): δ 1.2(s, 3H), 1.29 (s, 3H), 3.60-3.67 (m, 1H), 3.75 (s, 3H), 3.99-4.03(m, 1H), 4.30-4.51 (m, 3H), 5.92 (d, 1H, J= 6.70Hz), 6.24 (d, 2H, J= 8Hz), 7.32 (d, 2H, J= 8.28Hz), 7.39 (d, 2H, J= 5.34Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.18, 26.54, 26.6, 52.05, 52.13, 55.31, 66.27, 66.33, 68.62, 68.66, 73.9, 110.14, 110.17, 113.9, 122.60, 122.74, 127.70, 127.82, 134.39, 151.60, 151.7, 159.24, 159.27 ppm.

FTIR (ATR): ν (cm⁻¹) 3404, 3142, 2987, 2922, 1608, 1510, 1456, 1373, 1242, 1174, 1039, 833, 810.

LCMS(ESI): ELSD 100%, R_t= 4.04 min, *m/z* calcd for C₁₆H₂₁N₃O₄ 319.15 found [M+H]⁺ 320.15.

(S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(4-methoxyphenyl)methanol (234b):



Upon the general procedure 7, this product was found from a reaction between the propargyl alcohol (**171b**) (0.081 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a yellow oil (0.068 g, 43% yield).

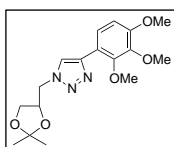
¹H NMR (300MHz, CDCl₃): δ 1.25 (s, 3H), 1.28 (s, 3H), 3.59-3.64 (m, 1H), 3.76 (s, 3H), 3.96-4.01 (m, 1H), 4.31-4.39 (m, 3H), 5.88 (d, 1H, J= 5.88Hz), 6.83 (d, 2H, J= 7.6Hz), 7.31 (d, 2H, J= 8.6Hz), 7.37 (d, 2H, J= 4.9Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.17, 26.54, 52.05, 52.14, 53.31, 66.26, 66.32, 68.62, 68.65, 73.91, 110.14, 110.17, 113.95, 114.12, 122.74, 122.61, 127.70, 127.82, 134.37, 151.59, 151.80, 159.25 ppm.

FTIR (ATR): ν (cm⁻¹) 3383, 3142, 2985, 2900, 1610, 1510, 1456, 1373, 1244, 1172, 1031, 829, 796.

LCMS(ESI): ELSD 100%, R_t= 3.91 min, m/z calcd for C₁₆H₂₁N₃O₄ 319.15 found [M+H]⁺ 320.00.

(R,S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(2,3,4-trimethoxyphenyl)-1H-1,2,3-triazole (209a):



According to the general procedure 7, the reaction between the alkyne (**132e**) (0.096 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a yellow solid (0.173 g, 99% yield).

M.p.: 80.0-81.3°C

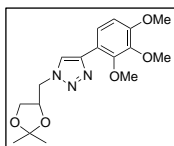
¹H NMR (300MHz, CDCl₃): δ 1.26 (s, 3H), 1.32 (s, 3H), 3.69-3.74 (m, 1H), 3.77 (s, 3H), 3.82 (d, 9H, J= 2.7), 4.02-4.06 (m, 1H), 4.38-4.54 (m, 3H), 6.72 (d, 1H, J= 8.89Hz), 7.86 (d, 1H, J= 8.89Hz), 8.00 (d, 1H, J= 1.50Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.22, 26.73, 52.09, 56.03, 60.32, 60.88, 66.90, 74.15, 107.92, 110.07, 117.47, 122.13, 123.13, 142.29, 143.14, 150.56, 153.56 ppm.

FTIR (ATR): ν (cm⁻¹) 3190, 2985, 2899, 1471, 1379, 1284, 1234, 1083, 1037, 835, 786.

LCMS(ESI): ELSD 97%, R_t= 4.88 min, m/z calcd for C₁₇H₂₃N₃O₅ 349.16 found [M+H]⁺ 350.15.

(S)1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4-(2,3,4-trimethoxyphenyl)-1H-1,2,3-triazole (209b):



From the general procedure 7, the reaction between the alkyne (**132e**) (0.096 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ gave this triazole as a yellow oil (0.130 g, 75% yield).

