TRIAZOLE-BASED LIGANDS FOR CLICK CHEMISTRY AND ASYMMETRIC CATALYSIS

Erhan Ozkal

Dipòsit Legal: T.61-2014

TRIAZOLE-BASED LIGANDS
FOR CLICK CHEMISTRY AND ASYMMETRIC CATALYSIS

PhD Thesis

By

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Prof. MIQUEL A. PERICÀS, Group Leader of Research Group and Director of the Institute of Chemical Research of Catalonia (ICIQ),

CERTIFIES, that the present Doctoral Thesis entitled "**TRIAZOLE-BASED LIGANDS FOR CLICK CHEMISTRY AND ASYMMETRIC CATALYSIS**" presented by **Erhan ÖZKAL** to obtain the degree of Doctor, has been carried out under my supervision in the Institute of Chemical Research of Catalonia (ICIQ) and fulfils all the requirements to be awarded with the "International Doctor" Mention.

Tarragona, October 1, 2013

PhD Thesis supervisor

Prof. Miquel A. Pericàs

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To my family

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Acronyms and Abbreviations

In this document the abbreviations and acronyms most commonly used in organic chemistry have been used, according to the recommendations of the ACS "*Guidelines for authors*" *J. Org. Chem.* **2008**, *73*, 23A-24A.

http://pubs.acs.org/paragonplus/submission/joceah/joceah_authguide.pdf

List of Publications

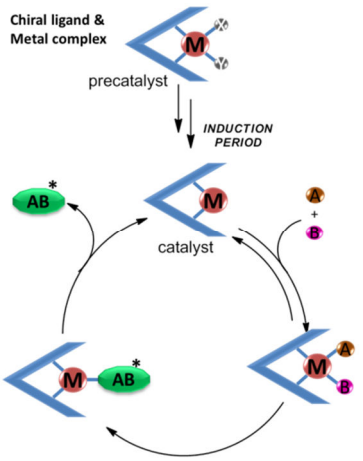
The PhD Thesis is based on the following publications:

- *"A Highly Active Catalyst for Huisgen 1,3-Dipolar Cycloadditions Based on the Tris(triazolyl)methanol - Cu(I) Structure"* Salih Özçubukçu, Erhan Ozkal, Ciril Jimeno, and Miquel A. Pericàs. *Org. Lett.* **2009**, 11 (20), 4680–4683.

- *"Covalently Immobilized Tris(Triazolyl)Methanol–Cu(I) Complexes: Highly Active and Recyclable Catalysts for CuAAC Reactions"* Erhan Ozkal, Salih Özçubukçu, Ciril Jimeno and Miquel A. Pericàs. *Catal. Sci. Technol.*, **2012**, *2*, 195-200.

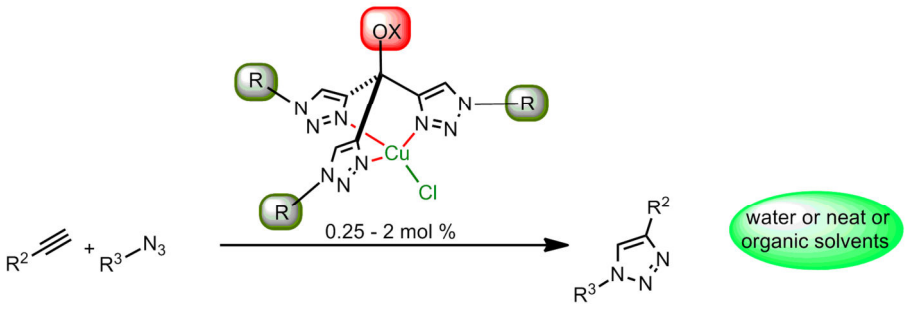
GRAPHICAL ABSTRACTS

CHAPTER I – General Introduction (1-28)



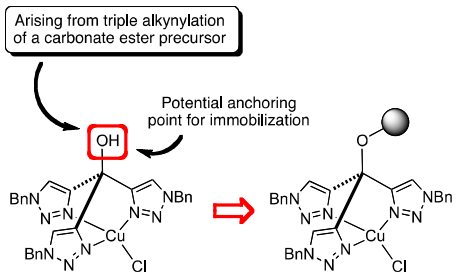
The purpose of this chapter is to familiarize the reader to the concepts behind in this thesis. General concerns of metal catalysis are described. Overall, the thesis is about metal-catalyzed reactions using triazole-based ligands and covalent immobilization of homogeneous metal catalyst onto polymeric support. A brief introduction is given on click chemistry parallel to main focus of this thesis. Finally, the objectives of the thesis have been defined.

CHAPTER II – PAPER A & B (33-84 & 85-98)



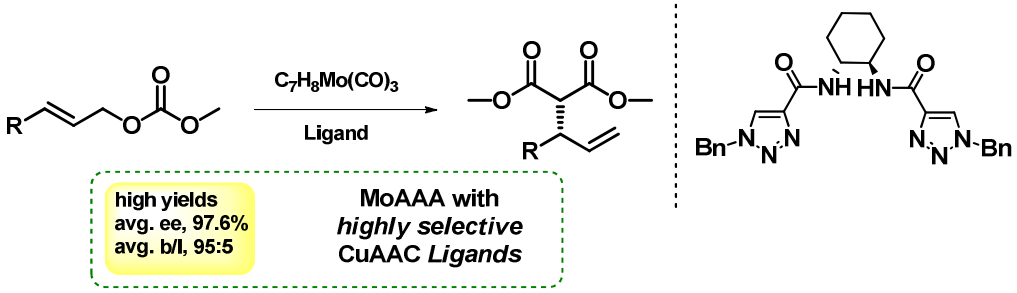
Synthesis, characterization and use of various types of tris(triazolyl)methanol ligands bearing different functional moieties have been studied. First, the initial ligand/copper(I) chloride complex have been used as catalyst for copper-catalyzed azide-alkyne cycloadditions (CuAAC) on water or neat. Later, practical large-scale synthesis has been optimized and upon systematic screening of different functional groups, a modified ligand has been found out to be performing well in organic solvents, too.

CHAPTER II – PAPER C (99-136)



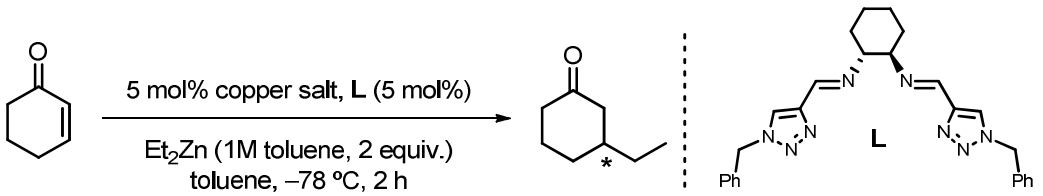
Tris(1-benzyl-1H-1,2,3-triazol-4-yl)methanol has been immobilized onto Merrifield resins through different strategies. The SN_2-supported Copper complex is stable in water and under air; it is active at low catalyst loadings (1 mol%) and at low concentration (down to 0.125 M) in both aqueous and purely organic media. Resin can be repeatedly reused in 1:1 MeOH–water for short reaction times (4 h) with the only precaution of Cu(I) reloading every five cycles.

CHAPTER III – PAPER D (141-190)



Preparation of cyclohexyldiamidotriazole from propiolic acid benzyl azide, and cyclohexyldiamine is described with its evaluation in molybdenum catalysed asymmetric allylic alkylation (MoAAA) reactions using aryl carbonates with dimethyl malonate. High enantio- and regioselectivities were obtained with the novel chiral triazole ligand either in batch or microwave assisted conditions; and its modular nature of synthesis with CuAAC and amide coupling reactions enable a different approach to ligands stemmed from click chemistry with potential novel diversity in asymmetric catalysis.

CHAPTER IV – ENANTIOSELECTIVE COPPER-CATALYZED CONJUGATE ADDITION OF DIETHYL ZINC (195-208)



Upon the development of the seminal work in the development of 1,2,3-triazole as ligands in metal-catalyzed reactions and we were encouraged with our results in TTM.CuCl, we would like to take one step further in such ligands for metal-catalyzed asymmetric reactions. Having our experience in our research group with diethylzinc chemistry and the copper chemistry, we sought to interpret that knowledge into chiral click ligands derived from CuAAC reaction for the asymmetric copper-catalyzed asymmetric conjugate addition of diethylzinc reagents.

CONCLUSIONS & OUTLOOK (209-212)

Chapter I

CONTENTS

1. GENERAL INTRODUCTION

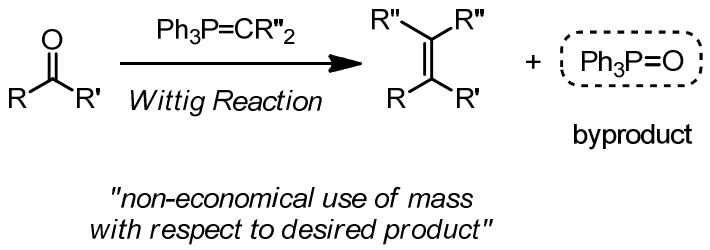
Chemistry is a fundamental science, which plays a central role in physics of condensed matter, biology and materials science. Chemical synthesis is at the core of the discipline. The fundamental aspect is to design and synthesize functional structures inspired by nature to solve modern day problems. These targets require efficient synthesis in as few steps as possible with minimal waste from raw materials. The use of catalytic systems is the key point to develop such efficient syntheses and, therefore, they play a major role in the industrial production of chemicals.

As living in the *Oil Age*, both the initial (petrochemical) conversion of petroleum into simple hydrocarbons and their subsequent elaboration by the chemical industry into more complex final products, involves countless catalytic transformations. Briefly, a catalyst is a substance that enhances the rate of a chemical reaction without being consumed in the process and without altering its equilibrium. In a chemical reaction, the catalyst may be sequentially transformed into a series of intermediate states, which is overall called catalytic cycle. The number of times that a catalyst can undergo such cycles along a reaction is the turnover number (TON). In other words, TON is the number of molecules that can be converted into products by a single molecule of catalyst. Turnover frequency (TOF) is TON per specified time unit. These numbers have significant importance in order to determine the efficiency of a catalytic reaction.

In addition to rate of reactions, selectivity of a chemical reaction is essential to obtain the desired products. The first parameter to control in a chemical reaction is *chemoselectivity,* which is the ability to discriminate between different functional groups of a molecule with respect to a specific chemical reagent. In modern chemical synthesis, there is a huge pool of different approaches to overcome this concern. Secondly, *regioselectivity* is the preference of one orientation of bond breaking/making process to afford only one product over all possible directions in a specific transformation. The remaining selectivity matters revolve around *stereoselectivity,* which is the control of absolute three-dimensional spatial arrangements of the molecules. Different synthetic

approaches are possible but still today; there is not a common solution for each case.[1] Ideally, regulation of these general concepts for efficient synthesis ensure reduced waste, adaptation to plant scale synthesis and a sustainable use of raw materials and energy.

In catalysis whenever a breakthrough solution to such selectivity constraints is developed, another limitation should be considered called atom economy.[2] As mentioned above, minimal byproduct formation for industrial scale applications is vital for a sustainable world and, to defeat selectivity obstacles, usually atom economy is overlooked. A classic non-atom economical example is the Wittig olefination (**Scheme 1.1**).[3] This methodology has been a unique solution for regioselective double bond functional group installation. The Nobel Committee appreciated the value and uniqueness of the transformation (Georg Wittig was awarded the Nobel Prize in Chemistry in 1979). However, the employed phosphonium ylide generates enormous amounts of triphenylphosphine byproduct with respect to its transferred unit of mass.



Scheme 1.1. Wittig olefination in terms of *Atom Economy*.

Pathways heading to successful sustainable and efficient synthesis are not always easy to find. Indeed, great obstacles in chemical synthesis remain to be overcome. For instance, a recent macro scale chemical problem, which triggered a synthetic challenge, was the well-known crisis in the treatment of swine flu (pig flu). The earliest treatments had been solely based on a molecule called Oseltamivir and its sustainable supply was dependent on a natural product called (–)-shikimic acid. It was economically isolated from *Illicium anisatum*, however lacking a global supply due to very low yielding isolation

[1] Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals, Second Revised and Enlarged Edition*, Wiley-VCH, Weinheim, **2008**.
[2] Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259.
[3] (a) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318. (b) Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

operations, which generated a worldwide shortage of Tamiflu® in 2005.[4] At that moment, there had been few initial efforts towards the chemical synthesis of shikimic acid. A number of chemists in academia and industry attempted to bypass the synthesis of the medicine using different and much simpler starting materials. Utilizing different approaches, very promising syntheses were accomplished. Most of them were possible applying several concepts in catalysis, such as Lewis acid catalysis, Lewis base catalysis, organometallic catalysis, heterogeneous catalysis and biocatalysis (**Figure 1.1**).

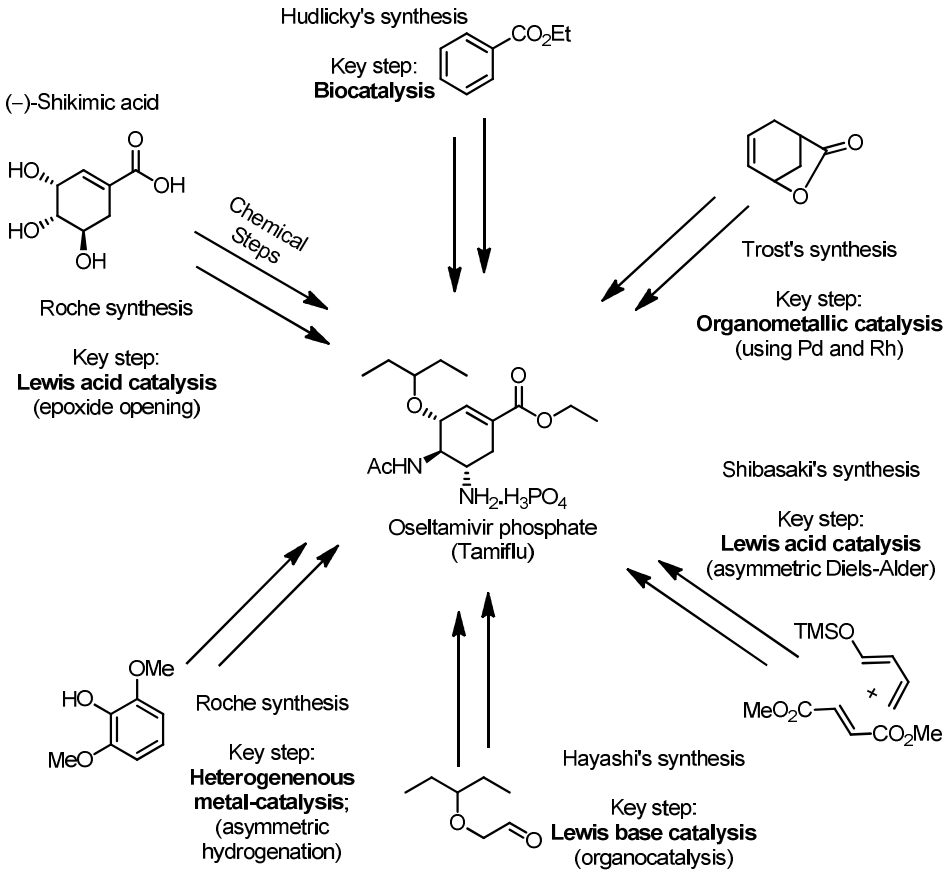


Figure 1.1. Several syntheses of Oseltamivir relying on different catalytic approaches.

It is worth noting that all approaches share the use of catalysis to fulfill the earlier concerns. Bearing the goal of efficient synthesis and atom economy in mind, all the authors coincided in resorting to catalysis to develop such syntheses. In the context of the thesis, the main discussion in the introduction will be focus on Lewis acid catalysis, organometallic catalysis and heterogeneous catalysis.

[4] Shibasaki, M.; Kanai, M.; Yamatsugu, K. *Isr. J. Chem.* **2011**, *51*, 316.

1.1. METAL-CATALYZED REACTIONS IN ORGANIC SYNTHESIS

To date, metal-catalyzed reactions are the best alternative to overcome all the restrictions of the efficient synthesis.[5] The main reason for an organic chemist to utilize a metal in synthesis is basically the ability of that particular metal to coordinate to functional groups (FG) in organic molecules in such a specific way that the reactivity of the FG in the target molecule changes dramatically. With the aid of complexation, the otherwise unreactive FG can afford the desired transformation. Creating these sort of separations in the broad spectrum of FG for chemical synthesis is vital.[6]

Although the use of metals has enabled a great number of improvements in synthesis, the difficulty in understanding the precise mechanisms in terms of stable oxidation states, geometries and coordination states within the proximity of each FG, makes it complicated to organize them in categories. The specifity in the mode of action of a metal can be greatly tuned by simple organic molecules, called ligands, by which the reactivity and the generalization of a methodology can be achieved in a simple manner. The role of the ligands in catalysis is also related to the solubility of organometallic species in organic solvents. Moreover, the strong electronic and steric influence of ligand-metal interactions has greatly affected the development of modern catalytic methodologies. Fine-tuning of these parameters through rational design has allowed very difficult synthetic challenges to be solved. At the same time, this has permitted to lower the amount of metal precursors used, so that the toxic (and often rather expensive) metal waste has considerably reduced.

Overall, the development of practical catalytic systems throughout the 20th century has transformed how an organic chemist acts in chemical synthesis. Much of these catalytic systems have been extensively developed via Lewis acid catalysis.

1.1.1. LEWIS ACID CATALYSIS

The most common mode of activation in metal-promoted organic synthesis is by far Lewis acid catalysis. In an optimal case, an electron deficient metal can complex with a FG (*e.g.* carbonyl group) to establish a Lewis acid/base equilibrium. The Lewis acid lowers

[5] Rothenberg, G. *Catalysis: Concepts and Green Applications*; Wiley-VCH, Weinheim, **2008**.
[6] Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books, Mill Valley, **1994**.

the LUMO (lowest unoccupied molecular orbital) energy level of the coordinated substrate, thus, narrowing the gap to the HOMO (highest occupied molecular orbital) of a nucleophilic partner. In short, for a nucleophilic addition to a carbonyl compound the carbonyl group becomes more electrophilic and the activation barrier of the reaction is correspondingly lowered (**Figure 1.2**).

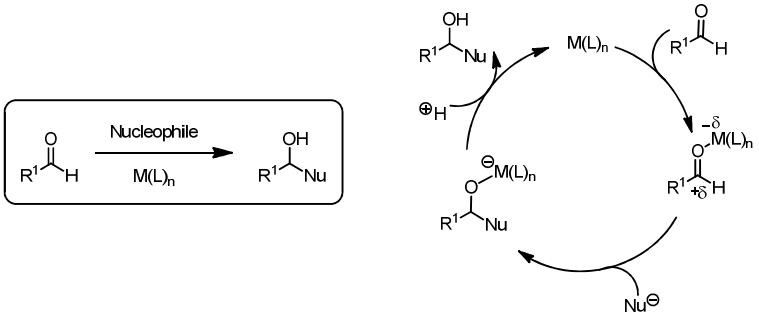


Figure 1.2. Simplified Lewis acid-catalyzed addition of a nucleophile to a carbonyl group.

Since many of the organic substrates possess Lewis basic functional groups, the use of such compounds accounts for a widespread use of Lewis acid activation.[7] Lewis acid-promoted carbon-carbon bond forming reactions are indispensable methodologies in organic chemistry.[8] By this approach classical examples have developed into more modern variations like in the case of Friedel-Crafts reaction,[9] Diels-Alder reaction,[10] 1,2-addition of organometallic carbon nucleophiles to carbonyl groups and various aldol-type reactions; they all had the benefit of the Lewis acid catalysis to full extent. However, taking one-step further in catalysis, using substoichiometric Lewis acid metals with small organic molecules as ligands allows fine-tuning of catalytic properties.

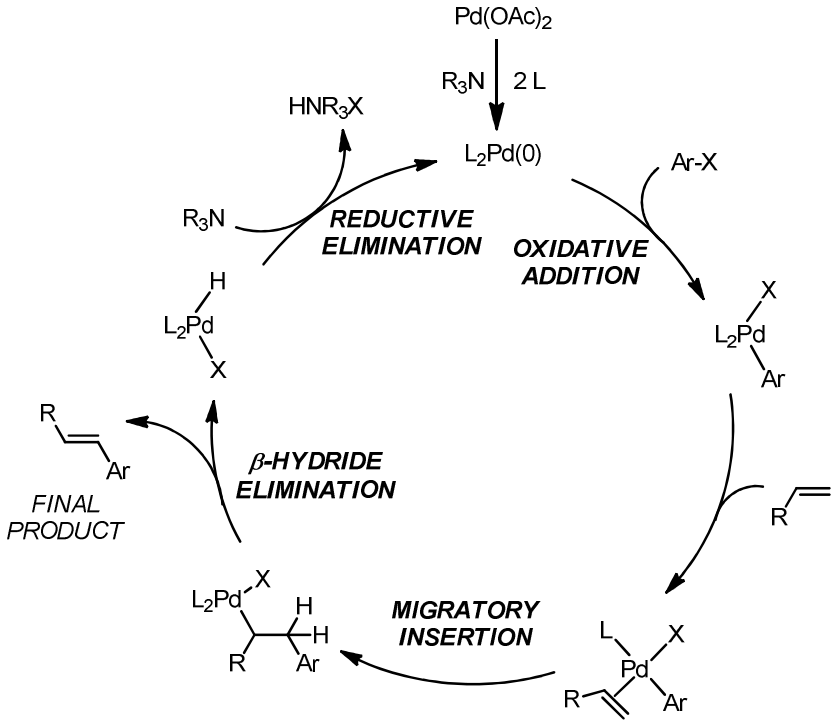
[7] Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books, Sausalito, **2009**.
[8] (a) Schinzer, D. *Selectivities in Lewis Acid Promoted Reactions*; Springer, Netherlands, **1989**. (b) Santelli, M.; Pons, J. M. *Lewis Acids and Selectivity in Organic Synthesis*; 1st ed.; CRC Press, Boca Raton, **1995**. (c) Yamamoto, H. *Lewis Acid Reagents: A Practical Approach*; 1st ed.; Oxford University Press, New York, **1999**. (d) Davies, A. G. *Appl. Organomet. Chem.* **2002**, *16*, 65. (e) Corma, A.; García, H. *Chem. Rev.* **2003**, *103*, 4307.
[9] Shiina, I.; Suzuki, M. *Tetrahedron Lett.* **2002**, *43*, 6391.
[10] Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.

1.1.2. ORGANOMETALLIC CATALYSIS

By definition, organometallic compounds are *"those having bonds between one or more metal atoms and one or more carbon atoms of an organyl group"*.[11] Some of the Lewis acid type metal-catalysts might be considered as organometallic compounds. However, their mode of action is different and those are not considered as organometallic catalysts. Only the ones in which the reactivity of the carbon–metal bond is vital for the catalytic process are referred to as organometallic catalysts.[12] This family of catalysts is generally based on late transition metals such as Ru, Co, Rh, Ir, Ni, Pd, Cu, etc. Their ability to form π–complexes makes them applicable for several bond forming reactions. There is quite a broad range of mechanisms involved but some general steps are common to most of them: oxidative addition, transmetalation, insertion, β–elimination and reductive elimination.

A very representative example for the catalytic cycle is exemplified by the mechanism of the Mizoroki-Heck reaction (**Scheme 1.2**). This is one of the most used C–C coupling reactions in which an aryl or vinyl halide or triflate couples with an alkene in the presence of Pd and a base.[13] The palladium(II) complex (*e.g.* palladium acetate) is reduced by trialkylamine to palladium(0). Oxidative addition of an aryl halide generates a palladium(II) intermediate after palladium insertion into an aryl–halide bond. Coordination of the alkene, π complex formation, and migratory insertion of the aryl group forms the desired C–C bond. β-Hydride elimination occurs and furnishes the desired product, transforming the Pd into a Pd(II) hydride, which undergoes deprotonation to release catalytically active palladium(0) and complete the catalytic cycle.

[11] Moss, G. P.; Smith, P. A. S.; Tavernier, D. *Pure Appl. Chem.* **1995**, *67*, 1307.
[12] (a) Hartwig, J. F. *Organotransition metal chemistry: from bonding to catalysis*; University Science Books, Sausalito, **2010**. (b) Crabtree, R. H. *The Organometallic Chemistry of the Transition Metals*; John Wiley & Sons, Hoboken, **2011**.
[13] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.



Scheme 1.2. General mechanism for the Mizoroki-Heck reaction.

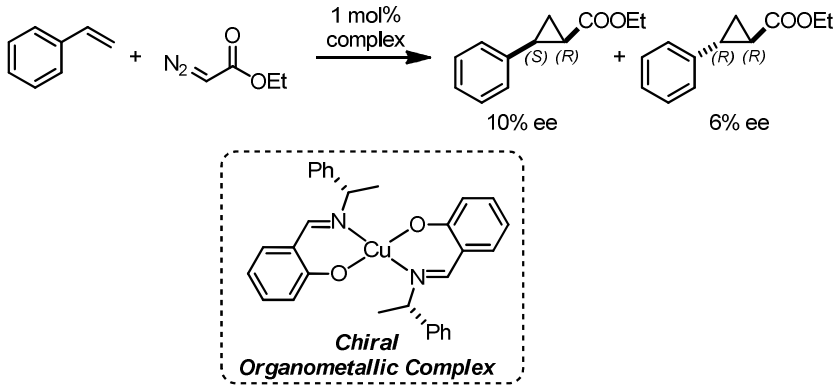
The Importance of the field has been recognized by awarding the Nobel Prize in Chemistry 2010 to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their pioneering contributions.

1.2. ASYMMETRIC CATALYSIS

Asymmetric synthesis consists in the generation of an optically active molecule where one enantiomer is provided selectively with respect to the other. Chemists are trying to develop stereoselective methodologies towards chiral compounds, which are a fundamental characteristic of life. Living systems are chiral and two enantiomers are only distinguishable in a chiral environment. Therefore, one molecule is likely to behave differently than its mirror image when it interacts with a living organism. This is simply exemplified by (+) and (–)-limonene; (+)-limonene smells like oranges and (–)-limonene is more citric and lemony. Another case with drastic side effects is thalidomide where only one molecule was an efficient drug and its enantiomer a teratogen. Thus, it is crucial to control with high selectivity the formation of one compound over its enantiomer. The ability to differentiate between two stereoisomers is a great concern of chemistry that deals with life and living systems such as pharmaceutical, biological and agricultural

compounds, flavors, fragrances and materials chemistry. In the hands of chemists, asymmetric synthesis is developing towards the generation of very general catalytic systems with a predictable behavior. In this way, very common and broad applications would be available in contrast to most enzymatic catalysis, which tend to be more substrate specific.