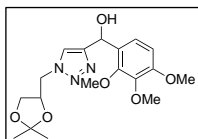
¹H NMR (300MHz, CDCl₃): δ 1.29 (s, 3H), 1.35 (s, 3H), 3.72-3.77 (m, 1H), 3.85 (d, 9H, J= 1.9Hz), 4.05-4.09 (m, 1H), 4.40-4.55 (m, 3H), 6.74 (d, 1H, J= 8.80Hz), 7.89 (d, 1H, J= 8.8Hz), 8.02 (s, 1H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.25, 26.75, 52.13, 56.03, 60.36, 60.92, 66.55, 74.17, 107.94, 110.13, 117.47, 122.18, 123.14, 142.32, 143.20, 150.59, 153.60 ppm.

FTIR (ATR): ν (cm⁻¹) 3169, 2937, 2837, 1707, 1606, 1552, 1469, 1354, 1280, 1230, 1083, 854, 800.

LCMS(ESI): ELSD 100%, R_t= 5.02 min, *m/z* calcd for C₁₇H₂₃N₃O₅ 349.16 found [M+H]⁺ 350.050.

(S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(2,3,4-trimethoxyphenyl)methanol (239b):



Upon the general procedure 7, this triazole was found from a reaction between the propargyl alcohol (**171f**) (0.111 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) as a green oil (0.176 g, 93% yield).

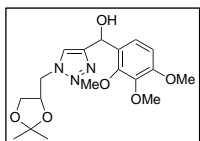
¹H NMR (300MHz, CDCl₃): δ 1.29 (s, 6H), 3.65-3.73 (m, 1H), 3.78 (s, 3H), 3.82 (s, 7H), 4.03-4.07 (m, 1H), 4.33-4.49 (m, 1H), 6.11 (d, 1H, J= 3.74Hz), 6.63 (d, 1H, J= 8.66Hz), 7.05 (d, 1H, J= 8.63Hz), 7.50 (d, 1H, J= 6.14Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.11, 25.18, 26.56, 26.60, 52.13, 52.20, 56.00, 60.75, 61.10, 65.19, 65.25, 66.30, 66.36, 73.97, 74.05, 107.28, 110.11, 110.15, 122.00, 122.09, 122.61, 122.72, 128.10, 141.96, 151.09, 151.19, 153.57 ppm.

FTIR (ATR): ν (cm⁻¹) 3383, 3130, 2983, 2935, 1749, 1598, 1492, 1463, 1373, 1253, 1217, 1151, 1091, 1043, 796, 720.

LCMS(ESI): ELSD 100%, R_t= 3.89 min, *m/z* calcd for C₁₈H₂₅N₃O₆ 379.17 found [M+H]⁺ 380.050.

(*R,S*){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(2,3,4-trimethoxyphenyl)methanol (239a**):**



Upon the general procedure 7, the reaction between the propargyl alcohol (**171f**) (0.111 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this triazole as a yellow oil (0.112 g, 59% yield).

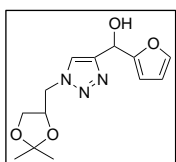
¹H NMR (300MHz, CDCl₃): δ 1.29 (d, 6H, J= 3.14 Hz), 3.66-3.71 (m, 2H), 3.79 (d, 3H, J= 2.41 Hz), 3.83 (d, 6H, J= 1.62 Hz), 4.04-4.10 (m, 1H), 4.36-4.51 (m, 2H), 6.12 (d, 1H, J= 2.96 Hz), 6.64 (d, 1H, J= 8.65 Hz), 7.05 (dd, 1H, J= 1.85 and 8.62 Hz), 7.51 (d, 1H, J= 5.93 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.12, 25.20, 26.58, 26.61, 52.23, 56.01, 60.74, 61.10, 65.34, 66.32, 66.39, 73.98, 74.06, 107.29, 107.31, 110.11, 110.14, 122.01, 122.10, 122.60, 122.73, 128.09, 141.99, 151.13, 153.60 ppm.

FTIR (ATR): ν (cm⁻¹) 3402, 2983, 2939, 1598, 1463, 1278, 1217, 1091, 1043, 1008, 898, 796, 690.

LCMS(ESI): ELSD 98%, R_t= 4.04 min, *m/z* calcd for C₁₈H₂₅N₃O₆ 379.17 found [M+H]⁺ 380.200.

(*R,S*){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(furan-2-yl)methanol (244a**):**



From the general procedure 7, the reaction between the propargyl alcohol (**171g**) (0.061 g, 0.50 mmol) and the azide (**179b**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a brown oil (0.111 g, 80% yield).

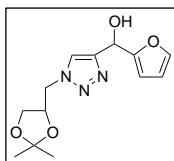
¹H NMR (300MHz, CDCl₃): δ 1.33 (d, 6H, J= 8.58Hz), 3.71 (ddd, 1H, J= 8.70Hz, 6.76Hz, 5.65Hz), 4.08 (ddd, 1H, J= 8.50Hz, 6.25Hz, 2.14Hz), 4.39-4.55 (m, 3H), 6.02 (d, 1H, J= 4.98Hz), 6.31 (d, 2H, J= 6.72Hz), 7.39 (s, 1H), 7.69 (d, 1H, J= 7.27Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.18, 26.56, 26.61, 52.24, 63.12, 63.17, 66.29, 73.93, 107.77, 110.25, 110.27, 110.42, 123.22, 132.70, 142.64, 154.02 ppm.

FTIR (ATR): ν (cm⁻¹) 3392, 3143, 2985, 2927, 1705, 1647, 1456, 1373, 1213, 1147, 1045, 827, 731.

LCMS(ESI): ELSD 100%, R_t= 3.27 min, *m/z* calcd for C₁₃H₁₇N₃O₄ 279.12 found [M+H]⁺ 280.10.

**(S){1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-1H-1,2,3-triazol-4-yl}(furan-2-yl)methanol
(244b):**



According to the general procedure 7, the reaction between the propargyl alcohol (**171g**) (0.061 g, 0.50 mmol) and the azide (**179a**) (0.086 g, 0.55 mmol) in the presence of A-21.CuI (0.033 g, 0.04 mmol) in CH₂Cl₂ (2 ml) gave this product as a brown oil (0.052 g, 38% yield).

¹H NMR (300MHz, CDCl₃): δ 1.32 (s, 3H), 1.35 (s, 3H), 3.68-3.75 (m, 1H), 4.09 (ddd, 1H, J= 9.67Hz, 5.09Hz, 2.12Hz), 4.40-4.55 (m, 3H), 6.03 (d, 1H, J= 4.82Hz), 6.32 (d, 2H, J= 8.59Hz), 7.40 (s, 1H), 7.69 (d, 1H, J= 7.41Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 25.18, 26.57, 26.62, 56.72, 63.16, 63.21, 66.30, 66.36, 73.94, 74.72, 107.81, 107.84, 110.25, 110.29, 110.43, 119.90, 123.06, 123.20, 123.21, 142.67, 142.70, 169.04 ppm.

FTIR (ATR): ν (cm⁻¹) 3392, 3143, 2985, 2927, 1705, 1647, 1456, 1373, 1213, 1147, 1045, 827, 731.

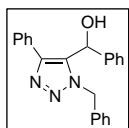
LCMS(ESI): ELSD 91%, R_t= 3.26 min, *m/z* calcd for C₁₃H₁₇N₃O₄ 279.12 found [M+H]⁺ 279.80.

- Synthesis of triazoles from internal alkyne:

General procedure 8:

Method A: To a solution of alkyne (**174a** or **336a**) (1 eq.) in a chosen solvent (2 ml) was added benzyl azide **77** (1.1 eq.) at r.t. This solution was then put under reflux and was stirred for 18h under reflux, then the solvent was evaporated and the residue was analyzed by NMR.

Method B: In a microwave reactor were introduced alkyne **336a** (1 eq.) and benzyl azide (1.1 eq.) in a chosen solvent (2 ml). This solution was then irradiated by microwave and by adjusting the parameters. The solvent was then evaporated *in vacuo* and the residue was analyzed by NMR.