In view of this, catalytic asymmetric synthesis is one of the essential areas of organic synthesis. With only small amounts of a chiral catalyst, the synthesis of large amounts of a chiral substance is possible from prochiral or racemic substrates. Around 50 years ago, Nozaki and co-workers discovered the first asymmetric catalytic reaction as a sheer mechanistic curiosity (**Scheme 1.3**).[14] The reaction of styrene with ethyl diazoacetate catalyzed by a copper complex, which afforded very low enantioselectivity, however, at that moment; it was a proof of concept in the development of asymmetric synthesis. Since this pioneering achievement, a variety of chiral organometallic complexes and more recently some organocatalysts became apparent as asymmetric catalysts.



Scheme 1.3. First asymmetric catalysis with an organometallic complex.

Metal-based Asymmetric Catalysis

Following similar trends than catalysis, asymmetric catalysis also evolved around metal-based systems. Asymmetric induction is generally controlled by chiral ligands around the central metal, in addition to all the parameters used to control metal-catalyzed reactions (solvent, temperature, concentration, etc.). Furthermore, reactivity of such complexes might also be increased by ligand-accelerated catalysis.[15] The catalytic

[14] Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *7*, 5239.
[15] Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1995**, *34*, 1059.

cycle for a general reaction is depicted in **Figure 1.3**. The catalytically active metal-ligand complex is able to activate prochiral substrates **A** and **B**, generating different energy pathways for each enantiomer of the product, which results in the asymmetric formation of **AB***.[16]

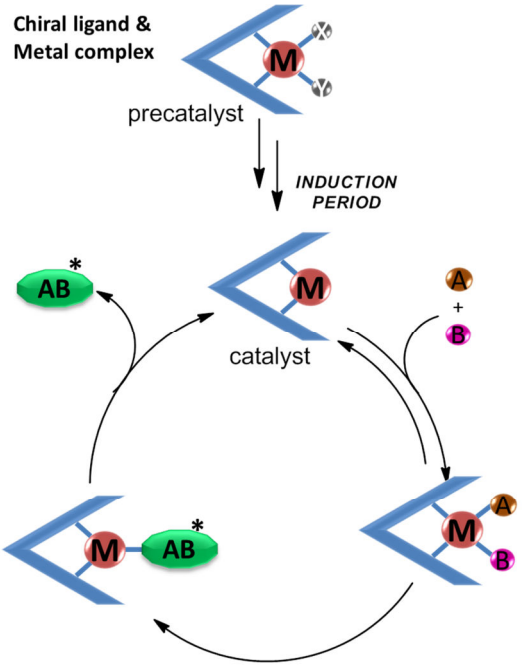
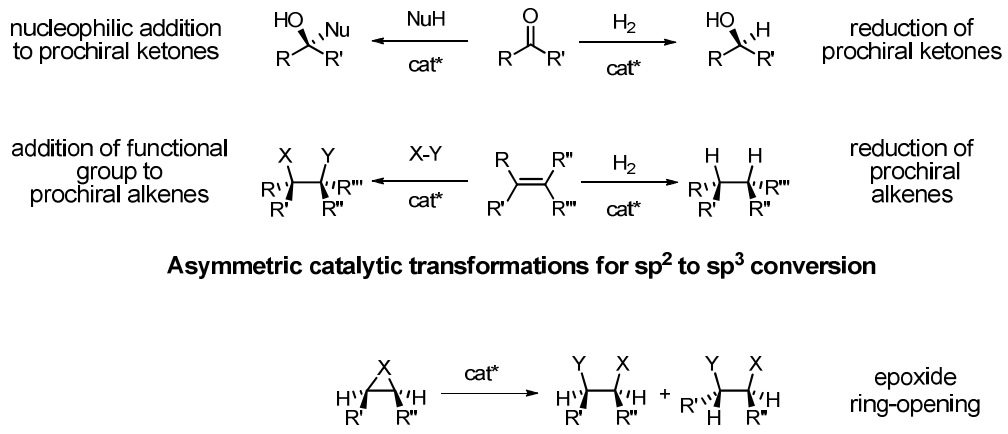


Figure 1.3. General mode of action for asymmetric metal catalysis.

Most of the asymmetric transformations involve conversion of a planar sp^2 carbon atom into a tetrahedral sp^3 carbon atom, as in the case of asymmetric hydrogenation of olefins and ketones, as well as addition reactions to the same functional groups. In a similar fashion, if a substrate is *meso* or achiral, breaking the symmetry that lies in the molecular structure affords enantiomerically enriched compounds by asymmetric catalysis.[17] General examples of these concepts are outlined in **Scheme 1.4**.

[16] Noyori, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 79.
[17] Caprio, V.; Williams, J. *Catalysis in Asymmetric Synthesis;* 2nd ed.; Wiley, Hoboken, **2009**.



Scheme 1.4. General asymmetric transformations.

Most of these transformations in the last decades grew around very general structural backbones, "*privileged chiral ligands*,"[18] (**Figure 1.4**) regardless of their catalytic mechanisms. Whenever a new methodology is developed for a specific reaction, use of these ligands with different metals is likely to induce good levels of asymmetry. Consequently, it is quite common when developing new asymmetric catalytic processes, to resort to the use of one of these privileged chiral ligands.

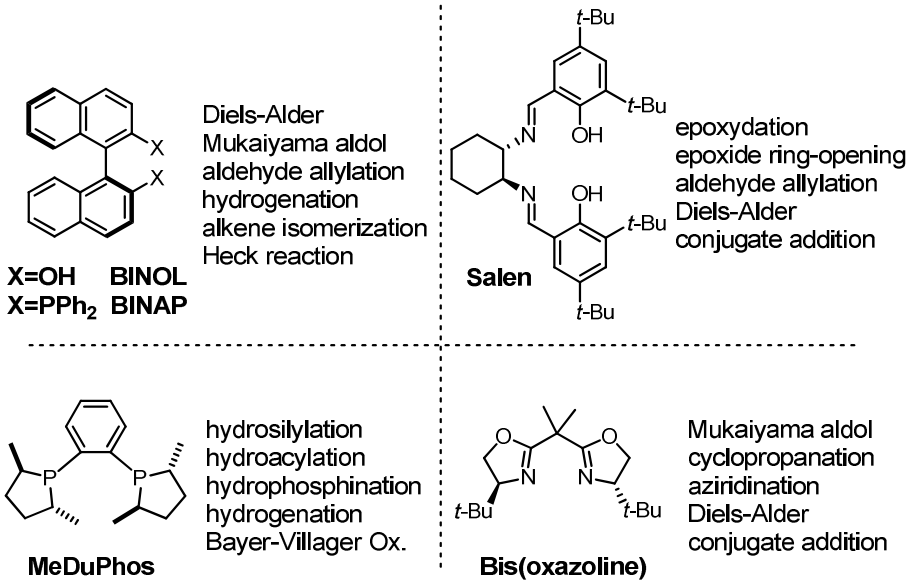


Figure 1.4. Some examples of privileged chiral ligands.

[18] (a) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691. (b) Zhou, Q.-L. *Privileged Chiral Ligands and Catalysts*; Wiley-VCH, Weinheim, **2011**.

Upon promising success, further optimization of those backbones greatly assures novel asymmetric synthesis in practice. The most classical representative examples of such privileged ligands and advances in asymmetric synthesis were appreciated later by the Nobel Committee, which awarded William S. Knowles, Ryoji Noyori and K. Barry Sharpless in 2001.

Overall, decades of advancement in asymmetric catalysis have completely changed the field of chemical synthesis. The total synthesis of ripostatin B by Christmann and co-workers[19] clearly exemplifies the developments in the field of catalysis and its impact in efficient synthesis. A complex natural product with a skipped-polyene macrolide system can be smoothly constructed applying the latest developments in catalysis, in this case using asymmetric α-chlorination of Jørgensen/MacMillan,[20] Jacobsen hydrolytic kinetic resolution,[21] ring-closing metathesis[22] and Stille coupling (**Figure 1.5**).[23]

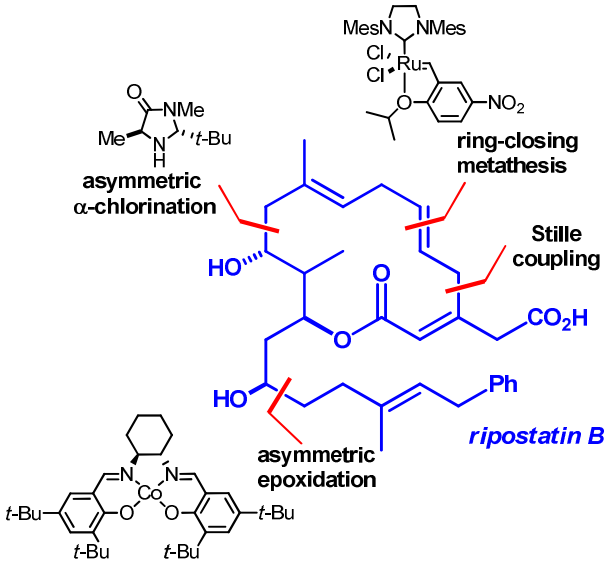


Figure 1.5. Advances in catalysis used for the total synthesis of ripostatin B.

[19] Winter, P.; Hiller, W.; Christmann, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3396.
[20] (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.
[21] Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.
[22] Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.
[23] Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.

1.3. COVALENTLY IMMOBILIZED CATALYSTS

Most of the fascinating improvements have taken place with homogeneous catalysis, have a direct impact in the development of industrial scale synthesis from fine chemicals to pharmaceuticals. However, the cost, preparation, handling and purification of such fine catalysts, most of the time, limit the direct impact to the industrial applications. In order to combine the efficiency of homogeneous catalysts with assets of heterogeneous catalysts such as easy separation, reuse and recycling, tremendous effort has been devoted to generate strategies for the immobilization of homogeneous catalysts onto bulk materials.[24] At this point, it is worth mentioning that catalysts are not modified during the reaction, but technical difficulties usually hamper the effective re-use of homogeneous catalysts.

Historically, heterogeneous catalysts have been mostly used for gas-solid phase reactions in petrochemical and related industries. In the scale of an organic chemist (mg to kg), it usually refers to liquid-solid reactions and in both cases the catalyst is the solid phase. More recently, liquid-liquid phase reactions have been developed where the catalyst and reagents are separated by difference of solubility in different media. Once implemented, heterogeneous systems in organic synthesis might take catalysis one step further towards continuous flow processes and decreasing metal contamination of the precious final product.

Certain considerations should be kept in mind for the design of a successful immobilization strategy. An optimal heterogenized catalyst should: i) be mechanically robust and stable under reaction conditions, ii) bear convenient sites for reagent interactions, iii) preserve practical catalyst loadings and iv) not deteriorate in activity. In other words, catalyst stability is the primary goal since it is a good indicator for potential recovery and reuse. Additionally, but not less important, high catalytic efficiency, chemoselectivity, and in some cases, regioselectivity and stereoselectivity are requirements for a successful catalyst immobilization. Ideally, the immobilization of catalyst should not add more complexity to the synthesis of the active species, which

[24] (a) Barbaro, P.; Liguori, F. *Heterogenized Homogeneous Catalysts for Fine Chemicals Production - Materials and Processes*; Springer, New York, **2010**. (b) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3215. (c) McMorn, P.; Hutchings, G. J. *Chem. Soc. Rev.* **2004**, *33*, 108. (d) Sheldon, R. A.; Bekkum, H. v. *Fine Chemicals Through Heterogeneous Catalysis*; Wiley-VCH, Weinheim, **2008**.

should be synthesized using very cheap reagents.[25] There are mainly two distinct types of immobilized catalyst, namely heterogenized systems (inorganic, organic polymeric and dendrimeric supports and organic-inorganic coordination polymers) and biphasic systems where the catalyst is soluble in a nonconvential solvent such as perfluorinated solvents, ionic liquids, and supercritical fluids. Thanks to synthetic organic chemistry, covalently bound homogeneous catalyst design has recently gained wide application in academia and industry, thus generating a wide array of robust immobilized homogeneous catalysts. It takes more time and synthetic effort to obtain a very good supported catalyst than the conventionally heterogenized systems used in fine chemicals industry.

There is a variety of support systems that can be used and each has its own advantageous properties related to the area of application. In this chapter, emphasis will be put on insoluble polymeric systems since our work and experience has been devoted to covalently immobilized homogeneous ligands.

Polymer supported Metal-catalysis

The roots of polymer-supported catalysts[26] can be traced back to the development of solid-phase peptide synthesis by R. Bruce Merrifield[27] who pioneered the application of polymeric supports in organic chemistry as a tool for almost all fields (Nobel Prize in Chemistry, 1984). These supports deeply enhanced the laboratory automation and separation techniques, mostly combinatorial chemistry and in our interest, catalysis.

Microporous beads of the Merrifield resins are made of weakly-crosslinked polystyrene with 1-2% divinylbenzene (DVB) functionalized with chloromethyl units. The benzylic chloride is prone to nucleophilic substitutions that enable easy modification to attach, in our case, different modular ligands. Another variation derived from the Merrifield resin is the Wang resin,[28] which is basically modified with phenylmethanol

[25] Albericio, F.; Tulla-Puche, J. *The Power of Functional Resins in Organic Synthesis*; Wiley-VCH, Weinheim, **2008**.
[26] (a) Buchmeiser, M. R. *Polymeric Materials in Organic Synthesis and Catalysis*; Wiley-VCH, Weinheim, **2006**. (b) Clark, J. H.; Macquarrie, D. J. *Handbook of Green Chemistry and Technology*; Wiley-VCH, Weinheim, **2008**. (c) Benaglia, M. *Recoverable and Recyclable Catalysts*, Wiley, Hoboken, **2009**. (d) Kirschning, A. *Immobilized Catalysts: Solid Phases, Immobilization and Applications*; Springer, Berlin, **2010**.
[27] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
[28] Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328.

units. In general, in their dry state the surface area is low. Thus, for successful mass transfer lower crosslinker ratio assures higher swelling and overall these resins are very well swollen in non-protic media (**Figure 1.6**).[29]

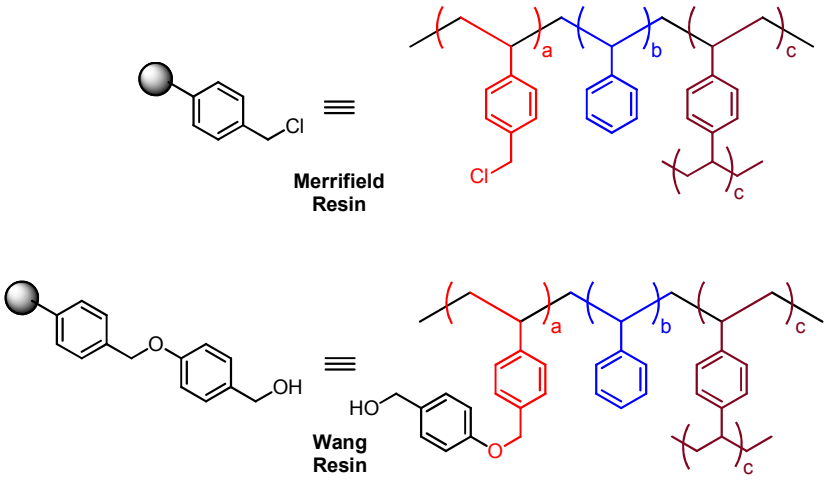


Figure 1.6. Schematic representation of Merrifield and Wang resins.

In catalysis, the greatest advantage of insoluble polymers over soluble ones is the easy separation by simple filtration. However, when the solvent used does not swell the insoluble polymers, the internal reactive sites cannot be accessed properly. As mentioned, operational simplicity in most of the cases surpasses the defined limitations. To overcome the solvent restrictions, longer and more flexible etheric cross-linkers with commercial resins like JandaJel® and TentaGel® (hybrid polystyrene-polyethylene glycol resins) have been introduced (**Figure 1.7**).[30]

[29] Santini, R.; Griffith, M. C.; Qi, M. *Tetrahedron Lett.* **1998**, *39*, 8951.
[30] (a) Jung, G. *Combinatorial Peptide and Nonpeptide Libraries*; 1st ed.; Wiley-VCH, Weinheim, **1997**. (b) Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329.

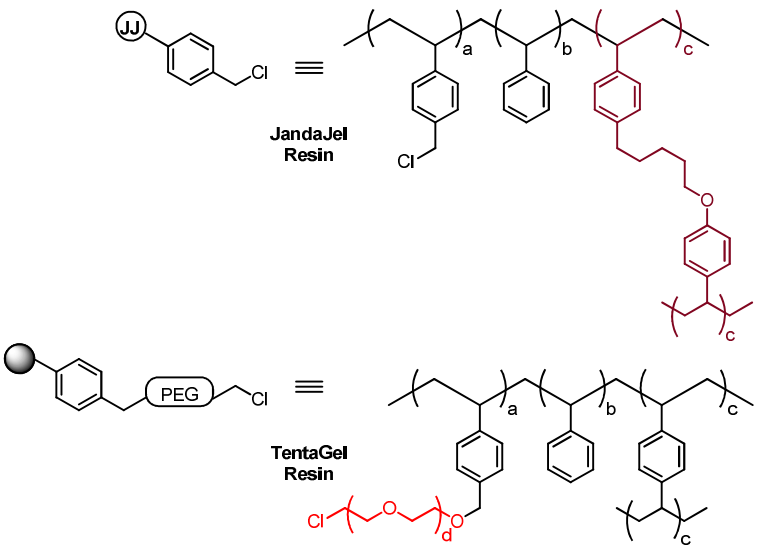


Figure 1.7. Schematic representation of JandaJel and Tentagel resins.

The degree of functionalization is an essential feature to choose polymers for catalyst immobilization. There should be an optimum degree of functional units per mass unit (0.5-0.9 mmol.g^{-1}) in order to have: i) a mass of catalyst practical to be used with respect to reagents, ii) active sites distant enough to avoid undesired interactions. With tailored PS resins other than the Merrifield resin the availability of beads with acceptable functionalization is very limited.

The selection of one of these commercial resins is mostly dependent on the desired reaction conditions. After this point (and once the functional unit has been selected), the only principle to modulate properties of a homogeneous catalyst is based on the detemination of the optimal distance between the catalytically active moiety and the polymeric matrix, which greatly affects the activity. Linker/spacer molecules or modified ligands with enough distance ensure optimal distance control from the polymer surface (**Figure 1.8**).

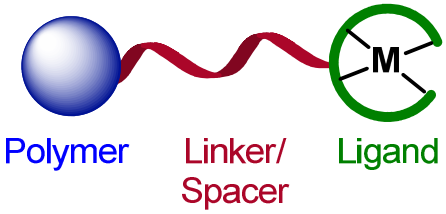
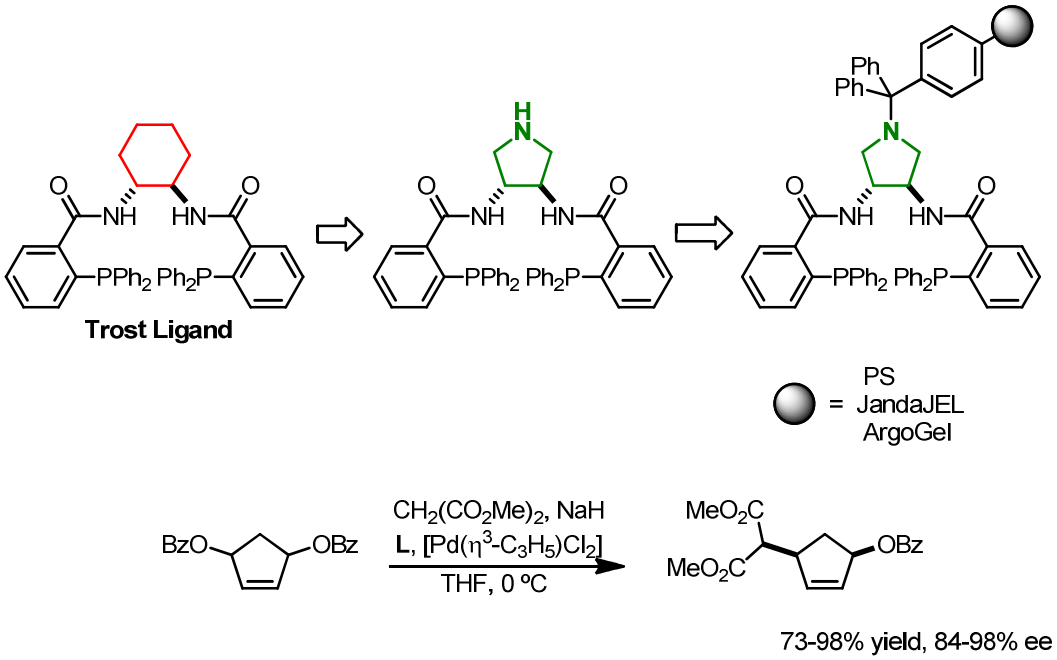


Figure 1.8. General schematic representation of supported catalyst.

In the case of the Wang resin, phenylmethanol units are the commercial solution to keep the active system further away from the polymeric matrix. However, this is not a universal solution. The most common application is the modification of ligands[31] with appropriate steric and electronic effects and the length. For an archetypical and successful representation of covalently immobilized metal catalysis, the Trost ligand[32] was modified with a pyrrolidinediamine unit and a suitable linker by Han and co-workers for the desymmetrization of 1,4-bis(benzoyloxy)cyclopent-2-ene with dimethyl malonate with excellent results, which parallel the homogeneous version (**Scheme 1.5**).[33] In other words, all discussed parameters regarding an ideal heterogeneous system were elegantly controlled in this example.



Scheme 1.5. Successful application of polymer supported metal-catalysis.

Nowadays, click chemistry (see section 1.4 for more information) has proven to be an extremely efficient strategy for the covalent immobilization of catalysts, thanks to its ease of handling and monitoring (by infrared spectroscopy). To follow this approach, a linker/spacer moiety with either an azide or an alkyne functional group is *clicked* with the respective counterpart of the most used click chemistry reaction, copper-catalyzed azide-

[31] Anelli, P. L.; Czech, B.; Montanari, F.; Quici, S. *J. Am. Chem. Soc.* **1984**, *106*, 861.
[32] Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59.
[33] Song, C. E.; Yang, J. W.; Roh, E. J.; Lee, S.-g.; Ahn, J. H.; Han, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3852.

alkyne cycloaddition (CuAAC) (see Chapter 2 for more information). In our research group, a great effort has been dedicated to the development of modular ligands and immobilization onto polystyrene, mostly for asymmetric additions of alkyl or aryl zinc species to aldehydes and recently for other types of asymmetric reactions (**Figure 1.9**).[34]

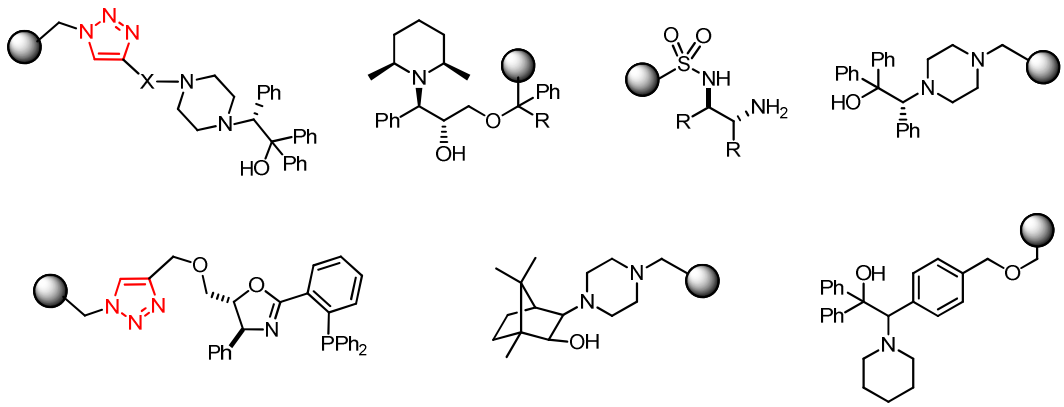


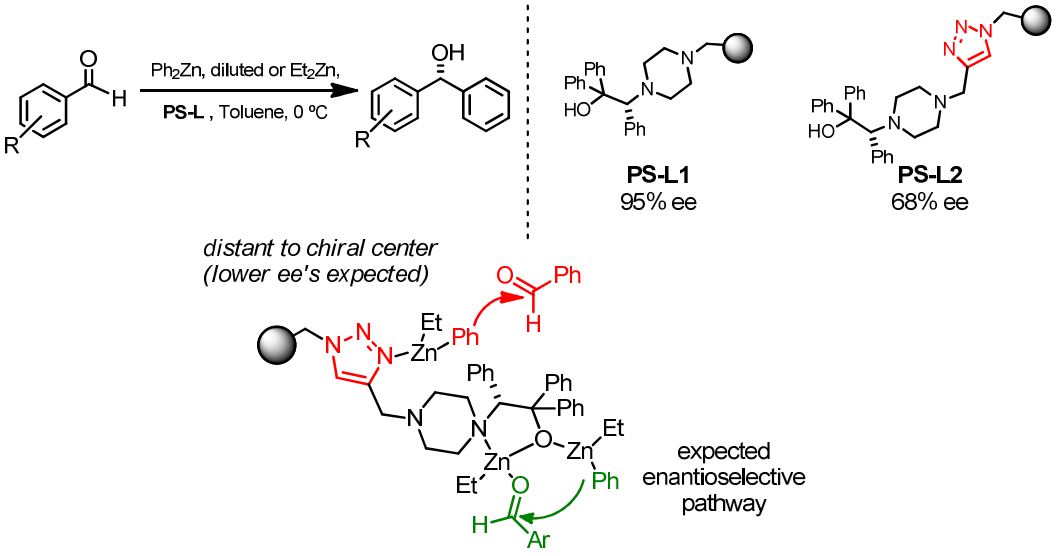
Figure 1.9. Structure of immobilized ligands for metal catalysis developed in our group.

However, this successful *click* strategy is case dependent when applied to the immobilization of metal-catalysts and/or metal containing substrates. Lewis basic nitrogen groups of 1,2,3-triazole might interfere with metal coordination of the ligand used and in the case of an stereoselective reaction, deterioration of enantioselectivity by achiral reaction pathways can be observed.

In an example shown in **Scheme 1.6**, it is clearly demonstrated that performing the enantioselective phenylation reaction of aldehydes with PS-supported ligands where the linker has a triazole unit afforded low enantioselectivity (68% ee) due to competitive triazole coordination; whenever classic immobilization strategies were used in the absence of triazoles, excellent selectivity was retained, comparable to the respective

[34] (a) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309. (b) Pericàs, M. A.; Castellnou, D.; Rodríguez, I.; Riera, A.; Solà, L. *Adv. Synth. Catal.* **2003**, *345*, 1305. (c) Castellnou, D.; Fontes, M.; Jimeno, C.; Font, D.; Solà, L.; Verdaguer, X.; Pericàs, M. A. *Tetrahedron* **2005**, *61*, 12111. (d) Castellnou, D.; Solà, L.; Jimeno, C.; Fraile, J. M.; Mayoral, J. A.; Riera, A.; Pericàs, M. A. *J. Org. Chem.* **2005**, *70*, 433. (e) Bastero, A.; Font, D.; Pericàs, M. A. *J. Org. Chem.* **2007**, *72*, 2460. (f) Popa, D.; Marcos, R.; Sayalero, S.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 1539. (g) Marcos, R.; Jimeno, C.; Pericàs, M. A. *Adv. Synth. Catal.* **2011**, *353*, 1345. (h) Raducan, M.; Rodríguez-Escrich, C.; Cambeiro, X. C.; Escudero-Adán, E. C.; Pericàs, M. A.; Echavarren, A. M. *Chem. Commun.* **2011**, *47*, 4893. (i) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 1816.