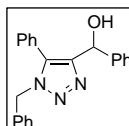
(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)(phenyl)methanol (334):

Upon the general procedure 8 (method A or B) this trisubstituted triazole was obtained as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 2.47 (d, 1H, J= 5 Hz), 5.26 (d, 1H, J= 15.15 Hz), 5.48 (d, 1H, J= 15.10 Hz), 6.32 (d, 1H, J= 4.87 Hz), 7.06 (dd, 2H, J= 2.84 and 6.54 Hz), 7.18-7.24 (m, 5H), 7.28 (dd, 3H, J= 1.86 and 5.08 Hz), 7.36-7.43 (m, 3H), 7.62 (dd, 2H, J= 1.65 and 7.91 Hz) ppm.

FTIR (ATR): ν (cm⁻¹) 3325, 2890, 1699, 1645, 1450, 1026, 731, 690.

LCMS(ESI): *m/z* calcd for C₂₂H₁₉N₃O 341.41 found [M+H]⁺ 342.100.

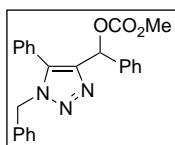
(1-benzyl-5-phenyl-1H-1,2,3-triazol-4-yl)(phenyl)methanol (335):

Upon the general procedure 8 (method A or B) this trisubstituted triazole was obtained as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 3.14 (br, 1H), 5.37 (d, 2H, J= 4.60 Hz), 5.79 (s, 1H), 6.97-7.01 (m, 4H), 7.21-7.25 (m, 4H), 7.28-7.43 (m, 7H) ppm.

FTIR (ATR): ν (cm⁻¹) 3340, 2922, 1454, 1049, 732, 694.

LCMS(ESI): *m/z* calcd for C₂₂H₁₉N₃O 341.41 found [M+H]⁺ 342.100.

Methyl 3-(1-benzyl-5-phenyl-1H-1,2,3-triazol-4-yl)-3-phenylpropanoate (337):

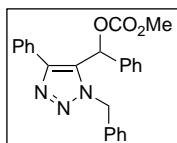
Upon the general procedure 8 this product was obtained as an orange oil.

¹H NMR (300 MHz, CDCl₃): δ 3.77 (s, 3H), 5.41 (s, 2H), 6.61 (s, 1H), 7.04-7.07 (m, 4H), 7.13-7.16 (m, 2H), 7.31-7.33 (m, 7H), 7.69-7.71 (m, 2H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 52.03, 54.89, 73.60, 126.24, 127.14, 127.63, 128.20, 128.29, 128.42, 128.71, 128.79, 129.76, 130, 135.03, 136.03, 137.74, 143.49, 154.90 ppm.

FTIR (ATR): ν (cm⁻¹) 2954, 1745, 1490, 1440, 1325, 1249, 756, 690.

LCMS (ESI) : *m/z* calcd for C₂₄H₂₁N₃O₃ 399.44 found 399.200.

methyl 3-(1-benzyl-4-phenyl-1H-1,2,3-triazol-5-yl)-3-phenylpropanoate (338) :

Upon the general procedure 8 this product was obtained as an orange oil.

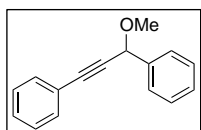
^1H NMR (300 MHz, CDCl_3): δ 3.88 (s, 3H), 5.53 (d, 1H, $J= 15.29$ Hz), 5.67 (d, 1H, $J= 15.32$ Hz), 6.74 (s, 1H), 7.06 (dd, 2H, $J= 3.24$ and 6.41 Hz), 7.18-7.24 (m, 7H), 7.33-7.40 (m, 4H), 7.62 (dd, 2H, $J= 1.65$ and 7.97 Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 53.10, 55.36, 70.34, 125.67, 127.59, 128.01, 128.33, 128.46, 128.54, 128.62, 128.69, 130.38, 130.44, 134.98, 135.35, 147.45, 154.79 ppm.

FTIR (ATR): ν (cm^{-1}) 2970, 2912, 1710, 1650, 1480, 1240, 732, 694.