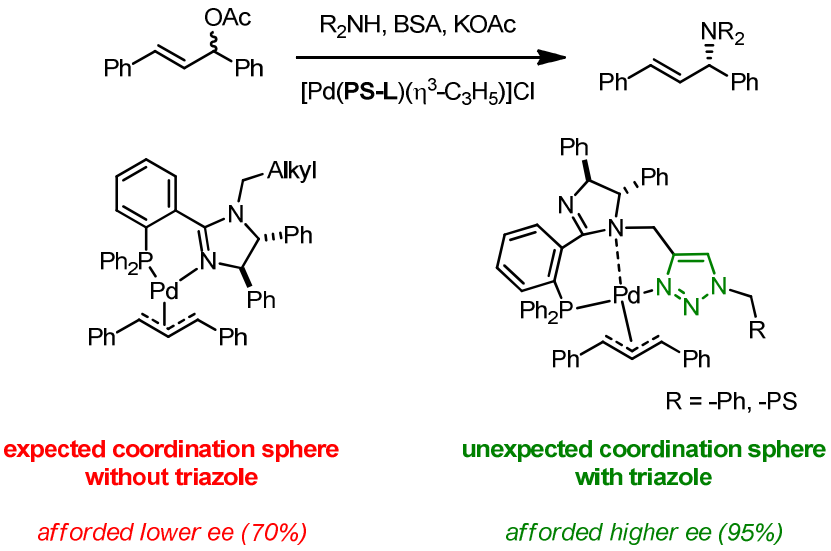
homogeneous ligands.[35] Even though lower enantioselectivity was obtained this observation encouraged us to further investigate the use of triazoles in PS-supported metal catalysis.



Scheme 1.6. Influence of a triazole unit on the enantioselectivity of a metal-catalyzed reaction.

In a very recent example, triazole/metal binding was again observed, interestingly, with increased enantioselectivity in palladium-catalyzed asymmetric allylic amination reaction (**Scheme 1.7**). The coordination of triazole was investigated by DFT calculations and NOE experiments of the corresponding homogeneous ligands. In this case, triazoles suppressed the binding of the imidazole moiety of the ligand.[36]

[35] Bastero, A.; Font, D.; Pericàs, M. A. *J. Org. Chem.* **2007**, *72*, 2460.
[36] de la Fuente, V.; Marcos, R.; Cambeiro, X. C.; Castillón, S.; Claver, C. and Pericàs, M. A. *Adv. Synth. Catal.* **2011**, *353*, 3255.



Scheme 1.7. Unexpected coordination and enhanced selectivity with triazole linker strategy.

Overall, when combining triazole and metals care should be taken to design a supported catalytic system that exploits its advantages without suffering from its drawbacks. This *"click"* strategy is especially well suited for work with organocatalysis and various types of such species have been covalently immobilized onto solid supports in our research group[37] (**Figure 1.10**) and by others.[38]

[37] (a) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653. (b) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 3717. (c) Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2007**, *9*, 1943. (d) Alza, E.; Pericàs, M. A. *Adv. Synth. Catal.* **2009**, *351*, 3051. (e) Alza, E.; Rodríguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericàs, M. A. *Chem. Eur. J.* **2009**, *15*, 10167. (f) Alza, E.; Sayalero, S.; Kasaplar, P.; Almaşi, D.; Pericàs, M. A. *Chem. Eur. J.* **2011**, *17*, 11585. (g) Riente, P.; Mendoza, C.; Pericás, M. A. *J. Mater. Chem.* **2011**, *21*, 7350. (h) Ayats, C.; Henseler, A. H.; Pericàs, M. A. *ChemSusChem* **2012**, *5*, 320. (i) Kasaplar, P.; Riente, P.; Hartmann, C.; Pericàs, M. A. *Adv. Synth. Catal.* **2012**, *354*, 2905. (j) Riente, P.; Yadav, J.; Pericàs, M. A. *Org. Lett.* **2012**, *14*, 3668.

[38] Review: Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367.

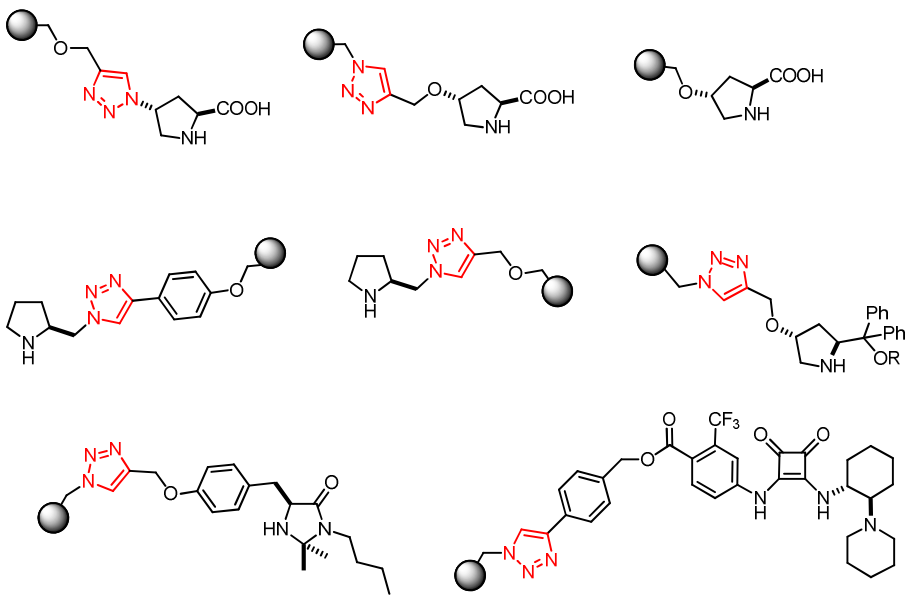


Figure 1.10. PS-supported organocatalysts synthesized in our research group.

1.4. CLICK CHEMISTRY

Keywords: click chemistry in *web of science®*

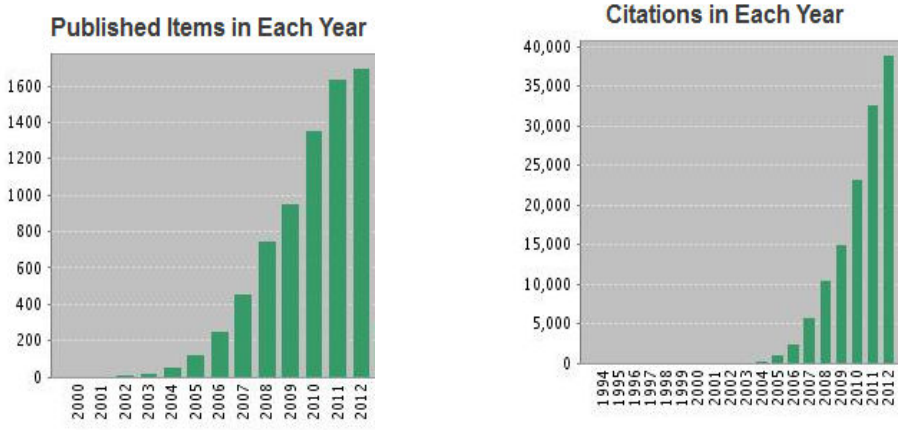


Figure 1.11. "Click Chemistry" in chemical literature.

Sharpless and co-workers originally introduced the idea of *click chemistry* in 2001[39] as a very broad term to idealize a reaction almost to the perfection of nature (**Figure 1.11**). An ideal click reaction would be "modular, wide in scope, afford very high yields, generate environmentally friendly byproducts, be favored by a large thermodynamic driving force and have atom economy." The process ideally would have simple reaction conditions, commercial materials and reagents, use sustainable solvents, and allow easy isolation.

[39] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.

Initially, the concept has been derived against general trends in the drug discovery and natural product synthesis where organic chemists are too much involved with mimicking very complex molecules. Even though chemical synthesis has evolved due to synthesis of very hard-to-reach targets, organic chemists are nowhere near to the efficiency and selectivity of complex enzymatic sequences to form those frameworks with many contiguous C–C bonds.

Contrary to this sophisticated complexity, Sharpless and co-workers thought of a *"click"* proposal to the chemical synthesis based on much simpler primary metabolites present in living organisms where there is much reduced amount of C–C bond complexity (mostly not exceeding six contiguous bonds, except aromatic amino acids, **Figure 1.12**). In the enormous chemical compound population, a refined and reasonable drug candidate population defined by Guida and co-workers [≤ 30 non–hydrogen atoms, ≤ 500 Dalton, containing only H, C, O, N, P, F, S, Cl and Br, likely to be stable at room temperature in the presence of water and oxygen] to be between 10^{62} and 10^{63} discrete molecules.[40] In a clear notion from Sharpless, such never-ending chemical space should be handled as simple as possible.

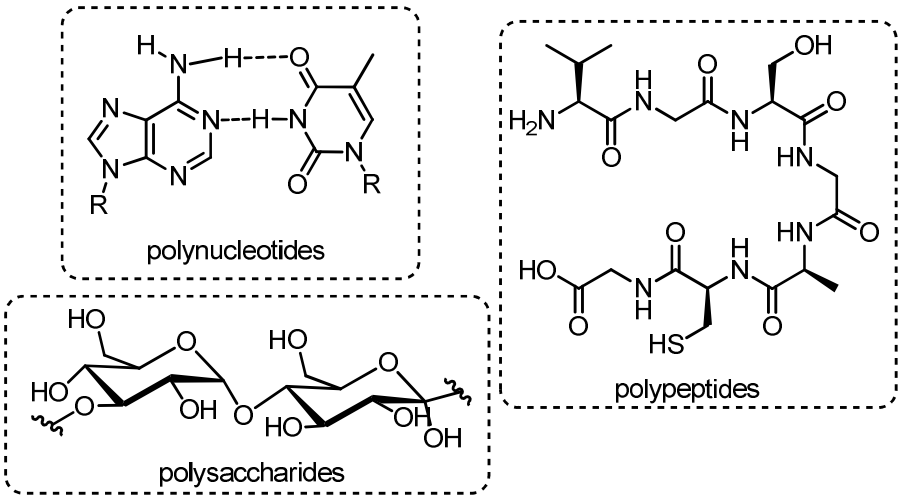


Figure 1.12. General backbone structures found in Nature.

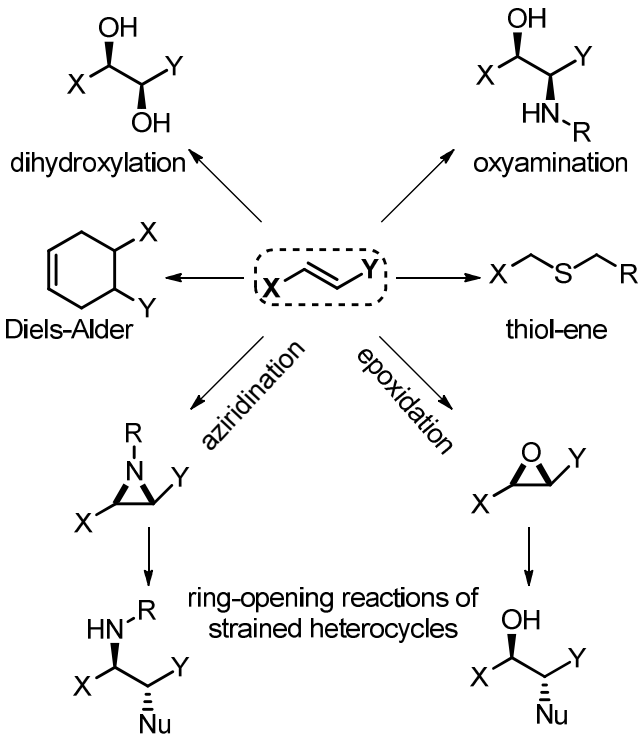
This logical concept can be further taken into account in many other areas of chemical synthesis, and in our particular interest, even to ligand design and catalyst discovery.

[40] Bohacek, R. S.; McMartin, C.; Guida, W. C. *Med. Res. Rev.* **1996**, *16*, 3.

Click Reactions

Usually carbon-heteroatom bond forming reactions are the most common family of "*click*" reactions and can be classified as following (**Scheme 1.8**):

- cycloadditions of unsaturated species: 1,3–cycloadditions and Diels–Alder reactions.
- nucleophilic substitution chemistry: ring–opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridinium ions or episulphonium ions.
- carbonyl chemistry of the non–aldol type: formation of (thio)ureas, aromatic heterocycles, oxime ethers, hydrazones and amides.
- additions to carbon–carbon multiple bonds: higher oxidative products of reactions such as epoxidation, dihydroxylation, aziridination and sulphenyl halide addition and Michael additions of Nu–H.

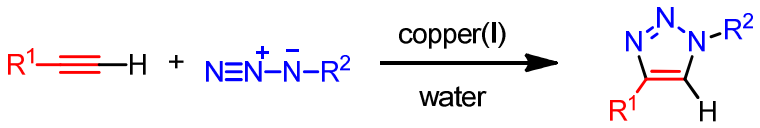


Scheme 1.8. Oxidized spring-loaded cyclic electrophiles or fusion processes from olefins.

Gathering all the input, the main idea behind click chemistry can be traced back to the notion of atom economy according to which the combined mass of reactants and mass of the desired product are exact in the ideal case. Processing petroleum into simple

saturated hydrocarbons to obtain useful unsaturated hydrocarbons with reactive π bonds enabled chemists to further develop more valuable products.[41,42,43] With a wide variety of nucleophiles, a diverse set of structures were already synthesized much before the idea of click chemistry.[44]

In practical terms, the very first reaction considered to be developed after the *click* idea was the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction (detailed information can be found at Chapter 2), which represented a breakthrough in almost every field of chemistry even beyond the scope of the concept (**Scheme 1.9**).



Scheme 1.9. Copper-catalyzed azide-alkyne cycloaddition reaction.

In particular, other reactions or modifications of CuAAC reaction have been required depending on the field. Mostly, because presence of metal catalyst might affect biological systems or color might be a problem in materials science. In order to avoid such constraints, other reactions as "*click*" as CuAAC reaction have become widespread and almost re-discovered by applied sciences. These are, to name a few, copper-free ring strain azide-alkyne cycloaddition,[45] Diels-Alder reaction[46] and thiol-ene reaction.[47]

From our point of view, in catalysis, various modular ligands have been developed using all types of spring-loaded cyclic electrophile opening strategies[48] that might be classified as click chemistry and CuAAC reaction derived triazoles cannot be ruled out.

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[41] Xia, Q. H.; Ge, H. Q.; Ye, C. P.; Liu, Z. M.; Su, K. X. *Chem. Rev.* **2005**, *105*, 1603.
[42] Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.
[43] (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) O'Brien, P. *Angew. Chem., Int. Ed.* **1999**, *38*, 326.
[44] (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
[45] Becer, C. R.; Hoogenboom, R.; Schubert, U. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4900.
[46] Iha, R. K.; Wooley, K. L.; Nyström, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J. *Chem. Rev.* **2009**, *109*, 5620.
[47] Dondoni, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8995.
[48] Cambeiro, X. C. *PhD. Dissertation*, University of Barcelona, **2010**.

1.5. OBJECTIVES

In this thesis, different approaches for the application of *click chemistry* to the preparation of catalysts and ligands are developed. Several strategies towards the use of 1,2,3-triazoles from CuAAC reaction as *click* ligands are explored. Mainly, 1,2,3-triazole is used as donor groups for transition metal complexes in metal-catalyzed reactions, following on the simplicity of the synthetic route.

In general, the metal/ligand complexes are used as catalysts in CuAAC reaction and catalytic asymmetric transformations.

In this context, the general summary of this thesis have been:

Chapter 2: The design & synthesis of tris(triazolyl)methanol (TTM) derivatives for CuAAC reaction have been deeply investigated. After the initial development of the TTM backbone, the conditions are optimized for CuAAC reaction under ambient conditions on water (**Paper A**). Having the modular nature of TTM structure, the extension of TTM copper complexes for CuAAC reaction in organic solvents would have been the complementary work In addition, practical large scale synthesis of TTM ligands were optimized, too.(**Paper B**). At the same time, PS-supported TTM·CuCl complexes have been prepared in order to obtain a recyclable CuAAC catalyst (**Paper C**).

Chapter 3: The use of amidation-CuAAC reactions for the preparation of amido-triazole ligands are described, together with its evaluation in molybdenum-catalyzed asymmetric allylic alklation reactions. With the high enantio- and regio-selectivity obtained, the triazole unit is clearly demonstrated to be a suitable donor group in asymmetric catalysis (**Paper D**).

Chapter 4: Preparation of imine- and amine-triazole ligands derived from readily accessible commercial materials and their evaluation in enantioselective copper-catalyzed conjugate additions of organometallic reagents are described. Despite moderate enantioselectivity obtained, the activities of these ligands have been promising to be further screened in other asymmetric catalytic transformations.

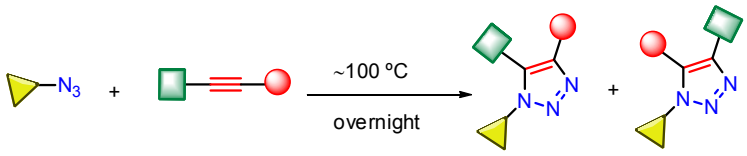
Chapter II

CONTENTS

2. TRIS(TRIAZOLYL)METHANOL LIGANDS FOR COPPER-CATALYZED AZIDE-ALKYNE CYCLOADDITION REACTIONS

2.1. AZIDE-ALKYNE [3+2] CYCLOADDITION

The non-catalytic, concerted 1,3-dipolar cycloaddition of an azide and alkyne to afford a 1,2,3-triazole was first developed by Huisgen[1] but it has several limitations as a long reaction time and high temperature (neat, ~100 °C, overnight) although it works well with either electron deficient[2] or strained alkynes.[3] In addition, a mixture of 1,4-adduct and 1,5-adduct were obtained and the scope was limited to symmetrical internal alkynes (**Scheme 2.1**).



Scheme 2.1. [3+2] Huisgen cycloaddition.

Decades after, the Cu(I)-catalyzed variation now it is referred as *"the cream of the crop"* of click chemistry[4,5] by K. Barry Sharpless. The independent development by Meldal[6] and Sharpless[7] has taken the concerted cycloaddition reaction to the Cu-catalyzed successor where 1,4-adduct are regioselectively obtained (**Scheme 2.2**).[8]

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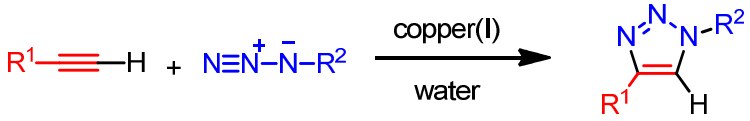
[1] Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565.
[2] Clarke, D.; Mares, R. W.; McNab, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1799.
[3] Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2004**, *126*, 15046.
[4] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
[5] (a) *QSAR Comb. Sci.* **2007**, *26*, 1110. (b) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674. (c) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (d) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (e) *Macromol. Rapid Commun.* **2008**, *29*, 943. (f) Kappe, C. O.; Van der Eycken, E. *Chem. Soc. Rev.* **2010**, *39*, 1280. (g) Lallana, E.; Riguera, R.; Fernandez-Megia, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8794. (h) Lau, Y. H.; Rutledge, P. J.; Watkinson, M.; Todd, M. H. *Chem. Soc. Rev.* **2011**, *40*, 2848. (i) Muller, T.; Bräse, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11844 (j) Sletten, E. M.; Bertozzi, C. R. *Acc. Chem. Res.* **2011**, *44*, 666. (k) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905.
[6] Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
[7] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
[8] (a) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (b) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302.



Scheme 2.2. Copper(I)-catalyzed azide-alkyne cycloaddition.

In general, the CuAAC reaction can be catalyzed by commercial copper(I) salts like copper(I) bromide, iodide or by an indirect catalytic system based on *in situ* generation of the copper(I) species formed from copper(II) sulfate and a reducing agent (*e.g.* sodium ascorbate). Using such copper salts, the solvent of choice or the medium of CuAAC reaction is water. Whenever a reaction takes place *on water*, a great rate acceleration is observed.[9] Each component of the reaction has to be a hydrophobic liquid, and, briefly, the emulsion formation *on water* is responsible for the rate acceleration. Apart from the ideal case, most of the copper(I) salts are unstable and mostly insoluble in water. Nevertheless, copper(II) sulfate is soluble in water and *in situ* generated copper(I) "buffer" system enhances the stability and interaction of the catalyst with such emulsions and thus stabilizes the reactive intermediates in the catalytic cycle. Overall, this logic behind CuAAC reaction made it so popular in chemical synthesis. In addition, the reaction can also be performed in water–alcohol mixtures to include solid substrates into this logic. Later on, CuAAC reaction has been performed in organic solvents with the addition of a base such as trialkylamine or DBU. Bases have been speculated to assist the formation of an alkynylcopper complex, mostly thought to act as a stabilizing ligand to Cu(I) to minimize catalyst deactivation. After this point, various ligands have become widespread in CuAAC reaction. Albeit, CuAAC reaction works at room or moderate temperatures, microwave heating has been found out to accelerate the reaction.[10]

There are other metals which have been used to catalyze AAC reactions either to yield the same regioisomer as copper or form the 1,5 adduct. Recently, silver(I) ligated complexes were also found to be great catalysts to form 1,4-adducts presumably through a similar mode of action as copper(I) species (**Scheme 2.3**).[11]

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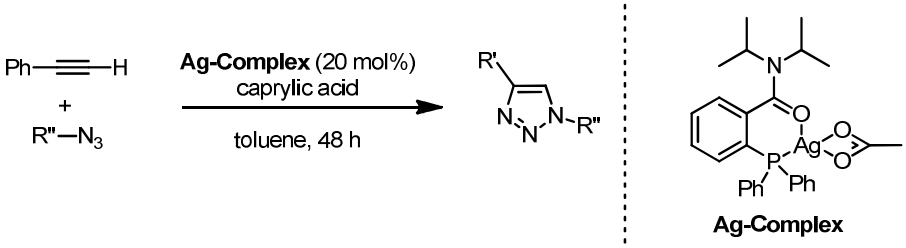
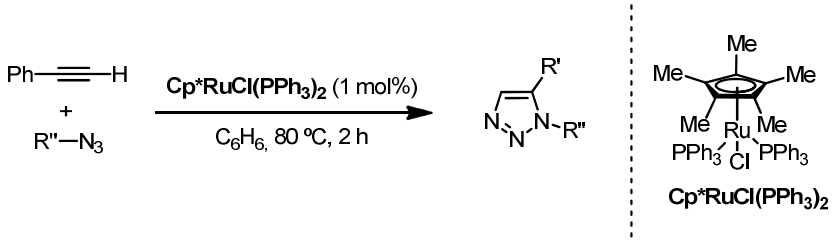
[9] (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275. (b) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302.
[10] Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004**, *6*, 4223.
[11] McNulty, J.; Keskar, K.; Vemula, R. *Chem. – Eur. J.* **2011**, *17*, 14727.



Scheme 2.3. Silver(I)-catalyzed AAC.

Interestingly, $Ru(Cp^*)(PPh_3)_2Cl$ has been another alternative which gives regioselective access to the 1,5-adducts (**Scheme 2.4**). However, the system does not really fit into the click chemistry idea due to solvent restrictions, need of relatively high reaction temperatures and limited scope. Expectedly, the growth of applications for this methodology develops slower and with a more limited scope.[12]



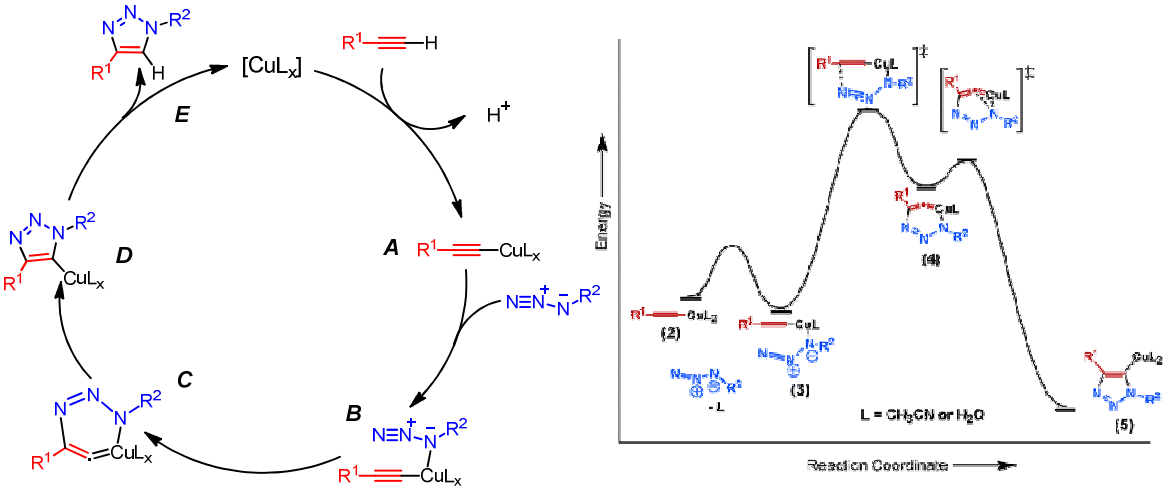
Scheme 2.4. Ruthenium-catalyzed AAC.