Preparation of propargyl ethers from propargyl carbonates under microwave conditions:**General procedure 9 :**

To a microwave reactor were introduced propargyl carbonate and a chosen alcohol (nucleophile) with a desired quantity (see chapter 3). This solution was then irradiated by microwave. The excess of alcohol was evaporated under reduced pressure and the residue was analyzed by NMR.

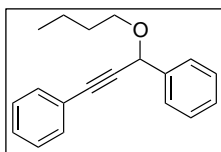
(3-methoxy-3-phenylprop-1-yn-1-yl)benzene (339):²⁸³

According to the general procedure 9, this compound was obtained by departing from propargylic carbonate **336a** (0.050 g, 0.190 mmol) in MeOH (2 ml) as nucleophile. The final product was found as an orange oil.

^1H NMR (300 MHz, CDCl_3): δ 3.52 (s, 3H), 5.34 (s, 1H), 7.34 (q, 3H, $J= 2.99$ Hz), 7.39-7.45 (m, 3H), 7.51 (dd, 2H, $J= 2.97$ and 6.65 Hz), 7.60 (d, 2H, $J= 7.08$ Hz) ppm.

^{13}C NMR (75MHz, CDCl_3): δ 55.98, 73.55, 86.70, 87.79, 122.59, 127.55, 128.33, 128.51, 128.57, 131.84, 138.57 ppm.

FTIR (ATR): ν (cm^{-1}) 2194, 1662, 1448, 1334, 1213, 1016, 746, 686.

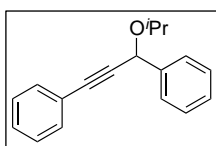
(3-butoxy-3-phenylprop-1-yn-1-yl)benzene (400a): ³²⁹

Upon the general protocol 9, this product was found from propargyl compound **336a** (0.050 g, 0.190 mmol) in the presence of butanol (2 ml) as nucleophile.

¹H NMR (300 MHz, CDCl₃): δ 0.93 (t, 3H, J= 7.33 Hz), 1.43 (dq, 2H, J= 7.41 and 14.98 Hz), 1.65 (dt, 2H, J= 7.06 and 14.59 Hz), 3.57 (dt, 1H, J= 6.57 and 9.03 Hz), 3.75 (dt, 1H, J= 6.63 and 8.99 Hz), 5.39 (s, 1H), 7.31-7.34 (m, 4H), 7.36-7.38 (m, 2H), 7.40-7.43 (m, 2H), 7.49 (dd, 2H, J= 3.05 and 6.64 Hz) ppm.

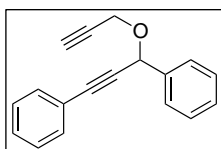
¹³C NMR (75MHz, CDCl₃): δ 13.97, 19.46, 31.81, 68.30, 72.03, 87.42, 122.74, 127.48, 128.32, 128.49, 128.52, 131.84, 139.07 ppm.

FTIR (ATR): ν (cm⁻¹) 2958, 2872, 2358, 2341, 1450, 1273, 707.

[3-phenyl-3-(propan-2-yloxy)prop-1-yn-1-yl]benzene (400b): ³³⁰

This product was found from a reaction between **336a** (0.050 g, 0.190 mmol) and isopropyl alcohol (2 ml) as the nucleophile.

¹H NMR (300 MHz, CDCl₃): δ 1.21 (d, 6H, J= 3.42 Hz), 4.02 (dtd, 1H, J= 3.22, 6.12 and 12.25 Hz), 5.29 (d, 1H, J= 3.11 Hz), 7.31-7.34 (m, 3H), 7.39-7.42 (m, 3H), 7.46-7.50 (m, 2H), 7.60-7.65 (m, 2H) ppm.

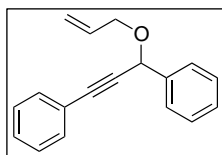
[3-phenyl-3-(prop-2-yn-1-yloxy)prop-1-yn-1-yl]benzene (400c): ³³¹

Compound **336a** was subjected into the reaction with propargyl alcohol (2 ml) to give compound **400c** as an orange oil.