2.1.1. MECHANISM OF COPPER(I)-CATALYZED AZIDE-ALKYNE CYCLOADDITION

Despite the fact that the exact mechanism is not very clear, a general mechanism has been accepted with the earliest effort to generalize the mechanistic cycle based on DFT calculations of monometallic systems (**Scheme 2.5**).[13] The cycle starts by a favorable formation of alkynylcopper complex (**A**), presumably by π-alkyne copper complex where the terminal hydrogen of the alkyne is acidified enough in aqueous media to form a σ-acetylide. Thus, the formation is reasonable even in neutral water. Azide coordination occurs to such alkynylcopper complex through the copper with low activation energy (**B**). At this point, the remote end of the azide is more electrophilic. Then, attack of this N to C2 position of the alkyne forms a strained metallacycle (**C**), with the highest energy

[12] Zhang, L.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998.
[13] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

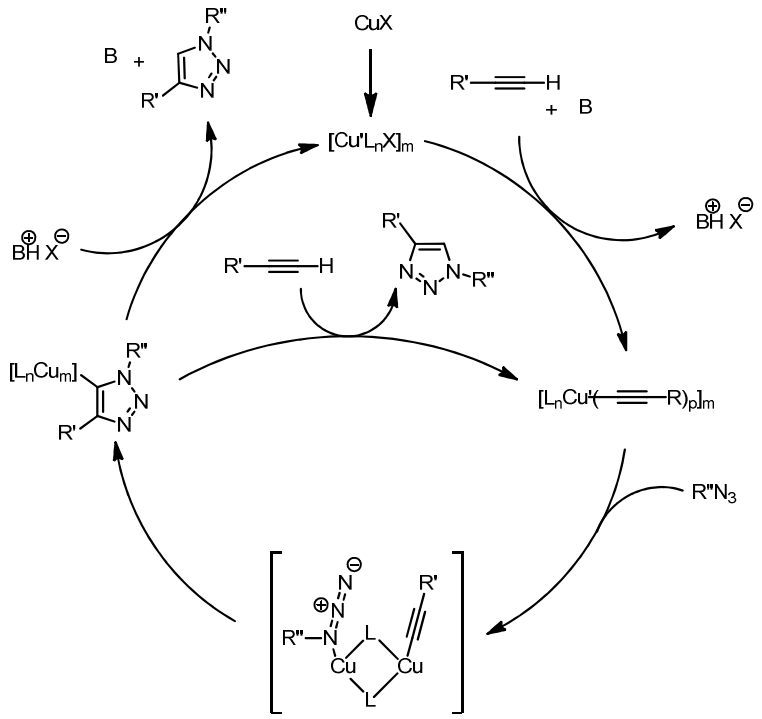
transition state, as the rate-determining step. The energy barrier of this stage is much lower than non-copper catalyzed concerted 1,3-cycloaddition and this fact somehow supports the rate acceleration by copper(I) species. A ring contraction that is followed by a reductive elimination generates triazolylcopper complex (**D**) which is protonated to generate liberates the product (**E**) and regenerates the active catalyst.



Scheme 2.5. Generally accepted simple mechanism of CuAAC reaction by DFT calculations.

On the other hand, kinetic experiments showed a second order rate equation in the presence of some bimetallic copper species (**Scheme 2.6**). Theoretical and experimental data, in general, are rather consistent. However, it remains to be established if equilibrating copper aggregates rely on either mononuclear or binuclear copper species.[14]

[14] Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2210.



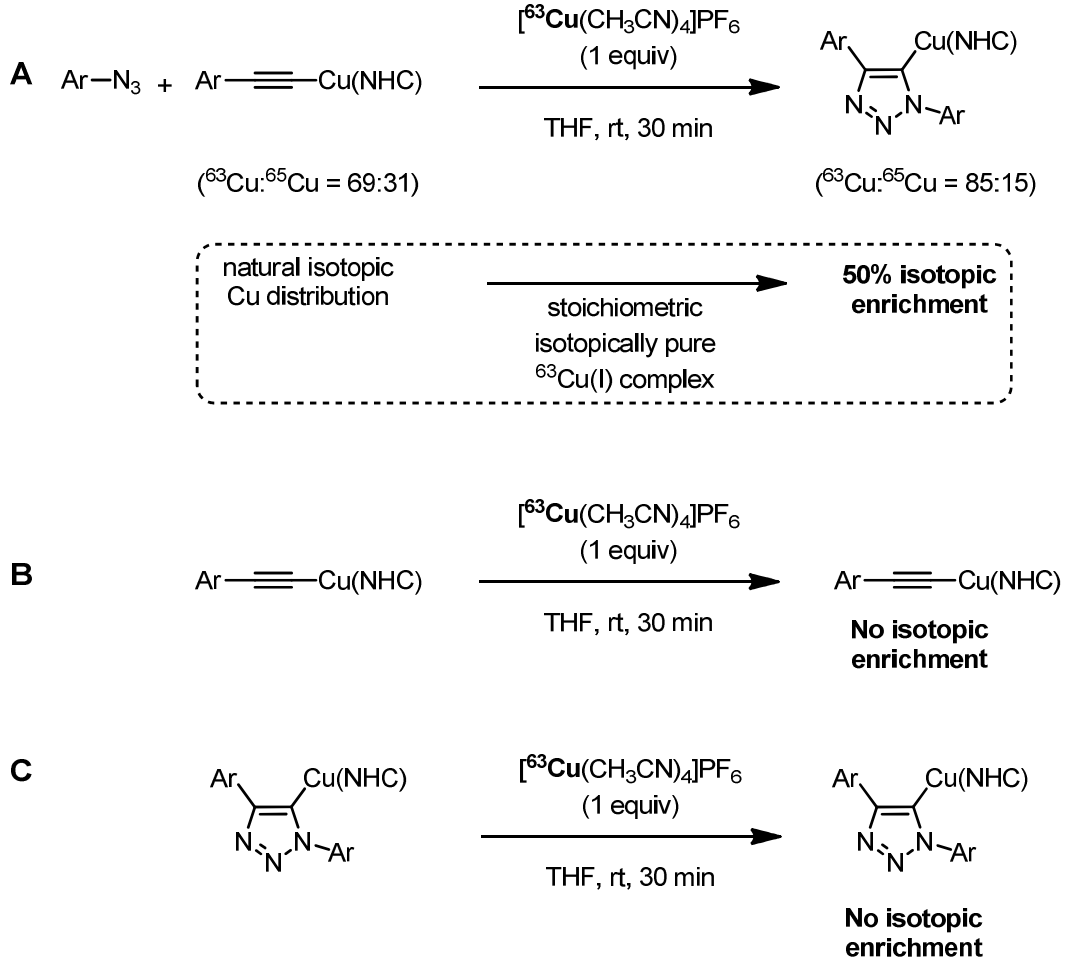
Scheme 2.6. Simplified catalytic cycle based on kinetic studies.

Very recently, a real-time monitor of a CuAAC process via heat-flow reaction calorimetry resulted in a conclusion that monomeric copper acetylide complexes are not reactive towards azide without addition of new copper catalyst to the reaction media. In the same work, newly utilized "copper isotope labeling" mass study revealed that binuclear copper species are responsible for carbon–nitrogen bond formation in the cycloaddition step.[15] In detail, first a σ-bound copper(I)-acetylide has been synthesized using naturally abundant distribution of copper isotopes (^{63}Cu:^{65}Cu = 69:31) and an isotopically pure ^{63}Cu, copper(I) complex, $[Cu(CH_3CN)_4]PF_6$ has been prepared from commercial copper(II) oxide (99.9% ^{63}Cu). Since they were able to isolate copper triazolide product with initial stoichiometric level experiments from σ-bound copper(I)-acetylide, later a set of stoichiometric experiments were constructed in order to observe the changes in the ratio of copper isotopes in the final product by mass spectrometric analysis (**Scheme 2.7**).

Experiment **A** yielded a 50% isotopic enrichment in the final product. With this result in mind, in experiment **B**, there was not any involvement of isotopic copper from the catalyst and finally when the product with naturally abundant copper species were

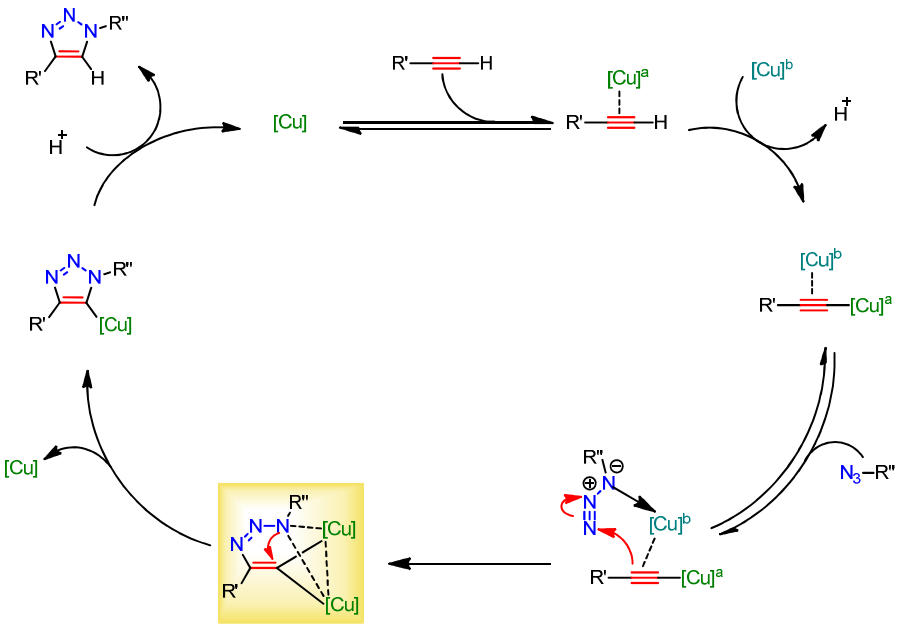
[15] Worrell, B. T.; Malik, J. A.; Fokin, V. V. *Science* **2013**, *340*, 457.

subjected to same reaction conditions at **C**, again there was not any involvement from pure isotopic catalyst. Overall, it means that presumably isotopic enrichment has nothing to do with any reversible or irreversible steps over neither the σ-bound copper(I)-acetylide nor the copper triazolide species.



Scheme 2.7. Copper isotopic label studies with mass spectrometry.

As postulated by the authors though, during the formation of the triazolide ring, a dinuclear copper intermediate should form. In terms of thermodynamics, a copper triazolide formation is preferentially ligated to the NHC. The equal proportions of isotopic enrichment in the experiment **A** dictate a rapid and reversible ligand exchange from a binuclear copper intermediate (highlighted in yellow, **Scheme 2.8**), from which the cycloaddition step occurs readily (lower in energy) with respect to previously proposed mononuclear cycloaddition steps.



Scheme 2.8. Proposed dinuclear copper intermediate in the catalytic cycle by isotope labeling.

Overall, even with the new tools in hand, the limitations in the determination of real active species in the reaction media make it hard to elucidate the real mechanism. Even in this recent study, the solvent is limited to aprotic media, which is inappropriate to draw conclusions for a reaction that is mostly performed *on water*.

2.1.2. LIGANDS

Even though CuAAC reaction operates without any need of additional ligands or using simple commercial tertiary amines, more than 10 mol% of copper salts are necessary and almost stoichiometric (or even higher) amounts of additives and/or ligands are utilized. Additionally, whenever a copper binding functional group is present in the reactants up to stoichiometric amounts of copper are required. In such cases, if the scale of the reaction is more than mg-scale, the isolation and purification become tiresome, the amount of copper is more than the allowed toxicity level, and colored products are obtained. For this reason, several alternatives were initially developed.[16] Designed ligands afford much better results at very low loading of copper complexes as low as ppm levels. Since the reaction is autocatalyzed by final products–triazoles, most efforts have been devoted to the development of triazole bearing ligands. In this manner, additives and inert conditions are unnecessary.

[16] Diez-Gonzalez, S. *Catal. Sci. Technol.* **2011**, *1*, 166.

After the initial copper(II) sulfate system was discovered, the second most archaic system has been the use of copper(I) iodide with some tertiary amines (*e.g.* triethylamine or *N*,*N*-diisopropylethylamine). Despite its cleaner work up, the functional group limitations were still unsolved and the rate of reaction was relatively slower and unpredictable in most cases. Other than amines, *N*(sp^2)-type chelating ligands have been employed from imines to imidazoles with various proposed binding geometries. However, these types of ligands never became common for CuAAC reaction, even though DBU is commercially available (**Figure 2.1**).

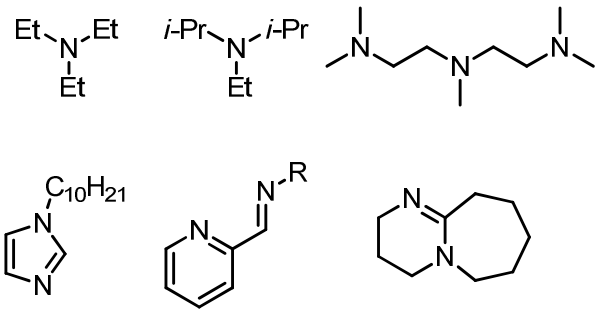
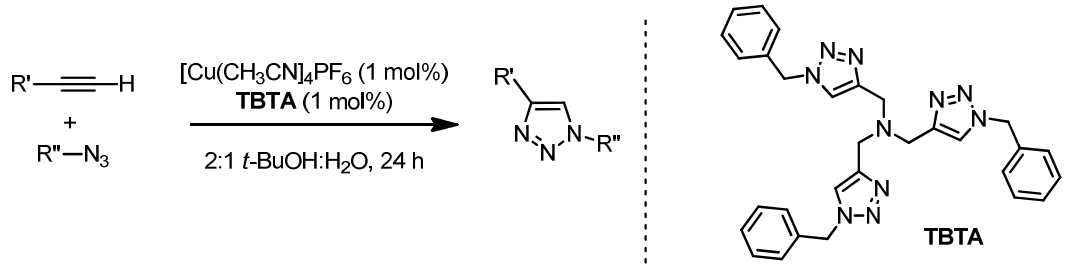


Figure 2.1. General amines and imines used as ligands in CuAAC reaction.

The most common type of ligands is polytriazoles that are themselves synthesized by CuAAC reaction. In the beginning, tris(benzyltriazolylmethyl)amine (TBTA) was the optimum system with its most probably cage-like structure around the copper center, even though in solid state bimetallic species were observed without coordination of the tertiary amine nitrogen.[17] Polymer-supported versions were also developed with very good activity (**Scheme 2.9**).



Scheme 2.9. CuAAC reaction with copper(I)-tristriazole complex.

[17] (a) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853. (b) Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2004**, *126*, 9152.

Since phosphorus-based ligands are among the most common in catalysis, it was inevitable to investigate their activity. The first ones utilized were $[CuBr(PR_3)_3]$ complexes with a basic amine additive in organic solvents. Very recently, a $[CuBr(PPh_3)_3]$ complex was found to be effective without any additive with 0.5 mol% under neat or aqueous conditions at room temperature. In other types of known phosphorus ligands only triphenyl phosphine has been involved in some catalytic activity using copper carboxylate complexes.[18,19] Interestingly, a BINOL-derived phosphoramidites[20] work pretty well using an *in situ* generated copper(II) sulfate system with as low as 1 mol% of catalyst loading (**Figure 2.2**).

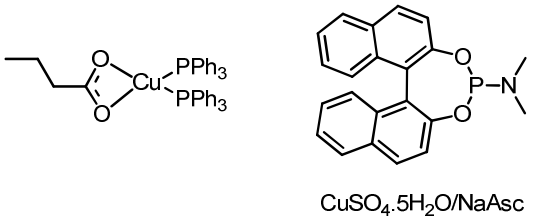
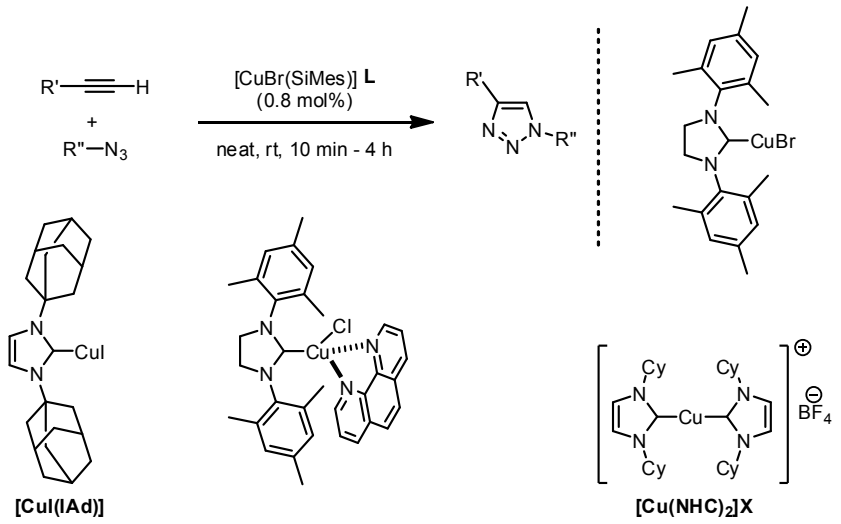


Figure 2.2. *P*-ligands for CuAAC reaction.

N-Heterocyclic carbenes (NHC) have outstanding activity for CuAAC reaction. The [CuI(IAd)] type of system was first utilized and, upon further development, $[Cu(NHC)_2]X$ type of general structures resulted to be much more effective and they allowed even ppm levels of catalyst loadings with exceptional TON and TOF numbers. In general, such NHC ligands and tris(triazole)s are among the best ligands in hand until now (**Scheme 2.10**).[21,22]

[18] Pérez-Balderas, F.; Ortega-Muñoz, M.; Morales-Sanfrutos, J.; Hernández-Mateo, F.; Calvo-Flores, F. G.; Calvo-Asín, J. A.; Isac-García, J.; Santoyo-González, F. *Org. Lett.* **2003**, *5*, 1951.
[19] Gonda, Z.; Novák, Z. *Dalton Trans.* **2009**, *39*, 726.
[20] Campbell-Verduyn, L. S.; Mirfeizi, L.; Dierckx, R. A.; Elsinga, P. H.; Feringa, B. L. *Chem. Commun.* **2009**, *0*, 2139.
[21] (a) Díez-González, S.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558. (b) Díez-González, S.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8881. (c) Díez-González, S.; Stevens, E. D.; Nolan, S. P. *Chem. Commun.* **2008**, 4747.
[22] Teyssot, M.-L.; Chevry, A.; Traïkia, M.; El-Ghozzi, M.; Avignant, D.; Gautier, A. *Chem. Eur. J.* **2009**, *15*, 6322.



Scheme 2.10. CuAAC reaction with [Cu(NHC)].

Strikingly, a recent player in the field is copper(I) acetate.[23] Without any additives, it was found to be very active for CuAAC reaction. Presumably, dinuclear structure present in its nature with respect to other copper(I) salts has been reasoned for such activity, as low as 0.01 mol% loadings have been practically active. To note, the use of copper(I) iodide/tertiary amine combinations is now suppressed in practical applications.

Neglected in a sense since thiols are strong binders for copper, only $CuBr{\cdot}SMe_2$, a commercial complex, was used in organic solvents and moderate results were obtained.[24] Some thioanisole derivatives were found to be successful ligands but with 10 mol% loadings. An (aminoarenethiolato)copper complex has afforded excellent yields in DMSO and acetonitrile. However, work in the inert atmosphere is required (**Figure 2.3**).[25]

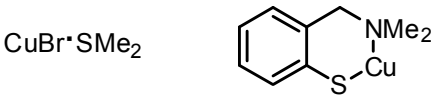


Figure 2.3. *S*-ligands in CuAAC reaction.

2.2. AIM

Following the seminal work by the Sharpless/Fokin groups,[17] a novel ligand based on the tris(triazolyl)methanol structure has been developed in our group. The initial idea

[23] Shao, C.; Cheng, G.; Su, D.; Xu, J.; Wang, X.; Hu, Y. *Adv. Synth. Catal.* **2010**, *352*, 1587.
[24] Wang, F.; Fu, H.; Jiang, Y.; Zhao, Y. *Green Chem.* **2008**, *10*, 452.
[25] Fabbrizzi, P.; Cicchi, S.; Brandi, A.; Sperotto, E.; van Koten, G. *Eur. J. Org. Chem.* **2009**, 5423.

has been the optimization of reaction conditions with the ligand for CuAAC reaction on water. Additionally, a tandem methodology using sodium azide, primary or benzyl bromides and alkynes has been developed for conventional heating and microwave conditions (**Paper A**).

Later, a scalable synthesis of the ligand has been developed in order to gain access to a small library of these fine tunable ligands. After a thorough investigation of this set of ligands, tolerance of the catalytic system further expanded to medium polarity organic solvents with a wide scope of azides and acetylenes (**Paper B**).

In a similar concept, the ligand system has been adapted into polymer supported covalently immobilized version without adding any synthetic complexity to the modularity. Excellent stability, activity and reusability have been obtained with a complete set of scope (**Paper C**).

PAPER A

A Highly Active Catalyst for Huisgen 1,3-Dipolar Cycloadditions Based on the Tris(triazolyl)methanol–Cu(I) Structure

Org. Lett., **2009**, *11*, 4680–4683

Publication Date (Web): September 23, 2009

Paper A – The initial experimental work on the synthesis of the ligand and the use as catalyst in CuAAC were performed by Dr. Salih Özçubukçu and the rest of the work was done together with Dr. Ciril Jimeno in Prof. M. A. Pericàs Group at ICIQ.

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A Highly Active Catalyst for Huisgen 1,3-Dipolar Cycloadditions Based on the Tris(triazolyl)methanol−Cu(I) Structure

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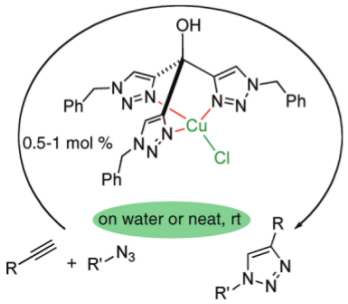
Received August 25, 2009

ABSTRACT



A new tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol ligand 3 has been prepared by a triple Cu(I)-catalyzed alkyne−azide 1,3-dipolar cycloaddition (CuAAC). Ligand 3 forms a stable complex with CuCl, which catalyzes the Huisgen 1,3-dipolar cycloaddition on water or under neat conditions. Low catalyst loadings, short reaction times at room temperature, and compatibility with free amino groups make 3·CuCl an outstanding catalyst for CuAAC.

Following its independent discovery by Meldal[1] and Sharpless,[2] the regioselective, Cu(I)-catalyzed alkyne−azide 1,3-dipolar cycloaddition (CuAAC) reaction has become the archetypal example of "click chemistry",[3] and the process has found application in almost every field of chemistry.[4]

In CuAAC reactions, a mixture of $CuSO_4$ and sodium ascorbate has been traditionally used as a precatalyst system which generates the Cu(I) species in the reaction media.[2] Later, it was discovered that polydentate nitrogen ligands not only stabilize Cu(I) intermediates[5] but also accelerate the catalytic process,[6] and this allowed the direct use of Cu(I) salts as catalysts in CuAAC reactions. Indeed, a tris(triazolylmethyl)amine **1** (Figure 1) was found to be an excellent ligand for this chemistry.[7] Tripodal tetraamino ligands like **2**[8] and *N*-heterocyclic carbenes[9] have also been successfully used to stabilize the catalyst in CuAAC.

[†] Institute of Chemical Research of Catalonia.
[‡] Universitat de Barcelona.

(1) Meldal, M.; Christensen, C.; Tornoe, C. W. *J. Org. Chem.* **2002**, *67*, 3057.
(2) Sharpless, K. B.; Fokin, V. V.; Green, L. G.; Rostovtsev, V. V. *Angew. Chem., Int. Ed.* **2002**, *114*, 2708.
(3) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
(4) Reviews: (a) *Macromol. Rapid. Commun.* **2008**, *29*, 943, special thematic issue. (b) *QSAR Comb. Sci.* **2007**, *26*, 1110, special thematic issue. (c) Angell, Y. L.; Burgess, K. *Chem. Soc. Rev.* **2007**, *36*, 1674. (d) Moses, E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (e) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (f) Wu, P.; Fokin, V. V. *Aldrichim. Acta* **2007**, *40*, 7. (g) Kappe, C. O.; Van der Eicken, E. *Chem. Soc. Rev.* **2009** (DOI: 10.1039/b901973c).
(5) (a) Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853. (b) Lewis, W. G.; Magallon, F. G.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2004**, *126*, 9152.
(6) (a) Rodionov, V. O.; Presolski, S. I.; Gardinier, S.; Lim, Y.-H.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12696. (b) Rodionov, V. O.; Presolski, S. I.; Díaz Díaz, D.; Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc.* **2007**, *129*, 12705.

10.1021/ol9018776 CCC: $40.75

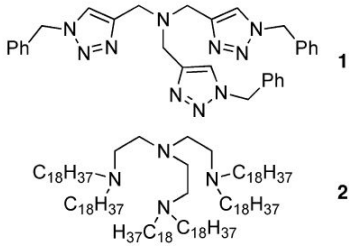


Figure 1. Polydentate N ligands for CuAAC.

Scorpionate ligands based on tris(pyrazolyl)borate moieties (Figure 2, top) form very stable metal complexes due to the

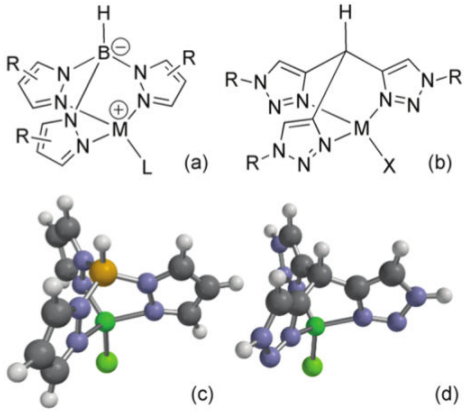


Figure 2. Top: Schematic representation of metal complexes of a tris(pyrazolyl)borate (a) and of a tris(triazolyl)methane (b). Bottom: DFT (B3LYP/LANL2DZ)-optimized geometries of the CuCl complexes of a tris(pyrazolyl)borate (c) and of tris(triazolyl)methane (d).

establishment of chelated, cage structures involving the formation of six-membered rings.[10] These complexes have found ample application as catalysts in a variety of relevant processes and, most notably, in C−H bond activation methods.[11] We wondered whether the analogous tris(triazolyl)methane complexes would depict similar stability and, in particular, if the corresponding Cu(I) complexes would consequently perform as highly efficient catalysts in CuAAC. In fact, DFT theoretical calculations (B3LYP/LANL2DZ) performed on Cu(I) complexes of both types of structures revealed essentially identical structures for both types of complex (Figure 2, bottom). Thus, the Cu−N optimized distance has average values of 2.179 Å (c) and 2.188 Å (d), while the Cu−Cl-optimized distances are 2.317 Å (c) and 2.260 Å (d).

We accordingly envisioned that tris(triazolyl)methanol **3** (Figure 3), constructed in turn through a "click" approach,

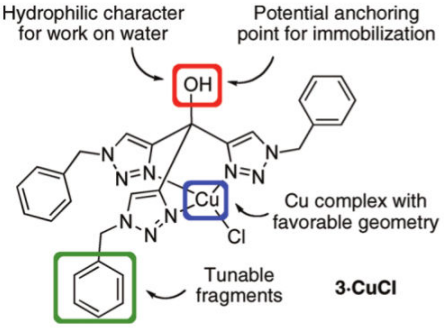


Figure 3. Structural features of **3**·**CuCl**.

could be an outstanding ligand for CuAAC. In effect, besides the presumed stability of its Cu(I) complex, the molecule presents two well-differentiated faces with complementary hydrophobic and hydrophilic characters that make it ideal for work *on water*, a most usual condition for CuAAC.[12] In addition, due to its modular construction,[13] **3** could be readily fine-tuned for specific applications by simply changing the nature of the azido compound employed for its synthesis. On the other hand, the hydroxyl group placed on the hydrophilic hemisphere of the molecule can also serve as an anchor for supporting **3** onto polymeric materials.[14]

The synthesis of **3** was planned through the intermediacy of tris(alkynyl)carbinol **4**[15] which, in turn, was readily prepared by addition of trimethylsilylacetylide to ethyl chloroformate (Scheme 1).

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(13) For modular approaches to catalytic ligands from our research, see: (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970. (b) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1999**, *64*, 7902. (c) García-Delgado, N.; Reddy, K. S.; Solà, L.; Riera, A.; Pericàs, M. A.; Verdaguer, X. *J. Org. Chem.* **2005**, *70*, 7426. (d) Rodríguez-Escrich, S.; Reddy, K. S.; Jimeno, C.; Colet, G.; Rodríguez-Escrich, C.; Solà, L.; Vidal-Ferran, A.; Pericàs, M. A. *J. Org. Chem.* **2008**, *73*, 5340. (e) Rodríguez-Escrich, S.; Solà, L.; Jimeno, C.; Rodríguez-Escrich, C.; Pericàs, M. A. *Adv. Synth. Catal.* **2008**, *350*, 2250.
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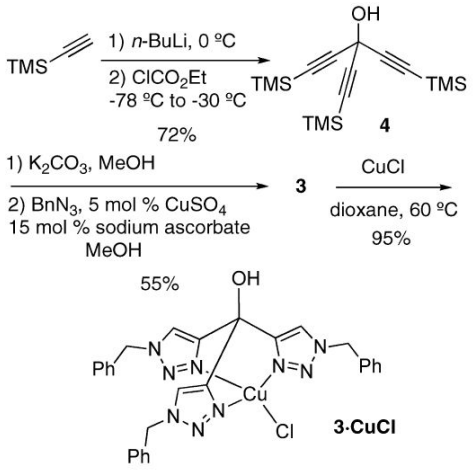
Scheme 1. Synthesis of the Tris(triazolyl)methanol/copper(I) Complex **3·CuCl**



Subsequent deprotection of the TMS groups with K_2CO_3 in methanol followed by cycloaddition with benzyl azide under the classical CuAAC conditions ($CuSO_4$, sodium ascorbate) led to the target tris(triazolyl)methanol **3**[16] in good overall yield. The final copper catalyst **3·CuCl** was easily prepared by treatment of **3** with 1 equiv of CuCl in dioxane. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, and hexane was added to the solution. A greenish solid (**3·CuCl**) precipitated inmediately and was isolated in almost quantitative yield.

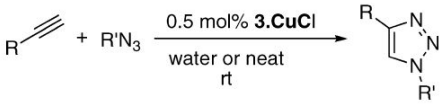
Most gratifyingly, **3·CuCl** turned out to be air and moisture stable. Although we have been unable to grow single crystals of **3·CuCl**, the coordination environment around copper can be inferred from the symmetry of the NMR spectra. In addition, a $CuCl_2$ complex of **3** presents in its crystal structure a hexacoordinated copper atom surrounded by two molecules of **3** acting as tridentate ligands (see the Supporting Information for details). The new catalyst was then tested in the CuAAC of benzyl azide and phenylacetylene under different experimental conditions. To our satisfaction, **3·CuCl** exhibited very high catalytic activity under mild reaction conditions, especially when water was present in excess in the reaction media. In fact, reactions were fast at room temperature under neat conditions or in the sole presence of water, with catalyst loadings of only 0.5 mol %.

The scope of applicability of **3·CuCl** was explored under these conditions (Table 1). Catalyst loadings as low as 0.25 mol % could be used too, but at the expense of longer reaction times. This decrease in reactivity was compensated by carrying out these reactions at 40 °C (Table 1, entries 9−11). As the inspection of Table 1 reveals, excellent yields are generally obtained in the CuAAC of a wide variety of alkyne with alkyl, benzyl, or aryl azides.

The result obtained in the cycloaddition of propargylamine with benzyl azide (entry 16) deserves special comment. In general, the CuAAC fails in the presence of free amino groups due to the strong tendency of amines to form complexes with Cu(I), thus deactivating the catalyst. With the use of **3·CuCl**, this deactivation did not occur, and the corresponding triazole product could be isolated in 47% yield. This result shows how the tight complexation present in **3·CuCl** can allow avoiding additional protection and deprotection steps when free amines have to be involved in CuAAC.

(16) Patent pending.

Table 1. CuAAC Using Catalyst **3·CuCl**



entry	R	R′	prod	time (h)	yield[a] (%)
1	Ph	Ph	**5a**	4	99[b]
2	Ph	*n*-Oct	**5b**	4	99[b]
3	Ph	$PhCH_2$	**5c**	4	94[b]
4	Ph	$PhCH_2$	**5c**	15	99[c]
5	CO_2Et	*n*-Oct	**5d**	15	99[b]
6	CH_2NMe_2	Ph	**5e**	4	95[b]
7	2-pyridyl	$PhCH_2$	**5f**	8	99[b]
8	$PhCH_2CH_2$	$PhCH_2$	**5g**	4	99[c]
9	*n*-Bu	$PhCH_2$	**5h**	16	98[b,d]
10	*n*-Hex	$PhCH_2$	**5i**	16	98[b,d]
11	4-chlorobutyl	$PhCH_2$	**5j**	18	64[b,d]
12	CO_2Et	$PhCH_2$	**5k**	12	96[b]
13	*p*-$HOCH_2C_6H_4$	$PhCH_2$	**5l**	2	92[b]
14	CH_2OH	$PhCH_2$	**5m**	6	84[b]
15	CH_2NMe_2	$PhCH_2$	**5n**	4	97[b]
16	CH_2NH_2	$PhCH_2$	**5o**	5	47[e]

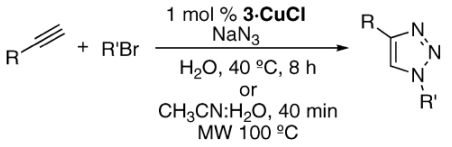
[a] Isolated yield. [b] Water. [c] Neat. [d] 0.25 mol % of catalyst at 40 °C. [e] 1 mol % catalyst in *n*-BuOH/water 2:1 and basic workup.

Taking into account the interest of avoiding storage and manipulation of organyl azides, the use of **3·CuCl** in a one-pot process involving the in situ formation of a benzyl-type or alkyl (octyl) azide from the corresponding bromides and sodium azide was explored (Table 2).

This tandem process performed nicely in water using a 1 mol % catalyst at 40 °C (entries 1−7). A microwave-promoted version, which allowed substantial reduction of reaction times, was also set up. In this case, a 1:1 mixture of acetonitrile/water was used, as well as reaction temperatures of 100 °C. Under these conditions, reaction times as short as 40 min were sufficient to allow the isolation of the cycloaddition products in good yields (entries 8−13).[4g] It must be noted that, due to the lower reactivity of octyl bromide in front of sodium azide, 2 equiv of this reagent with respect to the alkyne was used.

Finally, **3·CuCl** was also used to catalyze the cycloaddition of **4** with benzyl azide in water leading to the tris(triazolyl)-methanol ligand **3**. In this way, the target tris(triazole) can be routinely prepared in gram amounts in 86% isolated yield (Scheme 2). With this improvement, **3·CuCl** can be prepared in only three steps from commercially available precursors in 59% overall yield.

Table 2. One-Pot Azide Formation plus CuAAC Reaction Mediated by **3·CuCl**

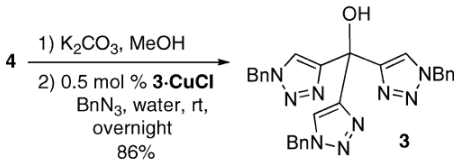


entry	R	R′	prod	yield[a] (%)
1	Ph	$PhCH_2$	**5c**	99[b]
2	Ph	p-^{t}BuC$_6$H$_4$CH$_2$	**5p**	98[b]
3	Ph	p-$NO_2C_6H_4CH_2$	**5q**	98[b]
4	Ph	p-$MeOC_6H_4CH_2$	**5r**	93[b]
5	Ph	o-$ClC_6H_4CH_2$	**5s**	80[b]
6	Ph	m-$NO_2C_6H_4CH_2$	**5t**	88[b]
7	p-$HOCH_2C_6H_4$	p-$NO_2C_6H_4CH_2$	**5u**	90[b]
8	Ph	n-Oct	**5b**	57[c]
9	CH_2OH	n-Oct	**5v**	38[c]
10	CH_2OH	$PhCH_2$	**5m**	88[c]
11	CMe_2OSiMe_3	$PhCH_2$	**5w**	98[c]
12	CH(OH)Ph	n-Oct	**5x**	89[c]
13	CH_2SPh	n-Oct	**5y**	70[c]

[a] Isolated yield. [b] In water at 40 °C. [c] In acetonitrile/water at 100 °C, under MW irradiation.

In summary, ligand **3** turns out to be a simple yet powerful complexing agent for Cu(I). Indirect evidence (XRD and NMR) suggests that **3** forms a 1:1 complex with CuCl, with all three triazole moieties interacting with the metal center. Probably due to the tight protecting cage formed around the metal center and to its particular functional groups arrangement, catalyst **3·CuCl** behaves as a very active promoter of the CuAAC, as it has been demonstrated with a broad variety of substrates (including free amines) under different reaction conditions. Application of metal complexes of analogs of **3**, readily available by cycloaddition from the key intermediate **4**, to a variety of catalytic processes is currently underway in our laboratories.

Scheme 2. Improved Preparation of **3** Using Catalyst **3·CuCl**



Acknowledgment. This work was funded by MICINN (Grant No. CTQ2008-00947/BQU), DIUE (Grant No. 2005SGR225), Consolider Ingenio 2010 (Grant No. CSD2006-0003), and the ICIQ Foundation.

Supporting Information Available: Experimental procedures. Spectral and analytical data for all new compounds. Calculated atomic coordinates. Crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Supporting Information

A Highly Active Catalyst for Huisgen 1,3-Dipolar Cycloadditions Based on the Tris(triazolyl)methanol-Cu(I) Structure.

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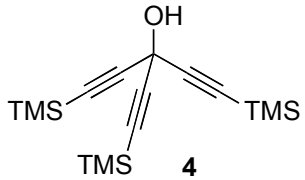
Institute of Chemical Research of Catalonia (ICIQ)

Tarragona, Spain

1. GENERAL CONSIDERATIONS:

All reagents were used as purchased. All reported yields are isolated yields. CuAAC were performed on vials at open air. ^{1}H (400 MHz) and ^{13}C (100 MHz) Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Ultrashield spectrometer at room temperature (unless otherwise stated). Chemical shifts (δ) are reported with respect to tetramethylsilane as internal standard, or to the corresponding solvent residual peak, in ppm. High Resolution Mass Spectra (HRMS) were performed by the High Resolution Mass Spectromety Service at the Institute of Chemical Research of Catalonia.



4

2. SYNTHESIS OF TRIS(TRIMETHYLSILYLETHYNYL)METHANOL (4):

In a flame-dried round bottom flask, a solution of trimethylsilylacetylene (2.3 mL, 16.6 mmol) in anhydrous THF (20 mL) was cooled to -78 ºC. Then, 2.5 M n-BuLi in hexane (6.1 mL, 15.2 mmol) was added dropwise, and the solution was stirred for 2 h. Ethyl chloroformate (442 μL, 4.61 mmol) was added, and the reaction was stirred overnight while warming to -30 ºC. Note that at that temperature the colour of the solution turns into dark red. The reaction was quenched with saturated NH_4Cl solution, diluted with water, and extracted with Et_2O (3 x 30 mL). The combined organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification by flash chromatography on a short pack of silica gel eluting with hexanes and hexanes:ethyl acetate 90:10 afforded **2** in 72% yield (1.06 g). The product can be recrystallized from hexane.

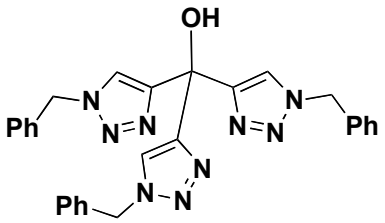
mp 61-62 ºC .

^{1}H NMR (400 MHZ, $CDCl_3$): δ 0.18 (s, 27H), 2.83 (s, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ -0.3 (CH_3), 55.0 (C), 88.3 (C), 101.7 (C) ppm.

FTIR (ATR): 3470, 2962, 1249, 1096, 1076, 1004 cm^{-1}.

3. SYNTHESIS OF TRIS(1-BENZYL-1*H*-1,2,3-TRIAZOL-4-YL)METHANOL (3):



3

a. Using CuSO4/ascorbate catalyst system:

In a round bottom flask, tris(trimethylsilylethynyl)methanol (**4**) (1.00 g, 3.13 mmol) in methanol (10 mL) was stirred in the presence of K_2CO_3 (4.20 g, 37.5 mmol) at room temperature for 4 h. The reaction was monitored by TLC (hexane:ethyl acetate 90:10 as eleuent) and after disappearance of starting material, the solution was filtered to remove excess K_2CO_3 and added to a solution of benzyl azide (1.25 g, 9.40 mmol) in methanol (10 mL). $CuSO_4.5H_2O$ (38.9 mg, 0.156 mmol) and sodium ascorbate (93.0 mg, 0.468 mmol) were added, and the mixture was stirred overnight. Solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and washed with saturated Na_2CO_3 solution (5 x 30 mL). At the end of the extraction, the aqueous phase is not blue any longer due to copper salts. The organic phase was dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification was performed by flash column chromatography, using ethylacetate as only eluent (0.866 g, 55%).

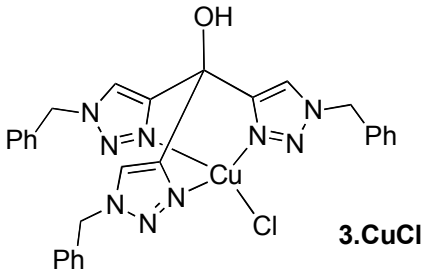
*b. Using **3.**CuCl complex as catalyst:*

In a round bottom flask with tris(trimethylsilylethynyl)methanol (**4**) (1.00 g, 3.13 mmol) in methanol (10 mL) was stirred in the presence of K_2CO_3 (4.20 g, 37.5 mmol) at room temperature for 4 h. The reaction was monitored by TLC (hexane:ethyl acetate 90:10 as eluent) and after disappearance of the starting material, the solution was filtered to remove excess K_2CO_3, and concentrated in the rotavap to less than half of the original volume. Then water (20 mL), benzyl azide (1.25 g, 9.40 mmol), and **3.**CuCl (9.4 mg, 0.0156 mmol) were successively added. The mixture was stirred overnight. During the reaction, the precipitation of the solid product could be seen. Note that a large excess of water respect to methanol is essential for the reaction to proceed. After completion of the reaction, water was added, and the solid product was obtained by simple filtration in very

good yield. Recrystallization from ethyl acetate/hexane gave analytically pure **1** (1.35 g, 86%).

mp 178-180 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.58 (s, 1H), 5.46 (s, 6H), 7.38-7.21 (m, 15H), 7.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 52.3 (CH_2), 67.1 (C), 122.2 (CH), 127.2 (CH), 127.3 (CH), 127.9 (CH), 135.2 (C), 151.4 (C) ppm. FTIR (ATR): 3245, 3116, 1496, 1223, 1059 cm^{-1}. HRMS (ES-TOF) calculated for $C_{28}H_{26}N_9O$: 504.2260. Found: 504.2250 ($[M+H]^+$).

4. SYNTHESIS OF 3·CUCL:

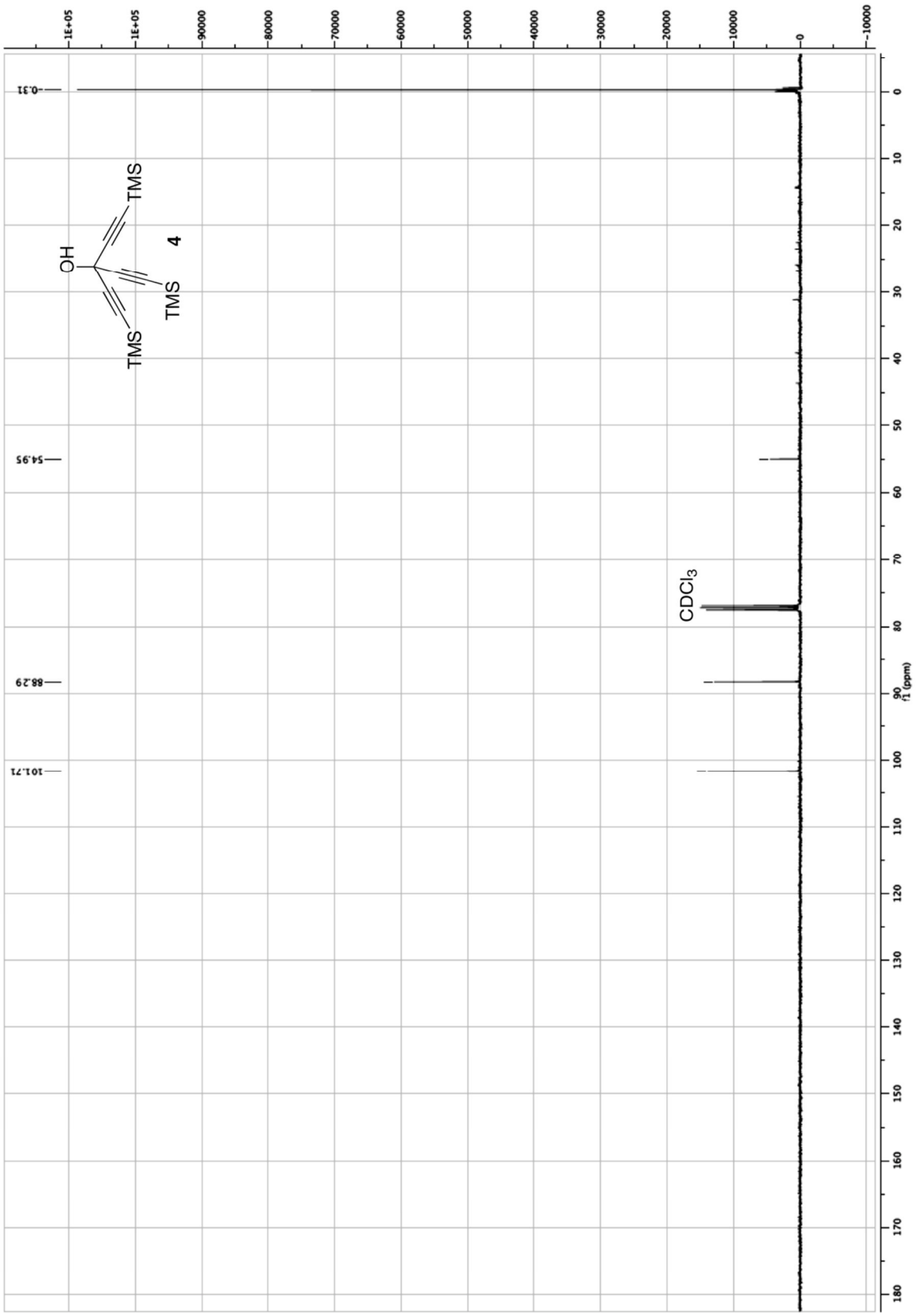


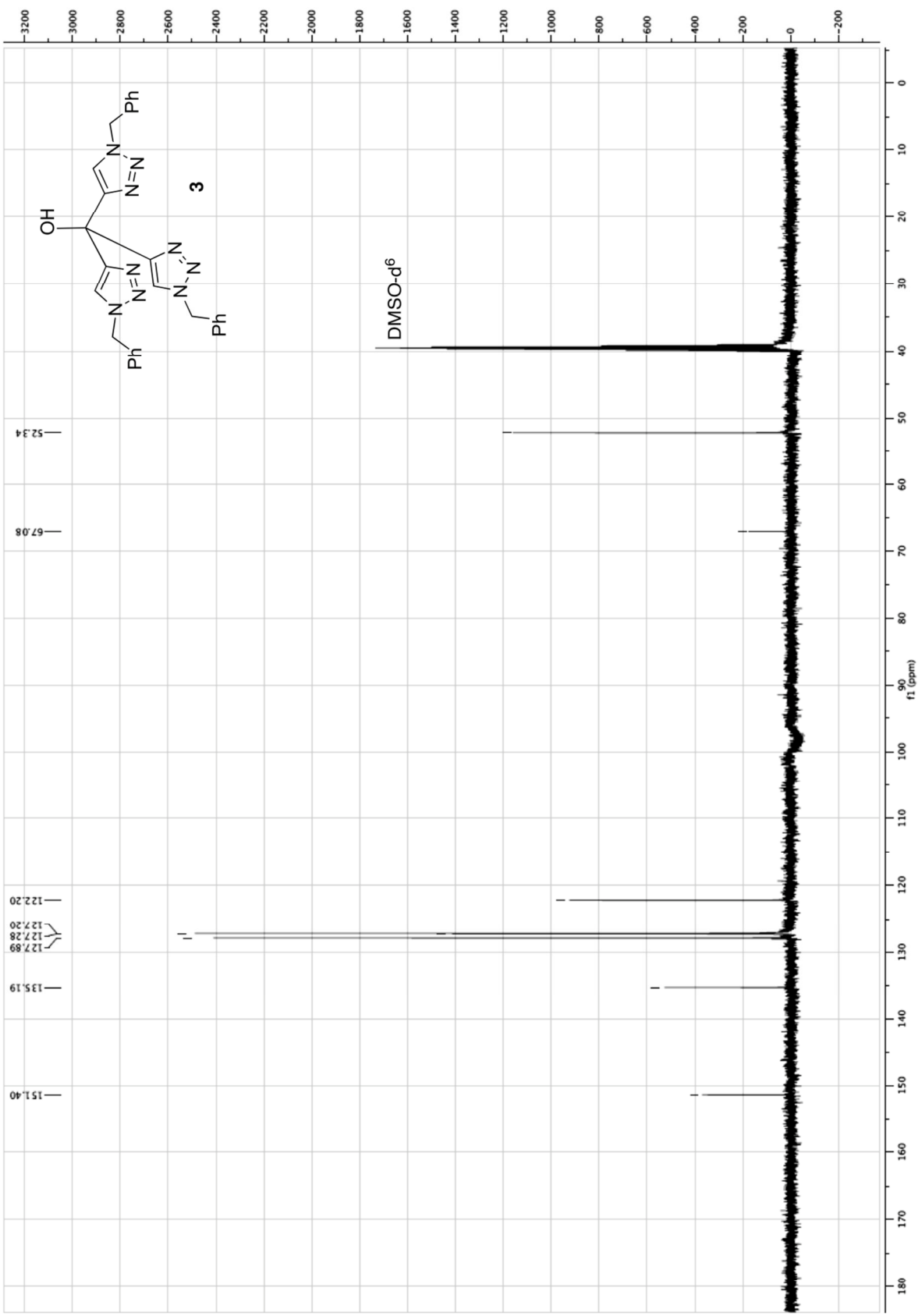
3.CuCl

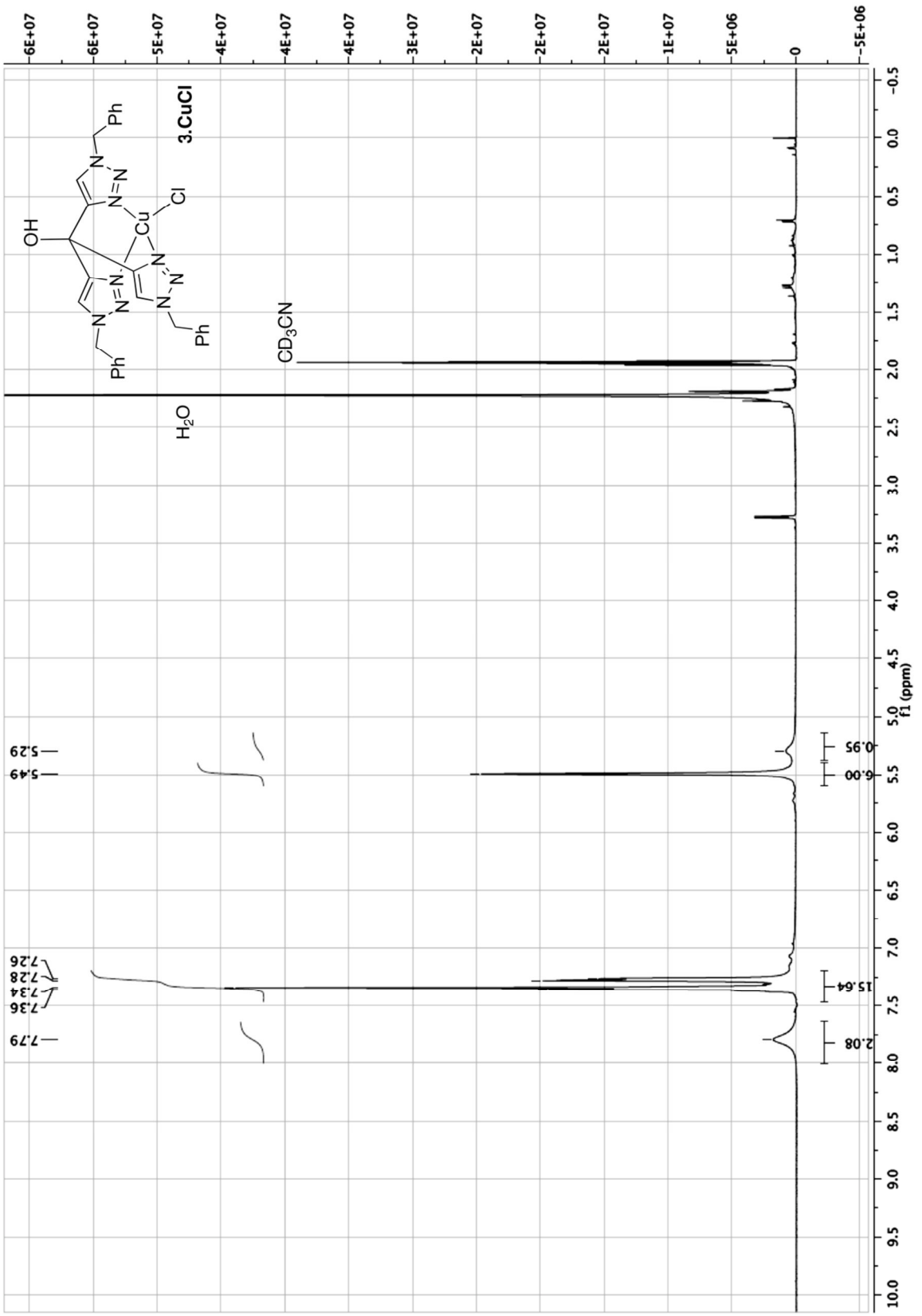
In a round bottom flask, ligand **3** (503 mg, 1.00 mmol) was dissolved in dioxane (10 mL). CuCl (98 mg, 1.00 mmol) was added, and the reaction mixture was heated up to 60 °C for 6 h. Then, the solvent was removed under reduced pressure, and the residue was dissolved in 2-3 mL dichloromethane and precipitated with 20 mL of hexane. After filtration, the pale greenish complex **4** was obtained (565 mg, 95%).

mp 153-ª58 ºC. ^{1}H NMR (400 MHz, CD_3CN): δ 4.58 (s, 1H), 5.46 (s, 6H), 7.38-7.21 (m, 15H), 7.59 (s, 3H) ppm. FTIR (ATR): 3380, 3111, 3062, 2949, 1718, 1584, 1432, 1142, 1077 cm^{-1}.