¹H NMR (300 MHz, CDCl₃): δ 2.49 (t, 1H, J= 2.40 Hz), 4.26 (d, 1H, J= 2.43 Hz), 4.33 (d, 1H, J= 2.42 Hz), 5.63 (s, 1H), 7.32 (td, 3H, J= 1.71 and 4.89 Hz), 7.35-7.42 (m, 3H), 7.45-7.49 (m, 2H), 7.58 (dd, 2H, J= 1.62 and 7.56 Hz) ppm.

FTIR (ATR): ν (cm⁻¹) 3290, 1597, 1489, 1442, 1267, 1056, 754, 688.

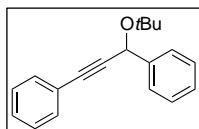
³²⁹Z.-P. Zhan, H.-J. Liu, *Synlett* **2006**, (14), 2278-80. ³³⁰G. Aridoss, V. D. sarca, J. F. Ponder Jr, J. Crowe, K. K. Laali, *Org. Biomol. Chem.* **2011**, 9, 2518-29. ³³¹K. Ohta, E. Koketsu, Y. Nagase, N. Takahashi, H. Watanabe, M. Yoshimatsu, *Chem. Pharm. Bull.* **2011**, 59, 1133-40.

[3-phenyl-3-(prop-2-en-1-yloxy)prop-1-yn-1-yl]benzene (400d): ³³¹

This product was found from the reaction between **336a** (0.050 g, 0.190 mmol) and allyl alcohol (2 ml) as a yellow oil.

¹H NMR (300 MHz, CDCl₃): δ 4.15-4.32 (m, 2H), 5.23-5.28 (m, 1H), 5.38 (dq, 1H, J = 1.62 and 17.22 Hz), 5.46 (s, 1H), 5.95-6.08 (m, 1H), 7.31-7.35 (m, 3H), 7.37-7.45 (m, 3H), 7.48-7.52 (m, 2H), 7.61 (dd, 2H, J = 1.23 and 7.85 Hz) ppm.

FTIR (ATR): ν (cm⁻¹) 3061, 2198, 1645, 1489, 1450, 1271, 1174, 1055, 756, 690.

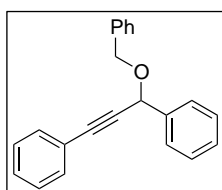
[3-(*tert*-butoxy)-3-phenylprop-1-yn-1-yl]benzene (400e): ²⁸³

Upon the general procedure 9, this product was found from a reaction between the propargyl carbonate **336a** (0.050 g, 0.190 mmol) and *tert*-butanol (2 ml) as nucleophile.

¹H NMR (300 MHz, CDCl₃): δ 1.41 (s, 9H), 5.51 (s, 1H), 7.31-7.52 (m, 8H), 7.60-7.66 (m, 2H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 28.53, 64.64, 70.28, 84.89, 88.10, 126.99, 127.76, 127.87, 128.24, 128.30, 128.33, 128.40, 128.77, 128.94, 129.27, 136.58 ppm.

FTIR (ATR): ν (cm⁻¹) 2922, 2850, 1639, 1440, 1230, 756, 690.

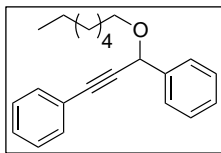
[3-(benzyloxy)-3-phenylprop-1-yn-1-yl]benzene (400f): ³³⁰

This compound was obtained from **336a** (0.050 g, 0.190 mmol) and benzyl alcohol as an orange oil.

¹H NMR (300 MHz, CDCl₃): δ 4.67 (s, 2H), 5.46 (s, 1H), 7.33-7.45 (m, 10H), 7.50-7.54 (m, 2H), 7.60-7.71 (m, 3H) ppm.

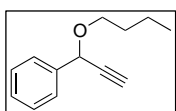
¹³C NMR (75MHz, CDCl₃): δ 70.13, 71.04, 86.98, 87.92, 122.65, 127.66, 127.85, 128.24, 128.38, 128.51, 128.60, 131.90, 137.86, 138.74 ppm.

FTIR (ATR): ν (cm⁻¹) 2924, 2860, 2358, 2341, 1597, 1489, 1452, 754, 690.