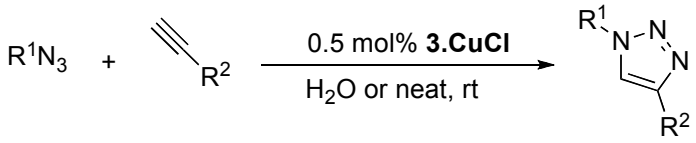
HRMS (MALDI-TOF) calculated for $C_{28}H_{25}N_9OCu$: 566.1478. Found: 566.1536


TMS
OH
4
TMS
TMS
CDCl3
0.31
54.95
88.29
101.71
f1 (ppm)





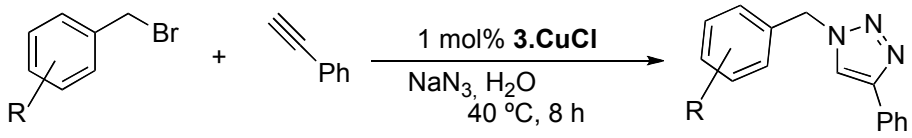
5. TYPICAL PROCEDURE FOR CUAAC AT RT:



In a vial fitted with a screw cap, **3.**CuCl (0.5 mol%; 3.0 mg) was added to a mixture of acetylene (1.05 mmol) and azide (1.00 mmol) in water (1 mL), and stirred at room temperature. Whenever the product precipitated, it was simply filtered and washed with water. Otherwise, the reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, and solvents removed *in vacuo*. When required, the product was purified by flash column chromatography.

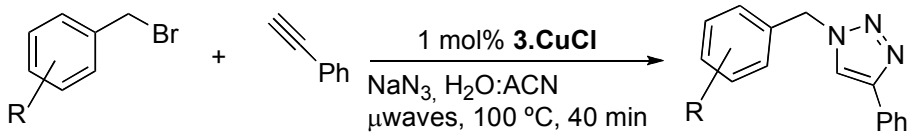
Azides were prepared according to literature procedures.[1,2]

6. TYPICAL PROCEDURE FOR CUAAC USING BENZYL BROMIDE DERIVATIVES:



In a vial fitted with a screw cap, **3.**CuCl (0.01 mmol, 6.0 mg) was added to a mixture of phenyl acetylene (102 mg, 1.00 mmol), benzyl bromide (171 mg, 1.00 mmol), and sodium azide (71 mg, 1.10 mmol) in water (1 mL), and stirred for 8 h at 40 °C. The product was filtered and washed with water. The crude product was purified by flash column chromatography using hexane:EtOAc (85:15) as eluent.

7. TYPICAL PROCEDURE FOR THE MICROWAVES ASSISTED CUAAC:

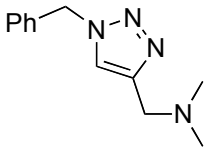


In a sealed microwaves tube, sodium azide (91 mg, 1.40 mmol) was dissolved in water (1 mL). Acetonitrile (1 mL) was added as co-solvent. Then, the benzyl bromide (1.20 mmol), the alkyne (1.0 mmol), and 1 mol% of catalyst **3.CuCl** (6.0 mg) were added, and the mixture was heated in the microwaves reactor (CEM Discover) at 100 ºC for 40 minutes (Constant temperature mode, 5 minutes heating ramp). After cooling to rt, the

reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, and solvents removed *in vacuo*. If necessary, triazoles were purified by flash chromatography on a short silica column, or by recrystallization.

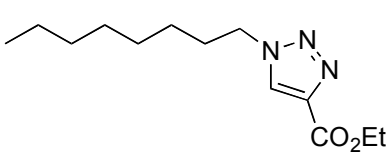
8. FULL CHARACTERIZATION OF NEW 1,2,3-TRIAZOLES.

1-(1-Benzyl-1H-1,2,3-triazol-4-yl)-*N,N*-dimethylmethanamine (5n):



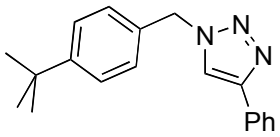
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.34-7.24 (m, 5H) 5.50 (s, 2H), 3.57 (s, 2H), 2.23 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.3, 134.6, 128.8, 128.4, 128.0, 122.4 (CH), 54.1, 53.8, 44.9 ppm. FTIR (ATR): 3362, 3135, 2943, 2775, 2362, 1497, 1076 cm^{-1}. HRMS (MALDI-TOF) calculated for $C_{12}H_{17}N_4$: 217.1453. Found: 217.1463 ($[M+H]^+$).

Ethyl 1-octyl-1H-1,2,3-triazole-4-carboxylate (5d):



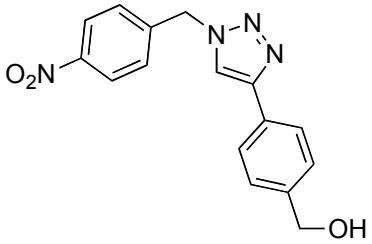
mp 54-55 ºC. ^{1}H NMR (400 MHZ, $CDCl_3$): δ 8.08 (s, 1H), 4.42 (m, 4H), 1.92 (m, 2H), 1.41 (t, J = 7.1 Hz, 3H), 1.29 (m, 10H), 0.88 (t, 3H, J = 7.0 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0 (C), 140.4 (C), 127.4 (CH), 61.4 (CH_2), 50.9 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 26.5 (CH_2), 22.7 (CH_2), 14.5 (CH_3), 14.2 (CH_3) ppm. FTIR (ATR): 3111, 2919, 2855, 1718, 1452, 1213 cm^{-1}. HRMS calculated for $C_{13}H_{23}N_3O_2Na$: 276.1688. Found: 276.1678 ($[M+Na]^+$).

1-(4-tert-Butylbenzyl)-4-phenyl-1H-1,2,3-triazole (5p):



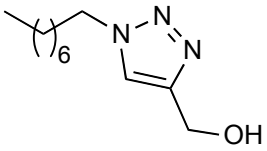
mp 164-165 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (m, 2H), 7.67 (s, 1H) 7.38 – 7.21 (m, 7H), 5.49 (s, 2H), 1.29 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9 (C), 148.1 (C), 131.8 (C), 130.7 (C), 128.2 (CH), 127.9 (CH), 126.1 (CH), 125.8 (CH), 119.7 (CH), 54.0 (CH_2), 34.7 (CH_2), 31.3 (CH_3) ppm. FTIR (ATR): 2960, 1468, 1350, 1217, 1061, 809, 761, 692 cm^{-1}. HRMS (MALDI-TOF) calculated for $C_{19}H_{22}N_3$: 292.1814. Found: 292.1824 ($[M+H]^+$).

(4-(1-(4-Nitrobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)methanol (5u):



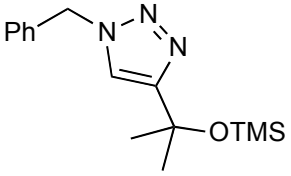
mp 135-136 ºC. ^{1}H NMR (400 MHZ, CD_3OD): δ 8.37 (s, 1H), 7.94 (d, *J* = 8 Hz, 2H), 7.55 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 5.55 (s, 2H), 5.05 (t, *J* = 4 Hz, 1H), 4.27 (d, *J* = 4 Hz ,1H) ppm. ^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 147.3 (C), 147.0 (C), 143.4 (C), 142.5 (C), 129.1 (CH), 129.0 (C), 127.1 (CH), 125.2 (CH), 124.0 (CH), 121.8 (CH), 62.8 (CH_2), 52.3 (CH_2). FTIR (ATR): 3251, 3077, 2860, 1509, 1340, 1016, 803 cm^{-1}. HRMS calculated for $C_{16}H_{15}N_4O_3$: 311.1144. Found: 311.1141 ($[M+H]^+$).

(1-Octyl-1*H*-1,2,3-triazol-4-yl)methanol (5w):



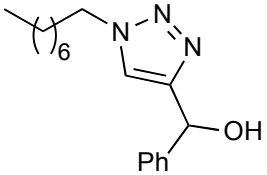
mp 46-49 ºC. ^{1}H NMR(400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 8 Hz, 3 H), 1.28 (m, 10 H), 1.90 (m, 2 H), 2.50 (b s, 1 H), 4.34 (t, *J* = 8 Hz, 2H), 4.79 (s, 2 H), 7.51 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.7, 26.6, 29.0, 29.1, 30.4, 31.8, 50.5, 56.2, 121.8, 148.0 ppm. FTIR (ATR): 3304, 2954, 2920, 2848, 1462, 1146, 1037, 1014, 783 cm^{-1}. HRMS calculated for $C_{11}H_{22}N_3O$: 212.1763. Found: 212.1761 ($[M+H]^+$).

1-Benzyl-4-(2-(trimethylsilyloxy)propan-2-yl)-1*H*-1,2,3-triazole (5x):



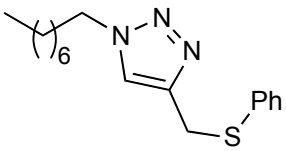
^{1}H NMR(400 MHz, $CDCl_3$): δ 0.03 (s, 9 H), 1.64 (s, 6 H), 5.50 (s, 2 H), 7.36 (s, 1 H), 7.27-7.40 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 2.5, 31.5, 54.2, 71.7, 120.1, 128.2, 128.8, 129.2, 135.2, 157.3 ppm. FTIR (ATR): 2980, 1636, 1457, 1250, 1218, 1173, 1037 cm^{-1}. HRMS calculated for $C_{15}H_{23}N_3ONaSi$: 312.1508. Found: 312.1507 ($[M+Na]^+$).

Phenyl(1-octyl-1H-1,2,3-triazol-4-yl)methanol (5y):



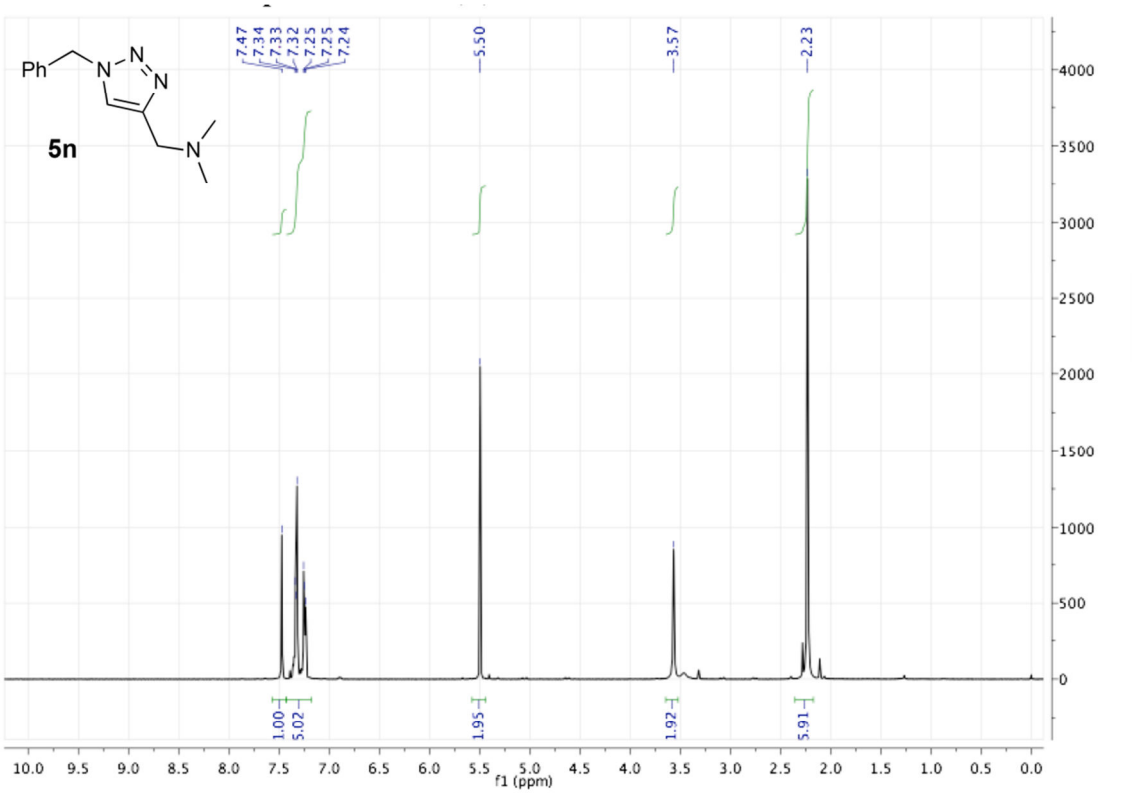
^{1}H NMR(400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 8 Hz, 3 H), 1.27 (m, 10 H), 1.86 (m, 2 H), 4.28 (t, *J* = 8 Hz, 2H), 6.03 (s, 1 H), 7.21 (s, 1H), 7.31-7.47 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 26.5, 28.9, 29.0, 30.2, 31.7, 50.4, 68.7, 121.3, 126.4, 127.7, 128.4, 133.3, 142.4, 151.6 ppm. FTIR (ATR): 3276, 2924, 2855, 1453, 1046, 728, 697 cm^{-1}. HRMS calculated for $C_{17}H_{26}N_3O$: 288.2076. Found: 288.2084 ($[M+H]^+$).

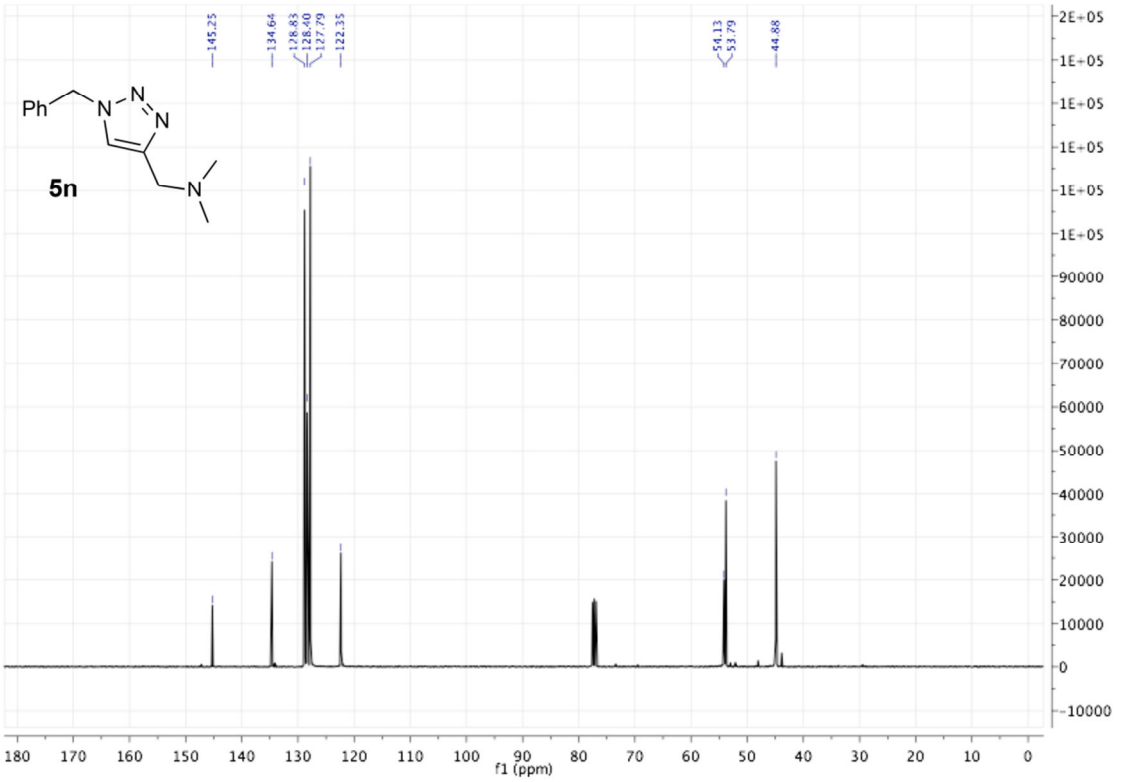
4-(Phenylthiomethyl)-1-octyl-1H-1,2,3-triazole (5z):

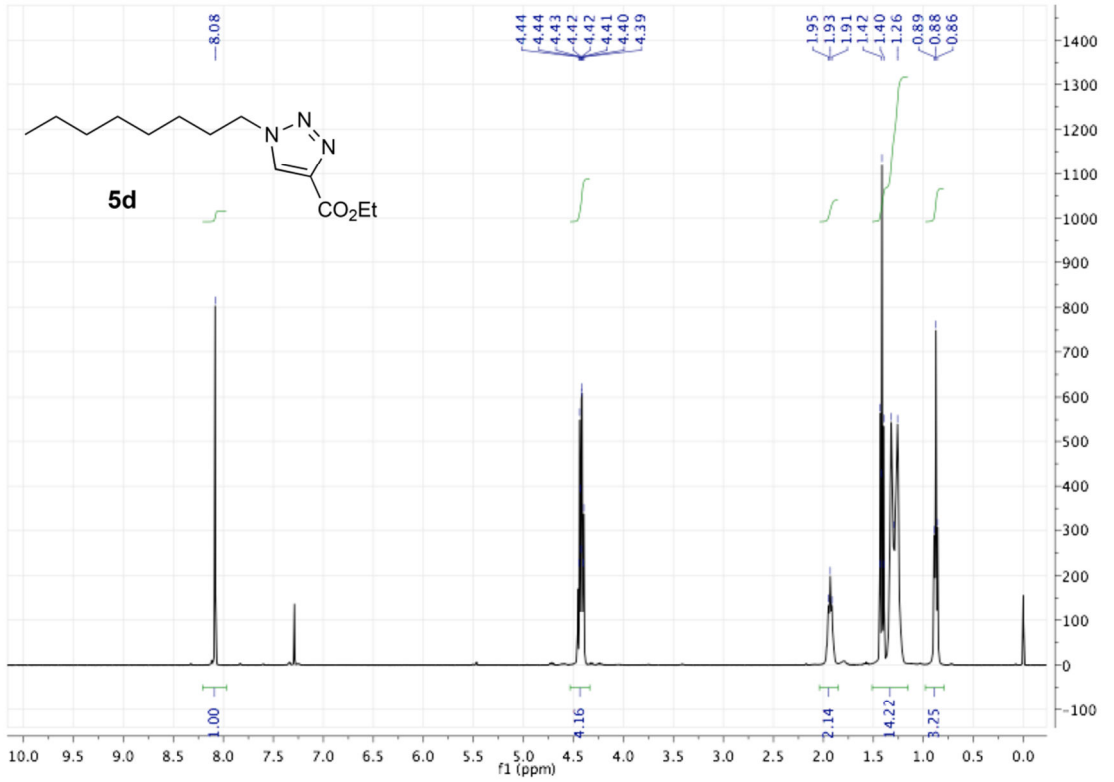


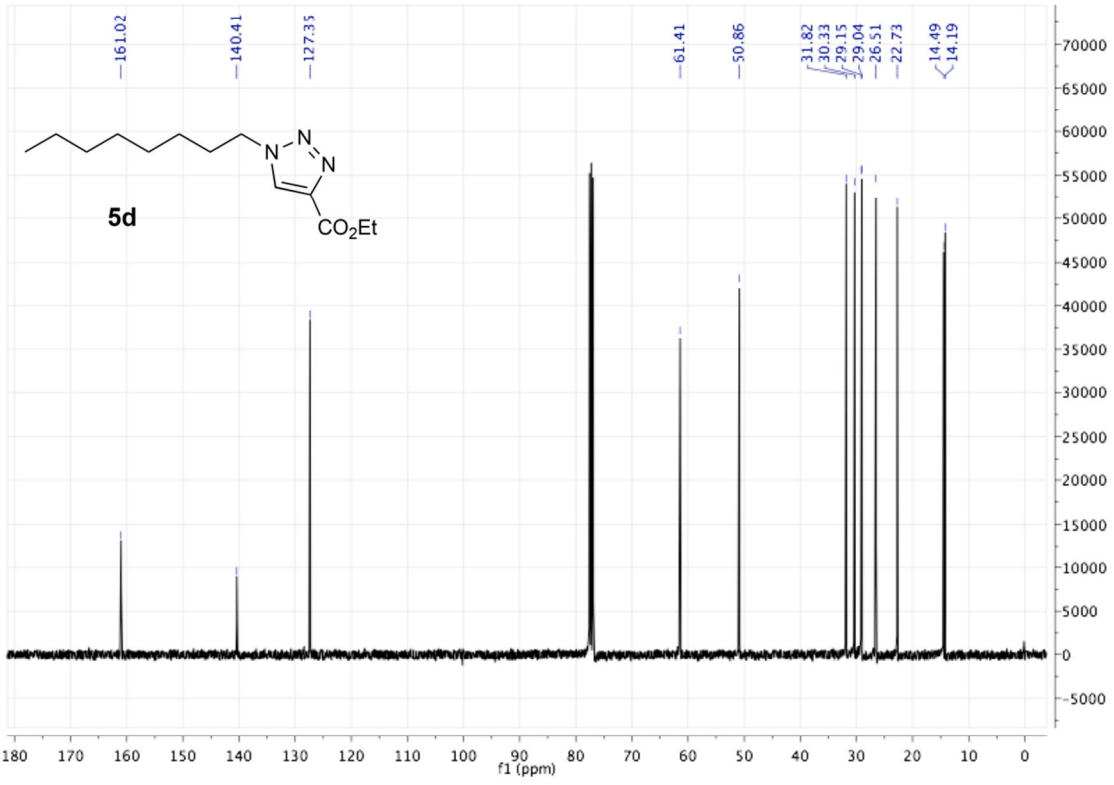
mp 61-63 ºC. ^{1}H NMR(400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 8 Hz, 3 H), 1.27 (m, 10 H), 1.83 (m, 2 H), 4.24 (s, 2 H), 4.26 (t, *J* = 8 Hz, 2H), 7.30 (s, 1H), 7.20-7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 26.5, 28.97, 28.99, 29.1, 30.3, 31.8, 50.4, 121.9, 126.5, 129.0, 129.6, 135.7, 144.8 ppm. FTIR (ATR): 3120, 3059, 2954, 2918, 2848, 1463, 1351, 1025, 730, 689 cm^{-1}. HRMS calculated for $C_{17}H_{26}N_3S$: 304.1847. Found: 304.1841 ($[M+H]^+$).

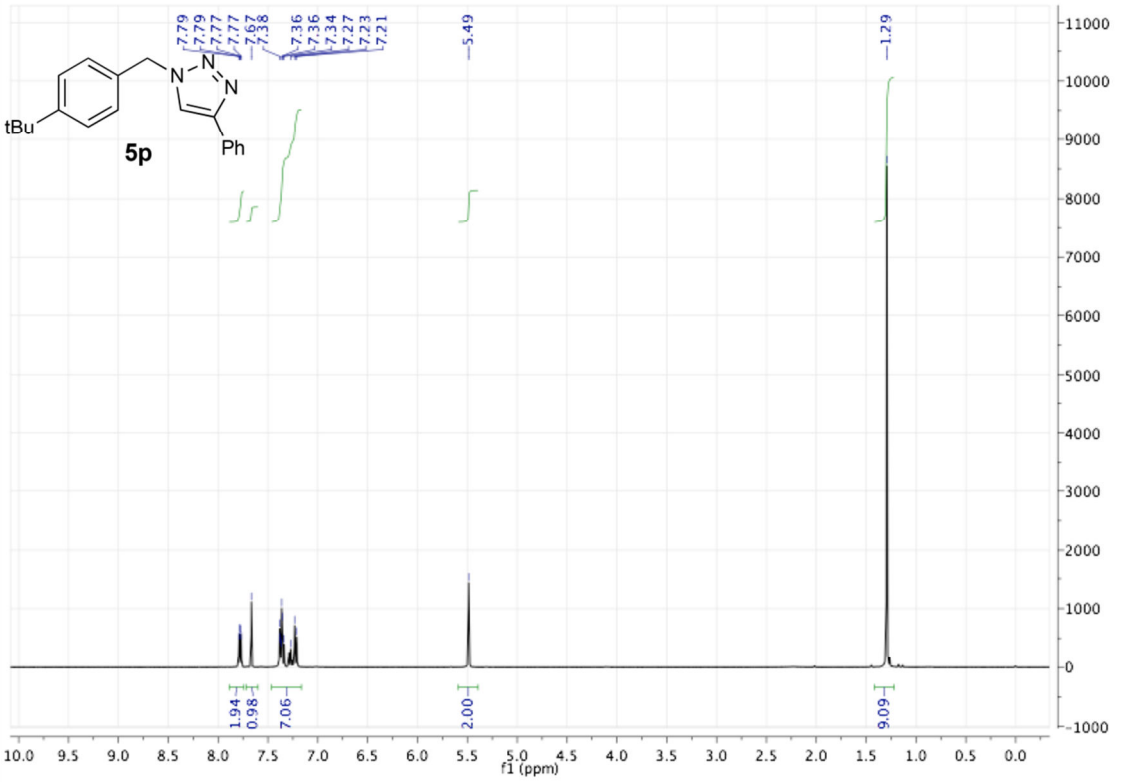
9. ^{1}H AND ^{13}C NMR SPECTRA OF NEW 1,2,3-TRIAZOLES

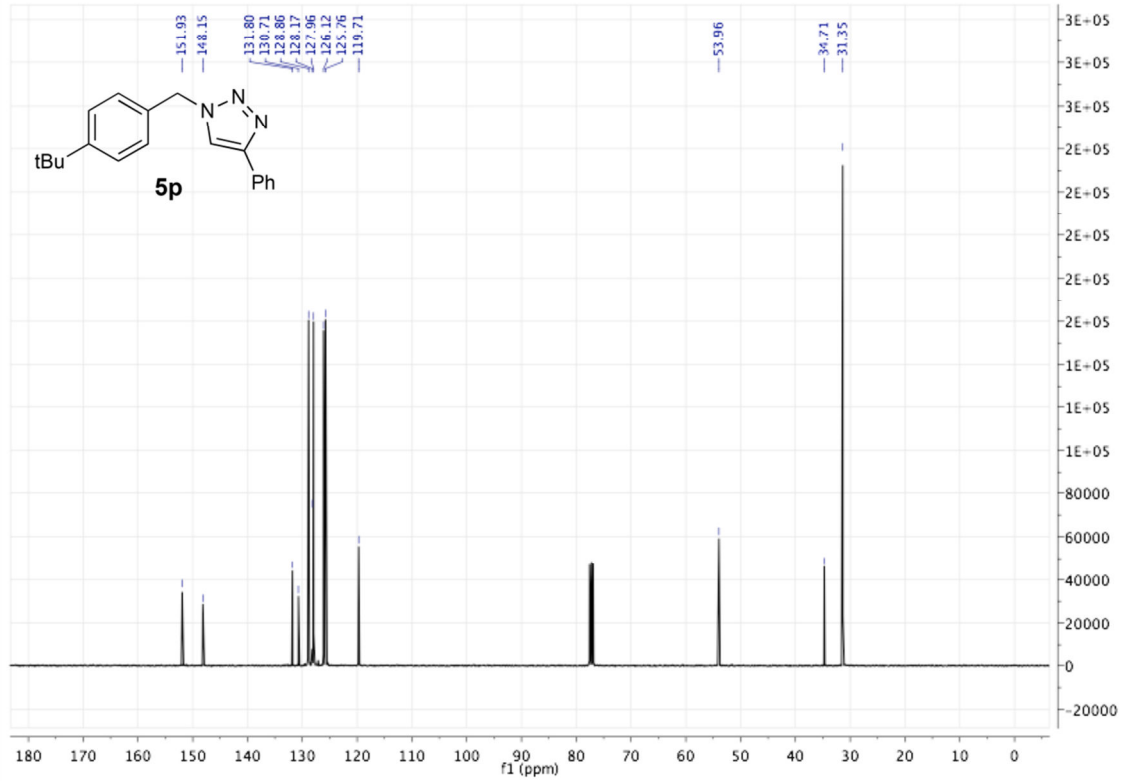


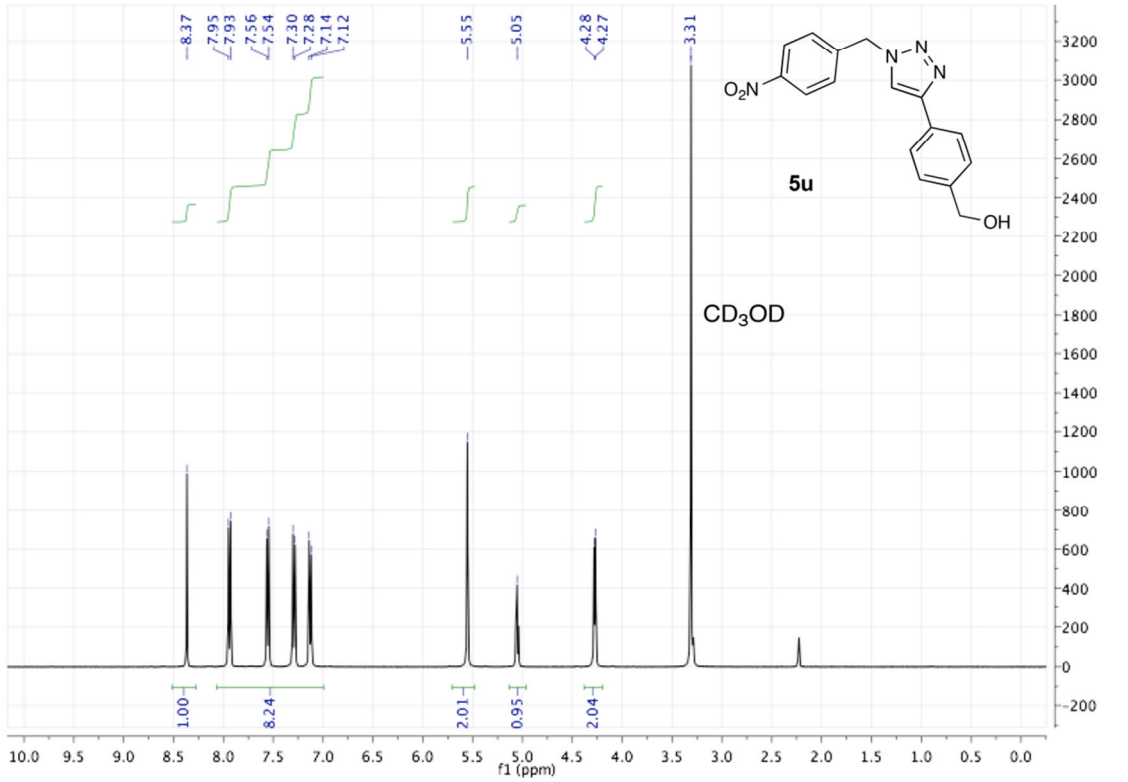


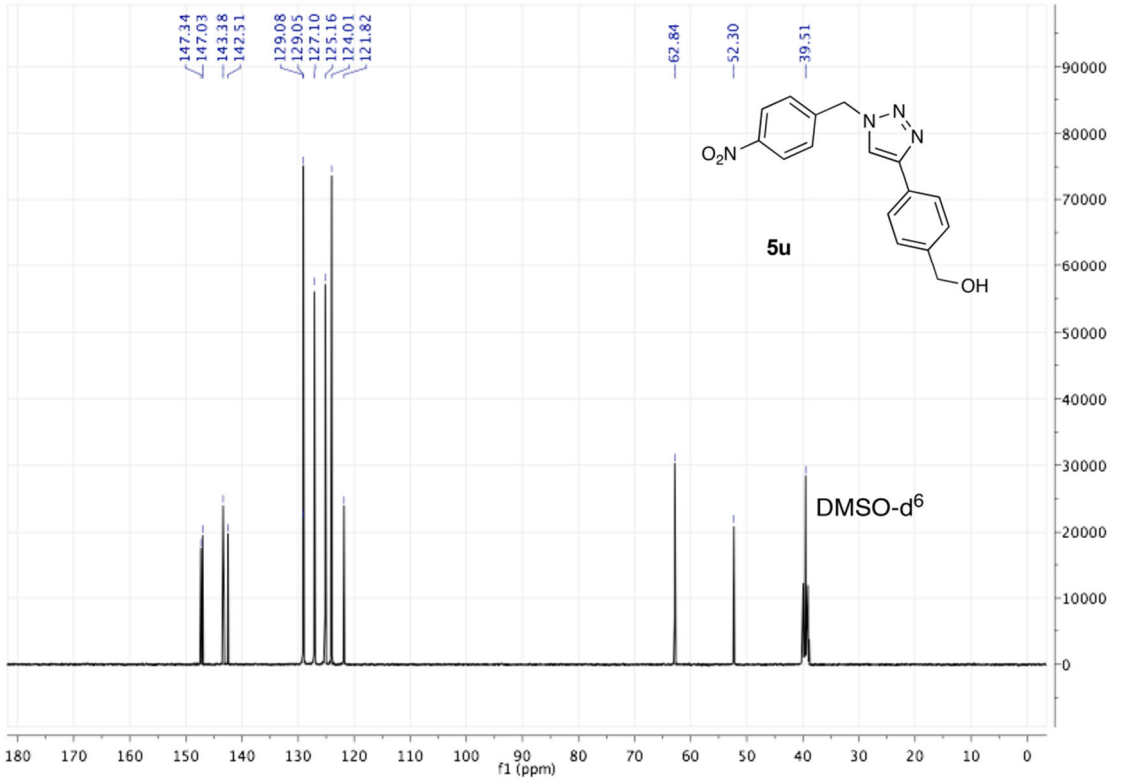

8.08
4.44
4.44
4.43
4.42
4.42
4.41
4.40
4.39
1.95
1.93
1.91
1.42
1.40
1.26
0.89
0.88
0.86
5d
CO2Et
1.00
4.16
2.14
14.22
3.25
f1 (ppm)

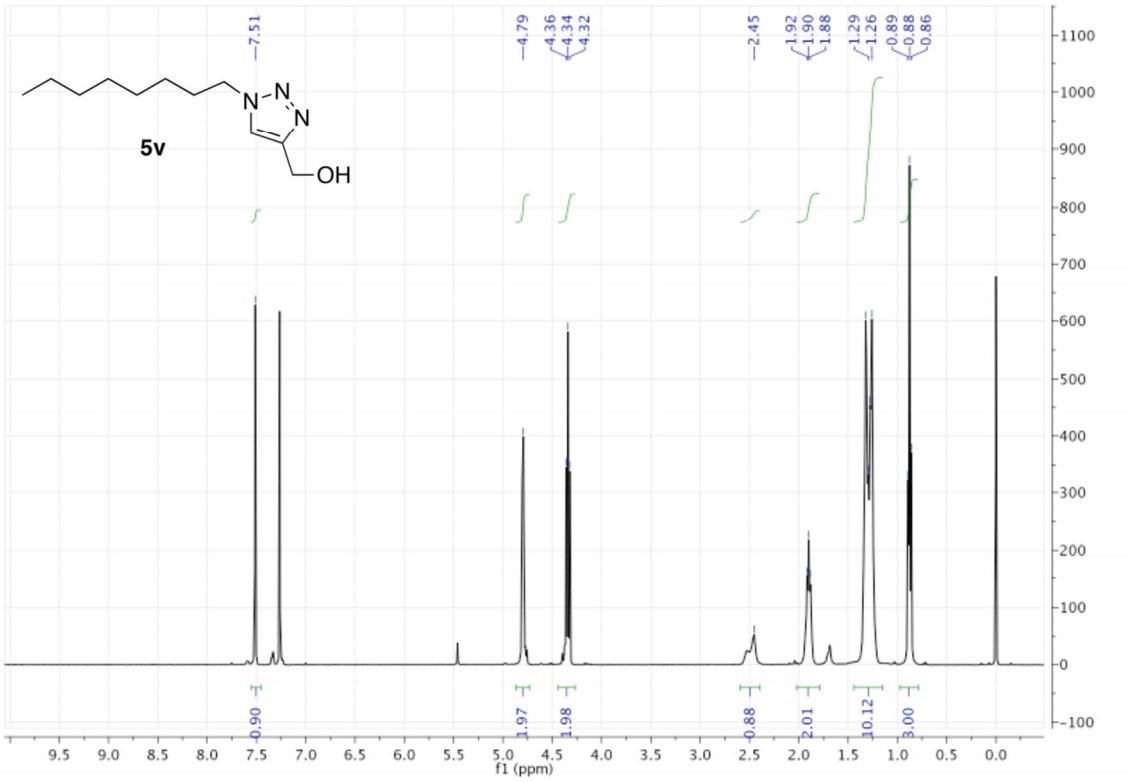

161.02
140.41
127.35
61.41
50.86
31.82
30.33
29.15
29.04
26.51
22.73
14.49
14.19
5d
CO2Et
f1 (ppm)

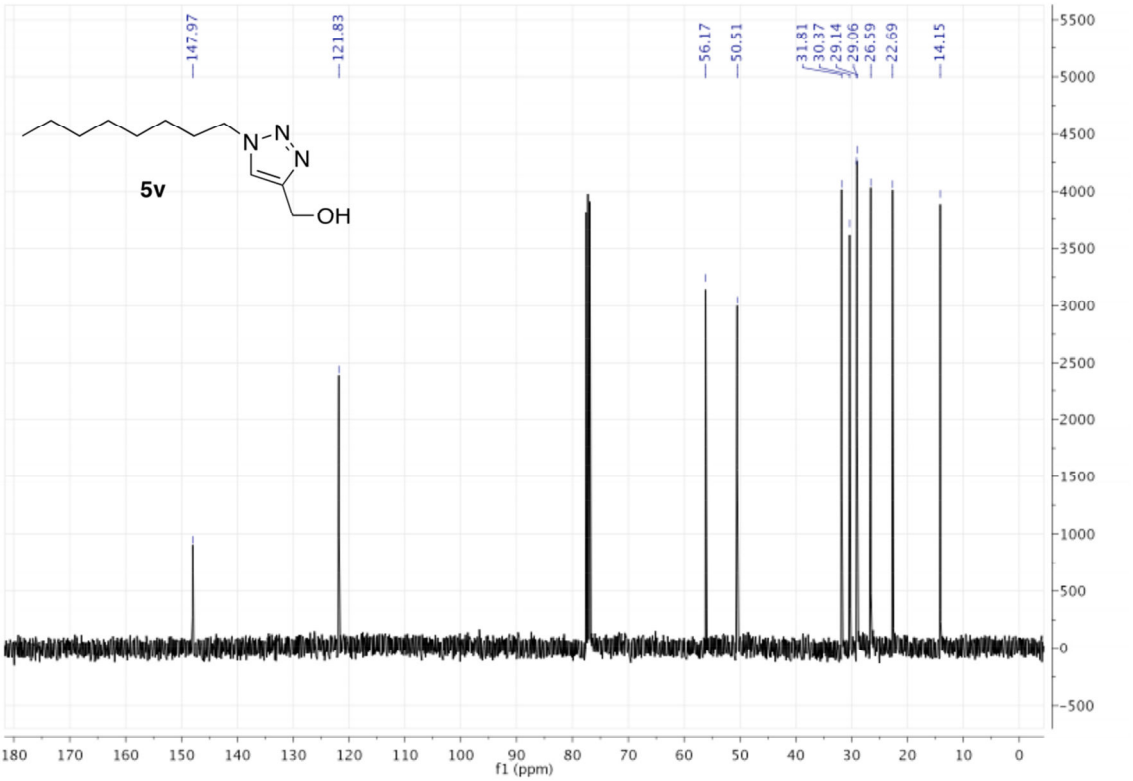

7.79
7.79
7.77
7.77
7.67
7.38
7.36
7.36
7.34
7.27
7.23
7.21
5.49
1.29
tBu
5p
Ph
1.94
0.98
7.06
2.00
9.09
f1 (ppm)

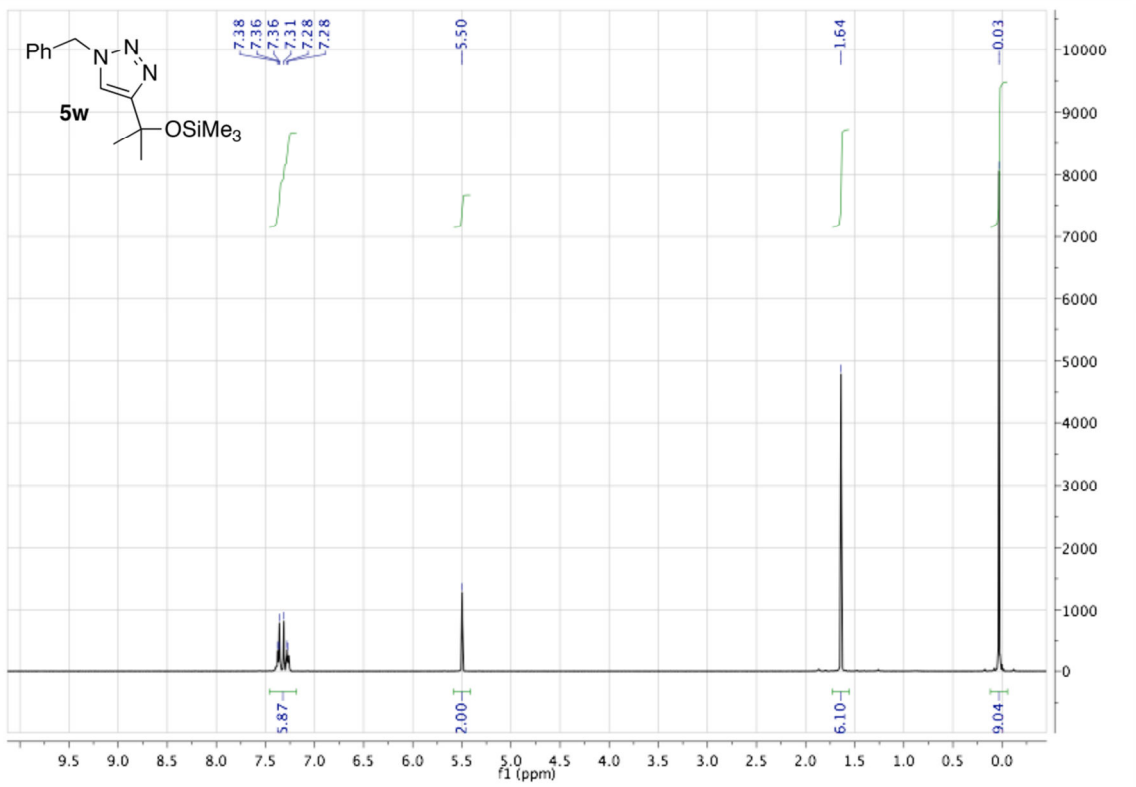

151.93
148.15
131.80
130.71
128.86
128.17
127.96
126.12
125.76
119.71
53.96
34.71
31.35
tBu
5p
Ph
f1 (ppm)

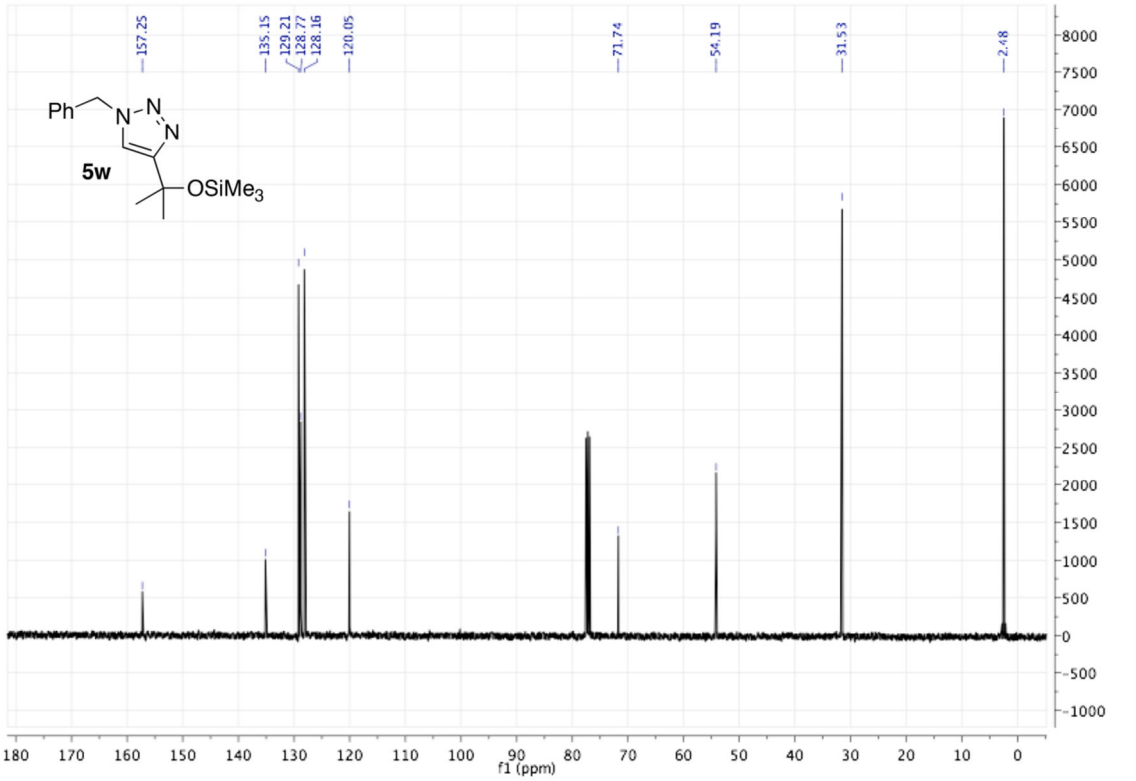

8.37
7.95
7.93
7.56
7.54
7.30
7.28
7.14
7.12
5.55
5.05
4.28
4.27
3.31
1.00
8.24
2.01
0.95
2.04
O_2N
N
N
N
OH
5u
CD_3OD
f1 (ppm)

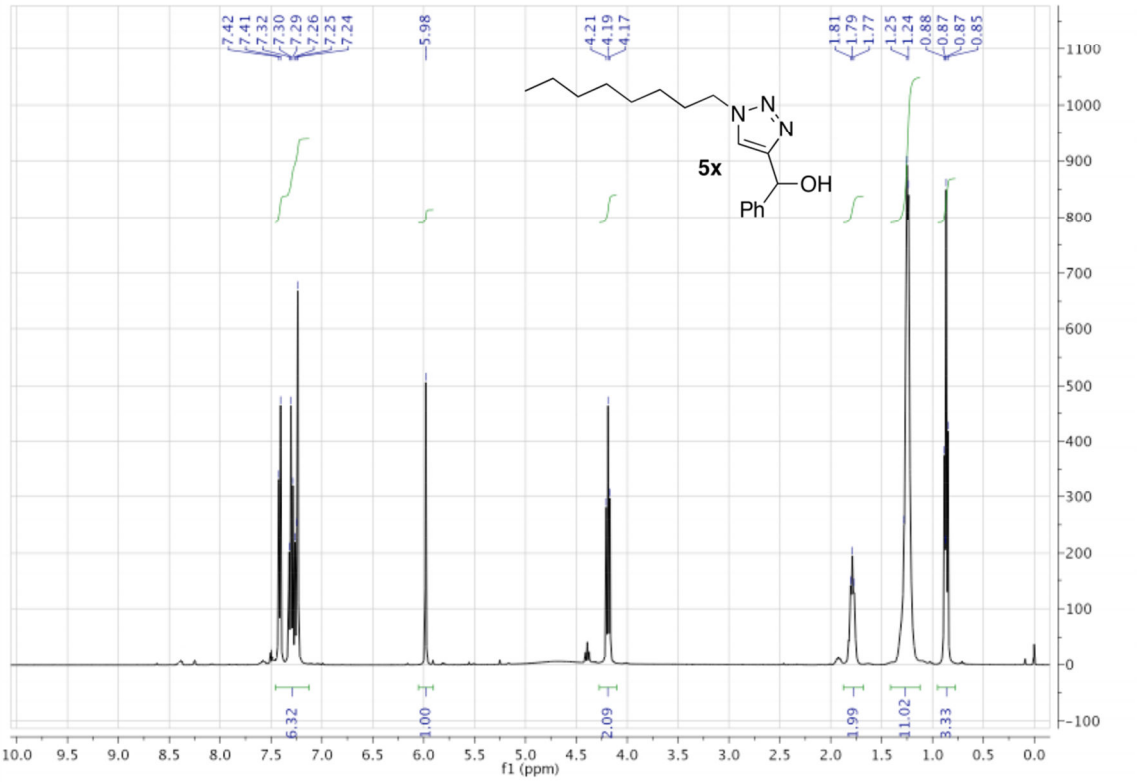

147.34
147.03
143.38
142.51
129.08
129.05
127.10
125.16
124.01
121.82
62.84
52.30
39.51
O_2N
N
N
N
OH
5u
DMSO-d^6
f1 (ppm)

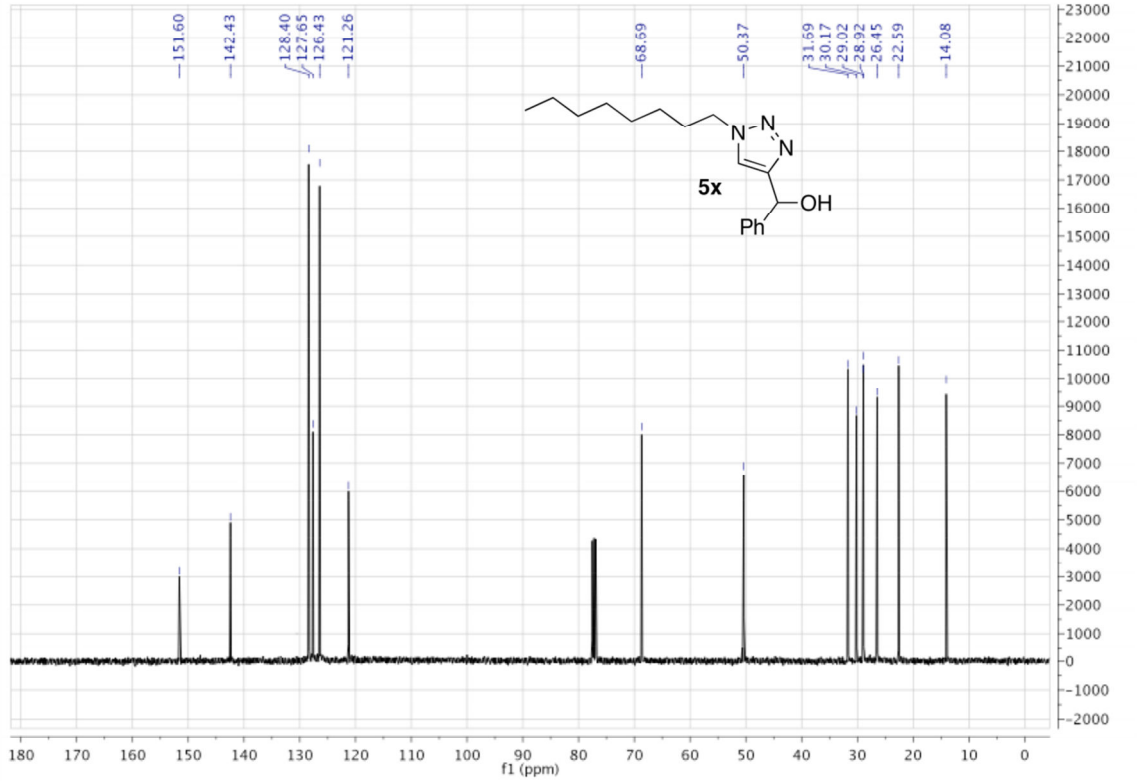


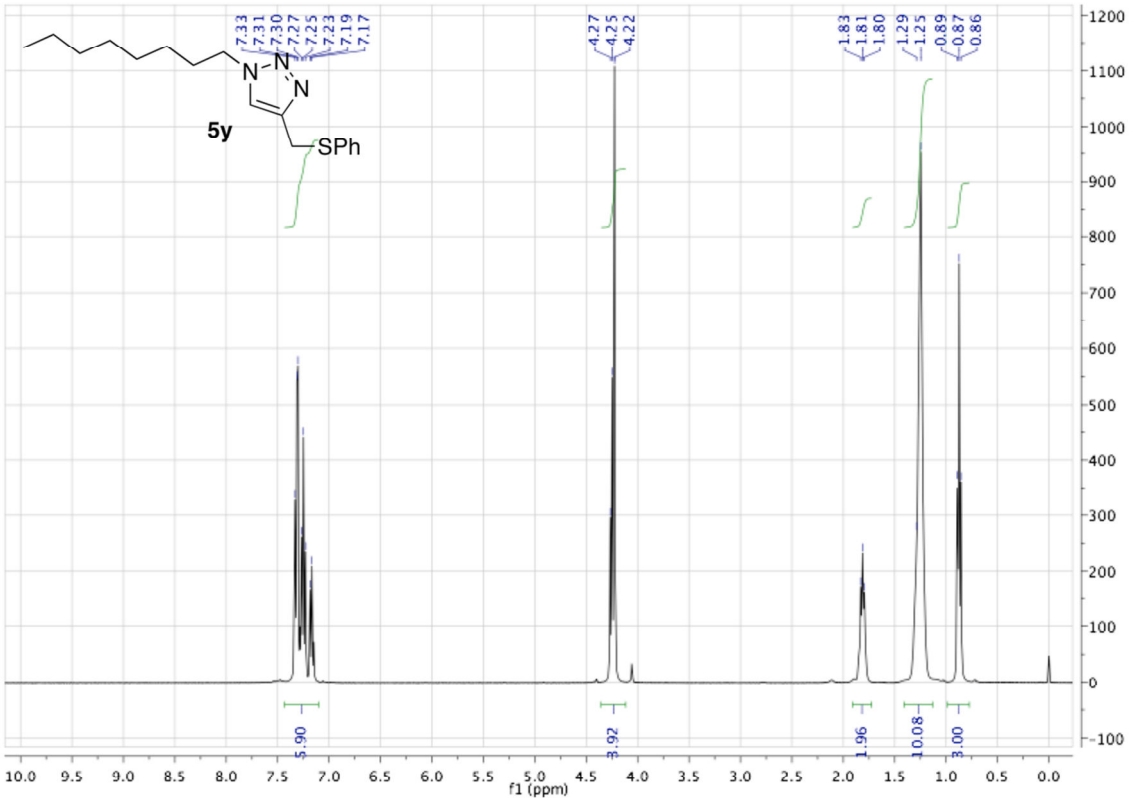


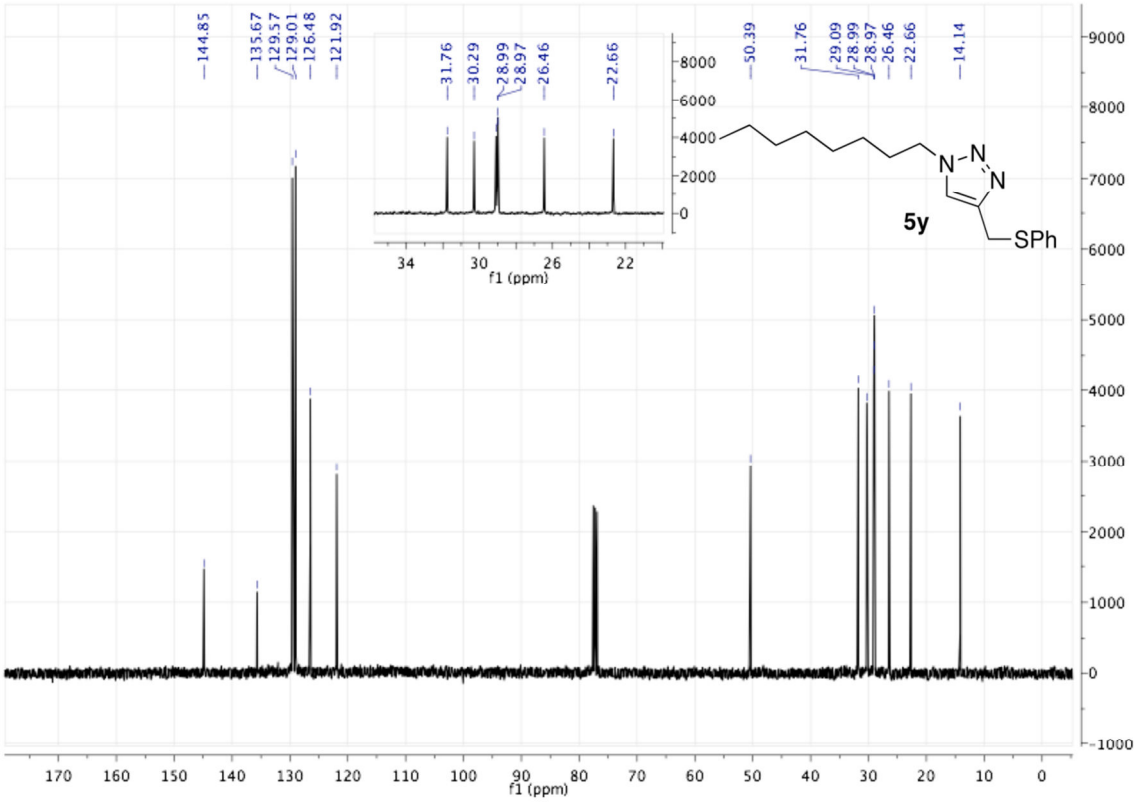

Ph
N
N
N
5w
OSiMe3
7.38
7.36
7.36
7.31
7.28
7.28
5.50
1.64
0.03
5.87
2.00
6.10
9.04
f1 (ppm)