[3-(octyloxy)-3-phenylprop-1-yn-1-yl]benzene (400g):

Upon the general procedure 9, compound **400g** was found by departing from **336a** (0.050 g, 0.190 mmol) in the presence of 1-octanol as nucleophile.

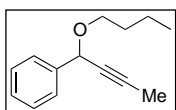
¹H NMR (300 MHz, CDCl₃): δ 0.87 (t, 3H, J= 6.72 Hz), 1.27-1.30 (m, 10H), 1.55 (dt, 2H, J= 7.05 and 14.02 Hz), 3.61 (t, 2H, J= 6.67 Hz), 5.28 (s, 1H), 7.29-7.49 (m, 8H), 7.56-7.59 (m, 2H) ppm.

(1-butoxyprop-2-yn-1-yl)benzene (401b’):

According to the general procedure 9, this product was obtained from the reaction between **336b** (0.050 g, 0.265 mmol) and butanol (2 ml).

¹H NMR (300 MHz, CDCl₃): δ 0.92 (td, 3H, J= 2.19 and 7.34 Hz), 1.35-1.47 (m, 2H), 1.59-1.67 (m, 2H), 2.63 (t, 1H, J= 2.37 Hz), 3.50 (dtd, 1H, J= 2.37, 6.57 and 8.96 Hz), 3.68 (dtd, 1H, J= 2.33, 6.59 and 8.96 Hz), 5.16 (t, 1H, J= 1.95 Hz), 7.33-7.42 (m, 5H) ppm.

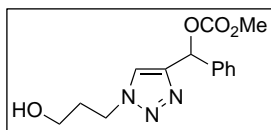
¹³C NMR (75MHz, CDCl₃): δ 13.89, 19.37, 31.69, 68.32, 71.30, 75.28, 82.00, 127.27, 127.73, 128.38, 128.50, 128.76, 129.38, 138.53 ppm.

(1-butoxybut-2-yn-1-yl)benzene (401c’):

Upon the general protocol, compound **401c’** was found from a reaction between **336c** (0.050 g, 0.247 mmol) and butanol (2 ml).

¹H NMR (300 MHz, CDCl₃): δ 0.91 (td, 3H, J= 2.63 and 7.33 Hz), 1.33-1.46 (m, 2H), 1.60 (quintet, 2H, J= 2.26 and 7.21 Hz), 1.91 (d, 3H, J= 2.22 Hz), 3.44 (dtd, 1H, J= 2.60, 6.49 and 9.01 Hz), 3.62 (dtd, 1H, J= 2.58, 6.56 and 9.10 Hz), 5.10 (t, 1H, J= 2.18 Hz), 7.30-7.40 (m, 5H) ppm.

¹³C NMR (75MHz, CDCl₃): δ 3.81, 13.91, 19.40, 31.75, 64.86, 68.05, 71.74, 83.43, 126.59, 127.28, 128.08, 128.38, 128.58, 139.66 ppm.

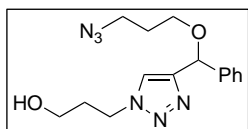
[1-(3-hydroxypropyl)-1H-1,2,3-triazol-4-yl](phenyl)methyl methyl carbonate (405):

According to the general procedure 9, this product was obtained from a reaction between propargyl carbonate **336b** (0.050 g, 0.265 mmol) and 3-azidopropan-1-ol.

¹H NMR (300 MHz, CDCl₃): δ 2.11 (dd, 2H, J= 6 and 12.50 Hz), 3.63 (td, 2H, J= 1.53 and 4.96 Hz), 3.79 (d, 3H, J= 1.73 Hz), 4.45-4.50 (m, 2H), 6.88 (d, 1H, J= 4.13 Hz), 7.36-7.48 (m, 5H), 7.49 (d, 1H, J= 1.87 Hz) ppm.

FTIR (ATR): ν (cm⁻¹) 3342, 2953, 2875, 2358, 2339, 1747, 1649, 1448, 1261, 1049, 943, 698.

LCMS(ESI): *m/z* calcd for C₁₄H₁₇N₃O₄ 291.30 found [M+H]⁺ 292.

3-{4-[(3-azidopropoxy)(phenyl)methyl]-1H-1,2,3-triazol-1-yl}propan-1-ol (406):

Upon the general procedure 9, the reaction between propargyl carbonate **336b** (0.050 g, 0.265 mmol) and 3-azidopropan-1-ol gave this triazole.

¹H NMR (300 MHz, CDCl₃): δ 1.88 (dt, 2H, J= 6.25 and 12.37 Hz), 2.07 (dt, 4H, J= 6.18 and 12.17 Hz), 3.39-3.44 (m, 2H), 3.60 (t, 2H, J= 5.67 Hz), 4.29 (br, 1H), 4.44 (t, 2H, J= 6.67 Hz), 5.61 (s, 1H), 7.35 (tt, 5H, J= 6.63 and 12.84 Hz), 7.50 (d, 1H, J= 4.43 Hz) ppm.

¹³C NMR (75MHz, CDCl₃): δ 29.19, 29.71, 32.54, 47.11, 48.53, 58.78, 65.87, 126.72, 127.43, 128.05, 128.63, 140.30 ppm.

FTIR (ATR): ν (cm⁻¹) 3352, 2926, 2873, 2094, 1647, 1452, 840, 698.

LCMS(ESI): *m/z* calcd for C₁₅H₂₀N₆O₂ 316.36 found [M+H]⁺ 317.

Cytotoxicity evaluation on B16 melanoma cells:

Murine B16 melanoma cells were grown in DMEM medium containing 2 mM L-glutamine, 10% foetal bovine serum, 100 U/mL penicillin and 100 µg/mL streptomycin (37°C, 5% CO₂). All compounds were initially dissolved in DMSO at a stock concentration of 10 mM and were further diluted in cell culture medium. Exponentially growing cells were plated onto 96-well plates at 5000 cells per well in 100 µl of culture medium. Twenty-four h after plating, 100 µl of medium containing the compound at final concentrations ranging from 0.01 to 100 µM were added to the wells (in triplicate) containing the cells, and incubated for 48h at 37°C and 5% CO₂. After the 48h exposure

period to the test compounds, cell viability was assayed using the MTT test³³² and absorbance was read at 562 nm in a microplate reader (BioKinetics Reader, EL340). The concentration of compound that inhibited cell viability by 50% (inhibitory concentration for 50% of cells, or IC₅₀) was determined using the GraphPad Prism software.

³³²D. A. Scudiero, R. H. Shoemaker, K. D. Paull, A. Monks, S. Tierney, T. H. Nofziger, M. J. Currens, D. Seniff, M. R. Boyd, *Cancer Res.* **1988**, *48*, 4827-33.

SUMMARY

Medicinal chemistry is the application of chemical research techniques to the synthesis of pharmaceuticals.

During this PhD project, we tried to synthesize small molecules based on terminal alkyne and propargyl alcohols. These molecules were prepared by departing from a simple aldehyde and by doing reactions like Bestmann-Ohira in order to prepare terminal alkynes or reaction with ethynylmagnesium bromide to prepare propargyl alcohols. These prepared small molecules were then subjected into the 1,3-dipolar Huisgen cycloaddition reaction in the presence of organic azides in order to prepare small triazolic derivatives. Cytotoxicity property of these small triazoles was then tested against *B16 melanoma cell lines*. Primary results showed some activities for some of our synthesized molecules that need more study like adding functionalities on the structure to improve their activities.

In the last part of this dissertation, a methodology study on the synthesis of propargyl ethers from their corresponding propargyl esters under microwave irradiations has been described. To the best of our knowledge preparation of propargyl ethers from propargyl esters or nucleophilic substitution of propargyl esters in order to find propargyl ethers has been reported in the literature only by use of catalysts such as Lewis acids or metal complexes. The advantage of our method was the absence of such catalysts and the time of the reaction which was less than 1h in comparison with the reported synthesis. Synthesis of such molecules can also be interesting in the synthesis of natural products.

Key words: Medicinal Chemistry, Huisgen cycloaddition reaction, Bestmann-Ohira reaction, *B16 melanoma cell lines*, microwave reaction, propargyl ethers.