Ph
N
N
N
5w
OSiMe3
157.25
135.15
129.21
128.77
128.16
120.05
71.74
54.19
31.53
2.48
f1 (ppm)

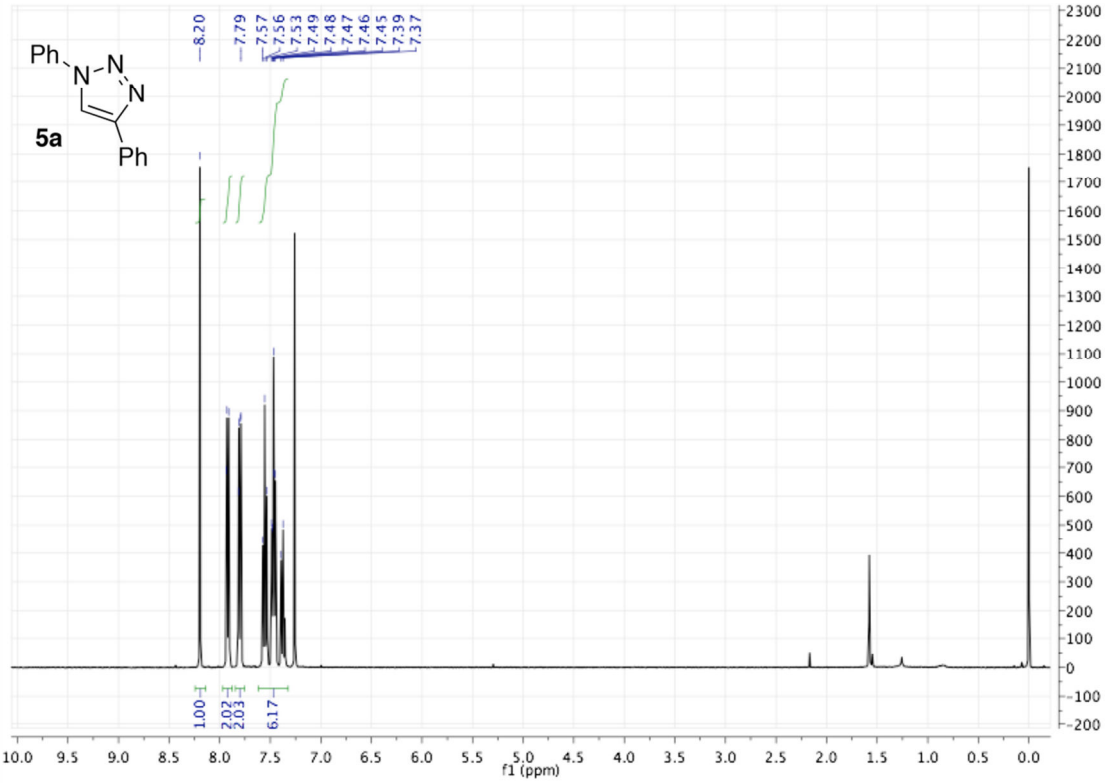


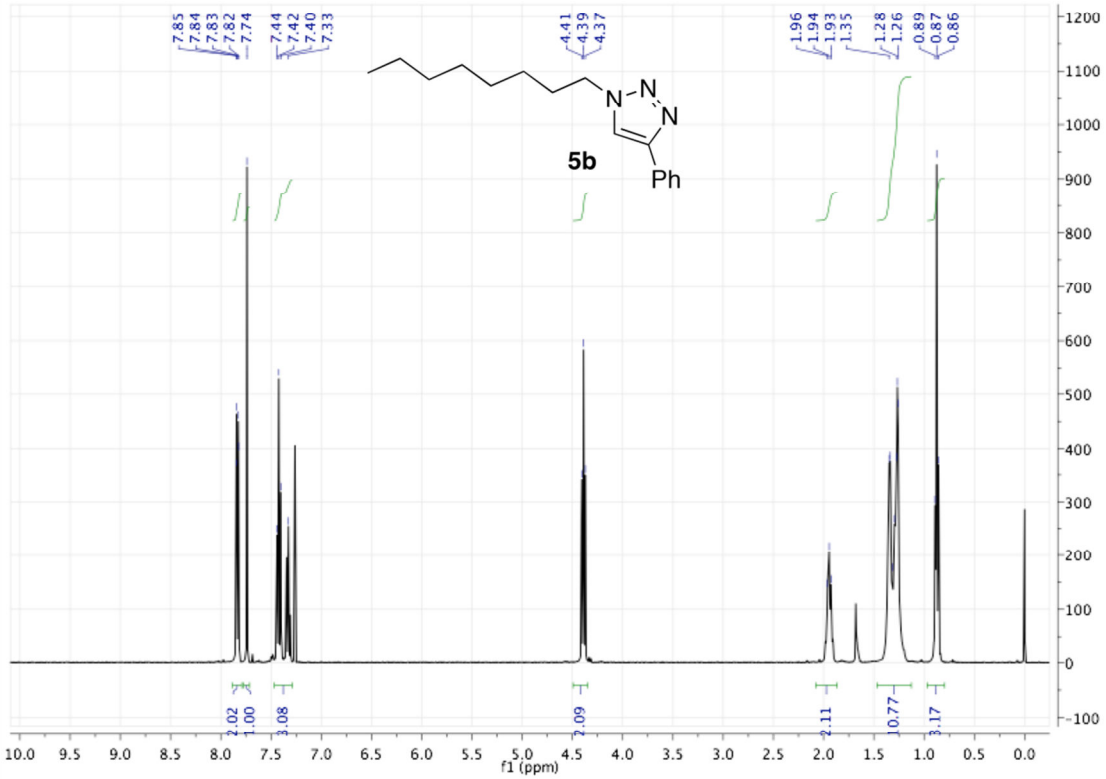


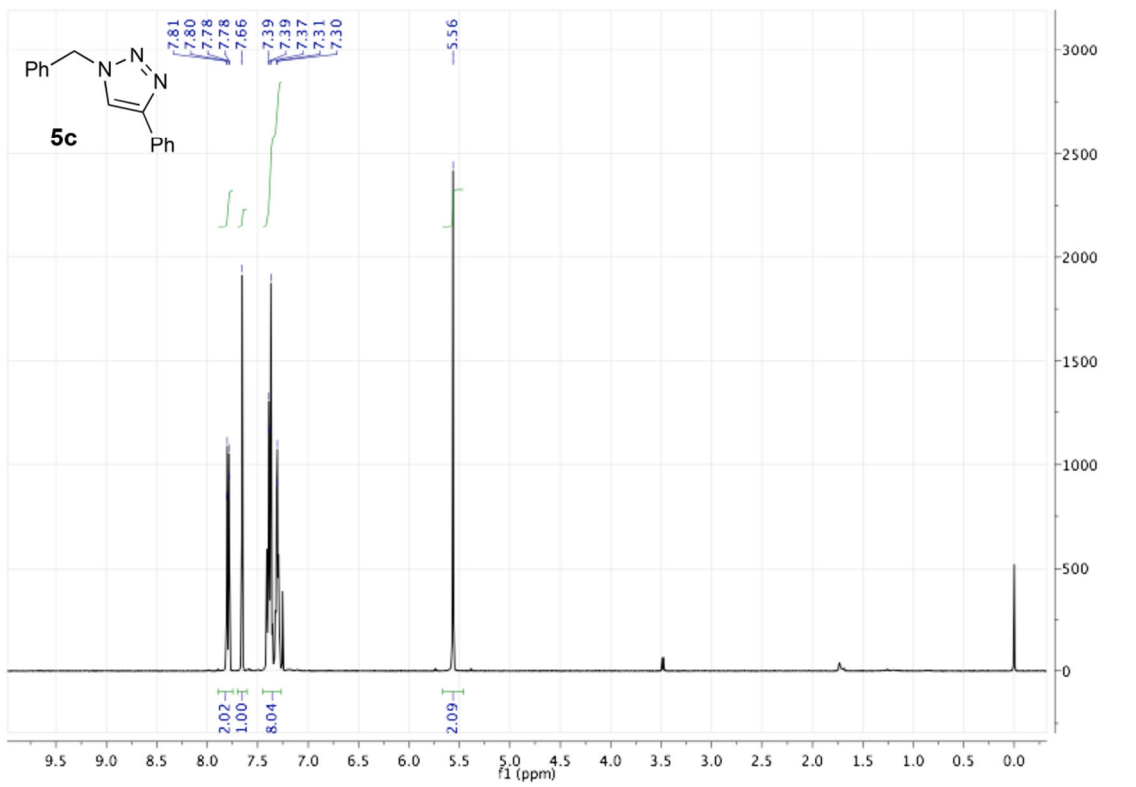

7.33
7.31
7.30
7.27
7.25
7.23
7.19
7.17
4.27
4.25
4.22
1.83
1.81
1.80
1.29
1.25
0.89
0.87
0.86
5y
SPh
5.90
3.92
1.96
10.08
3.00
f1 (ppm)

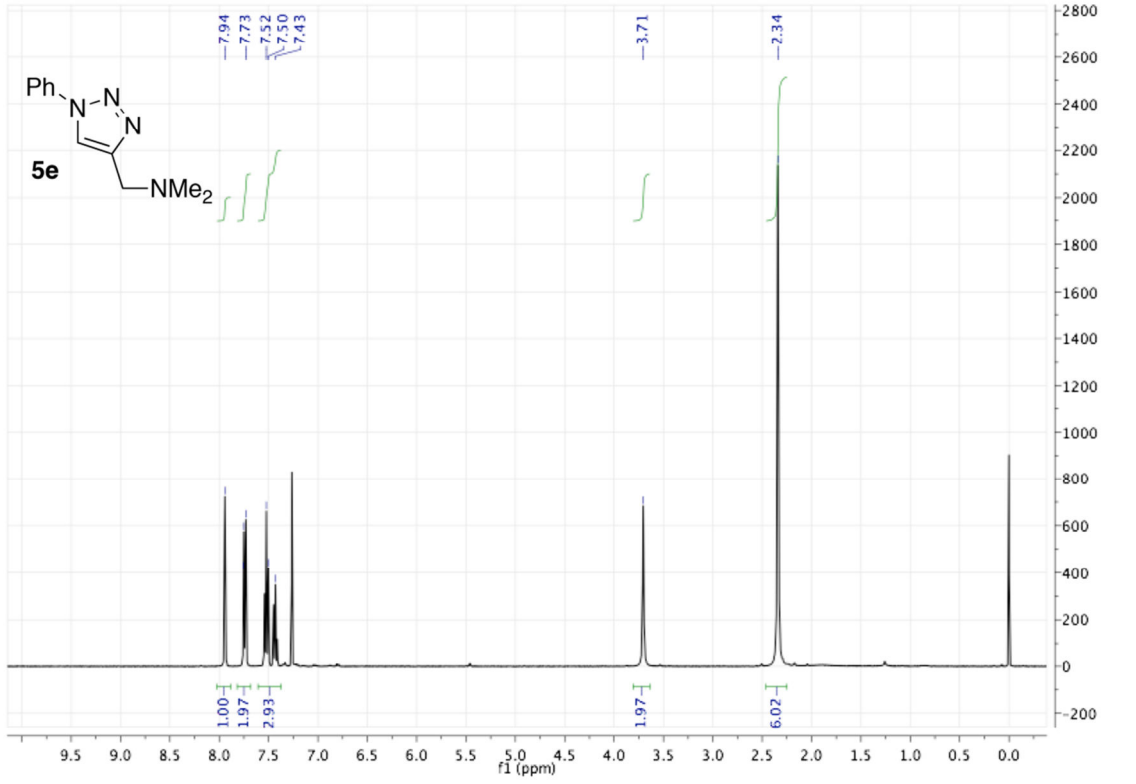

144.85
135.67
129.57
129.01
126.48
121.92
31.76
30.29
28.99
28.97
26.46
22.66
50.39
31.76
29.09
28.99
28.97
26.46
22.66
14.14
5y
SPh
f1 (ppm)

10. 1HNMR SPECTRA OF KNOWN 1,2,3-TRIAZOLES:[3-7]






Ph
N
N
N
Ph
5c
7.81
7.80
7.78
7.78
7.66
7.39
7.39
7.37
7.31
7.30
5.56
2.02
1.00
8.04
2.09
f1 (ppm)


Ph
N
N
N
NMe2
5e
7.94
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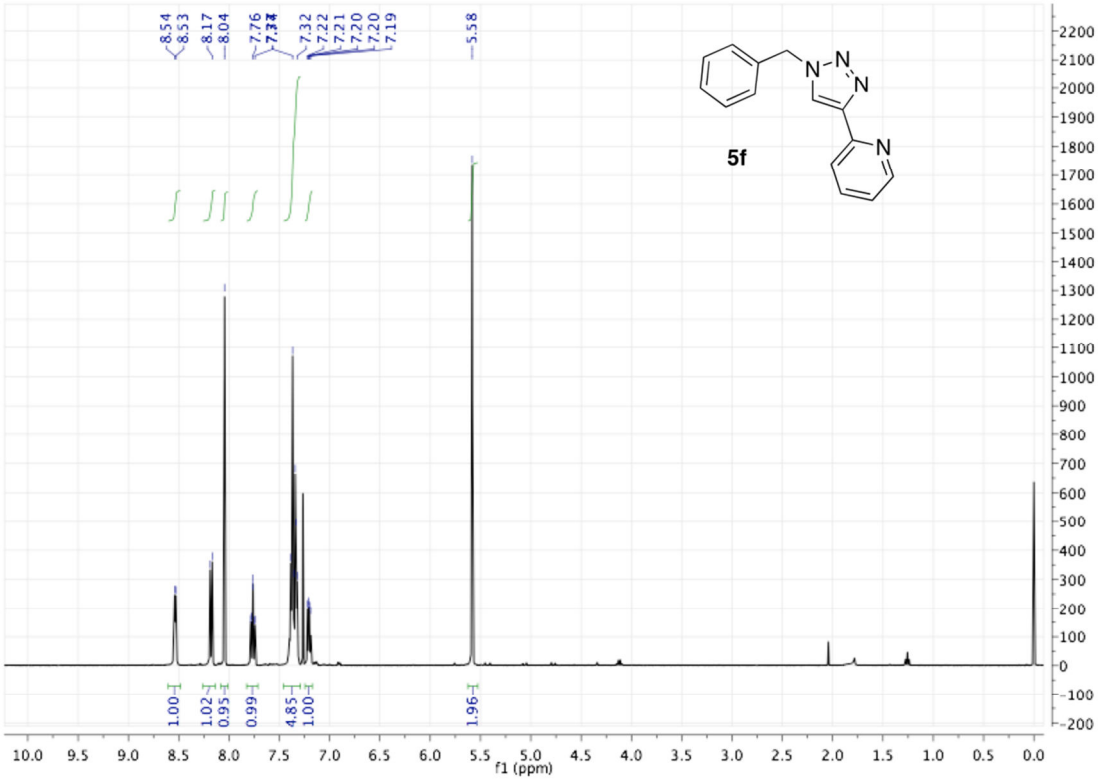
f1 (ppm)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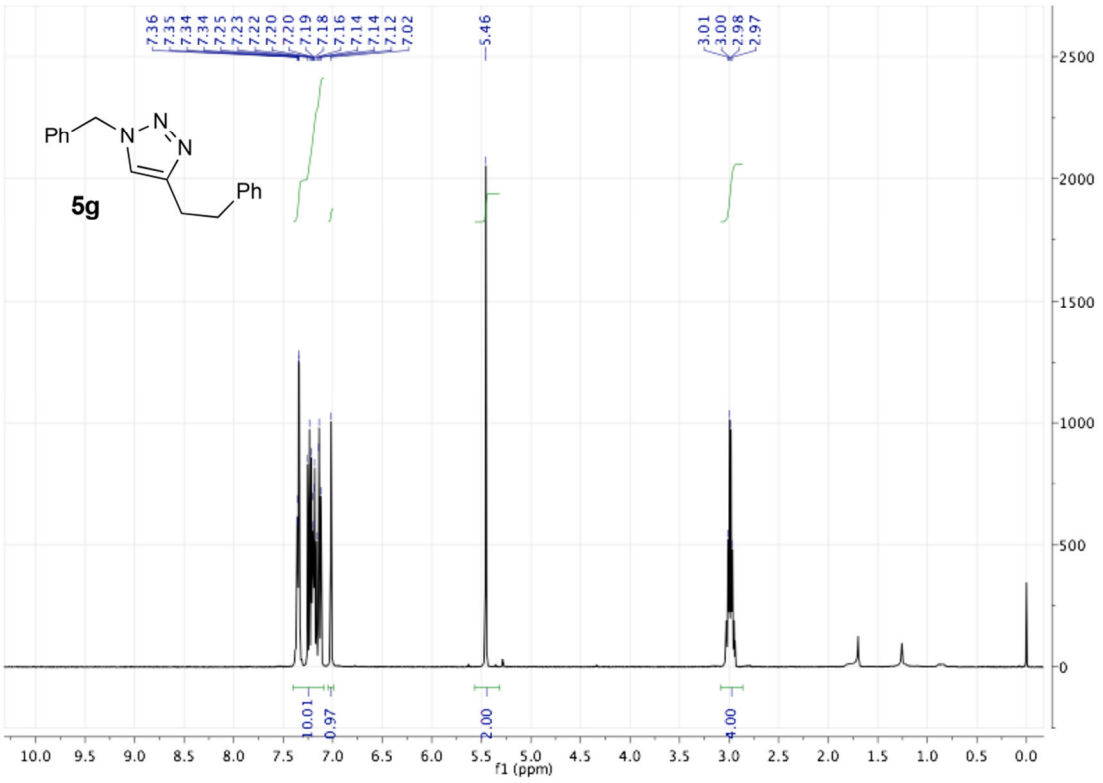
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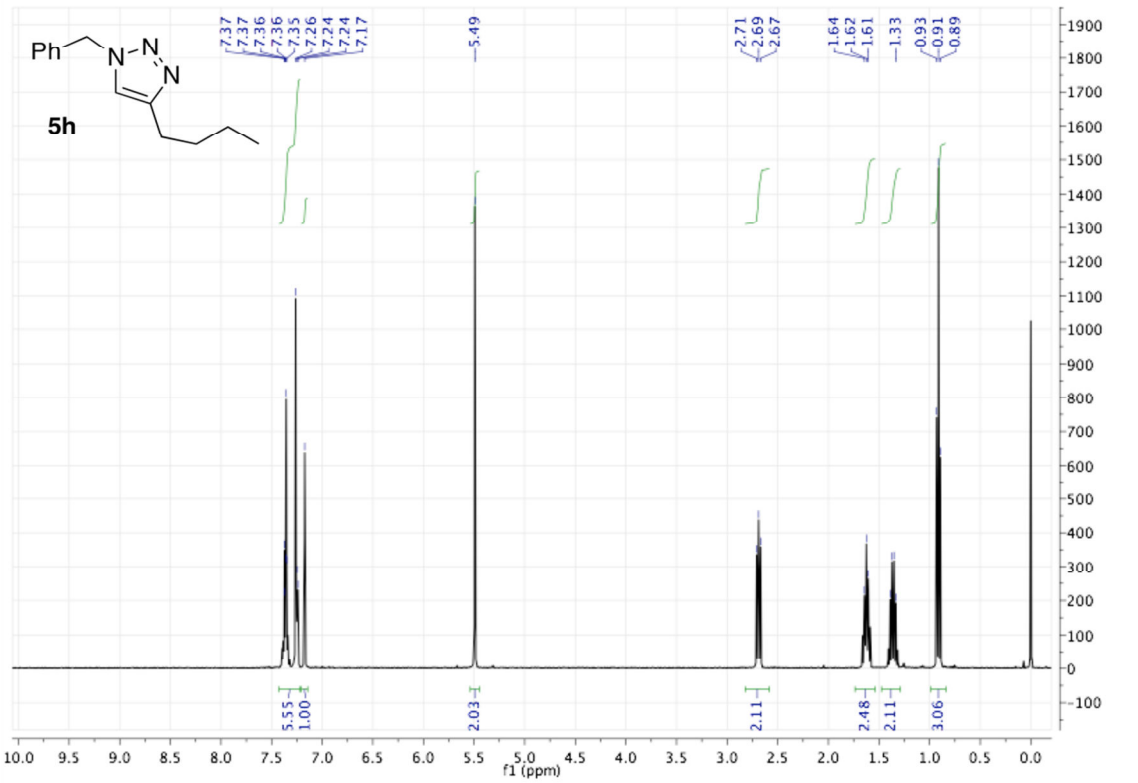
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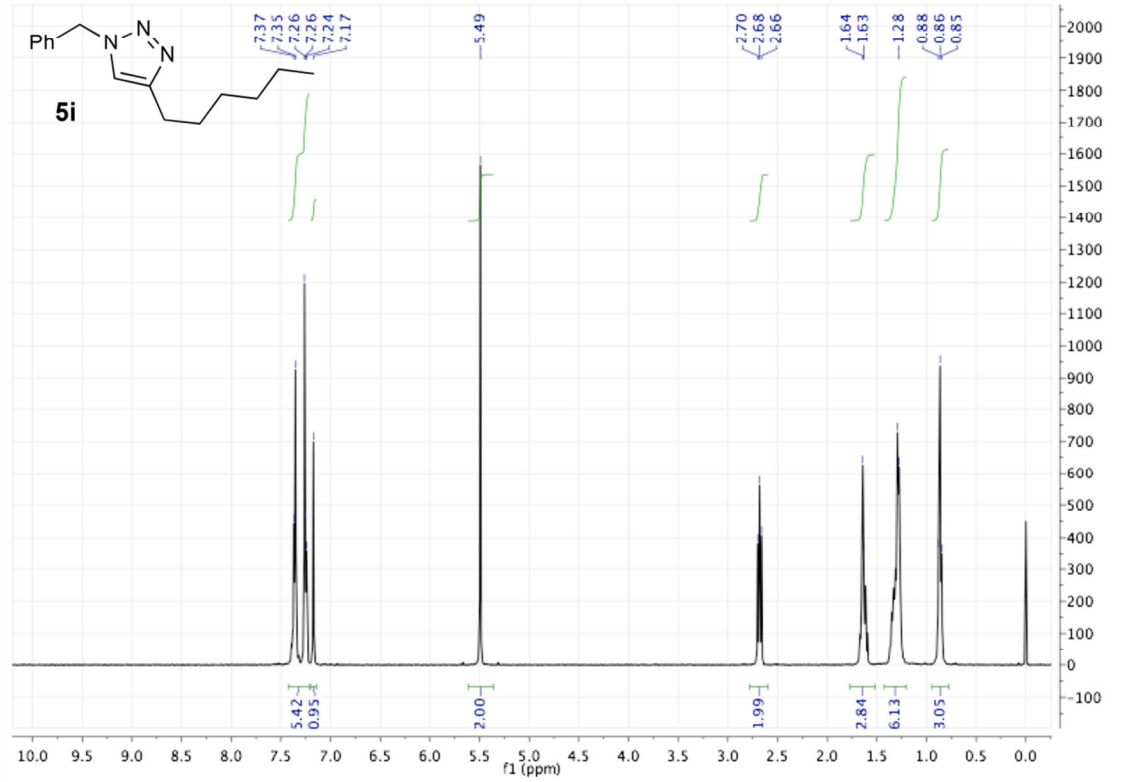
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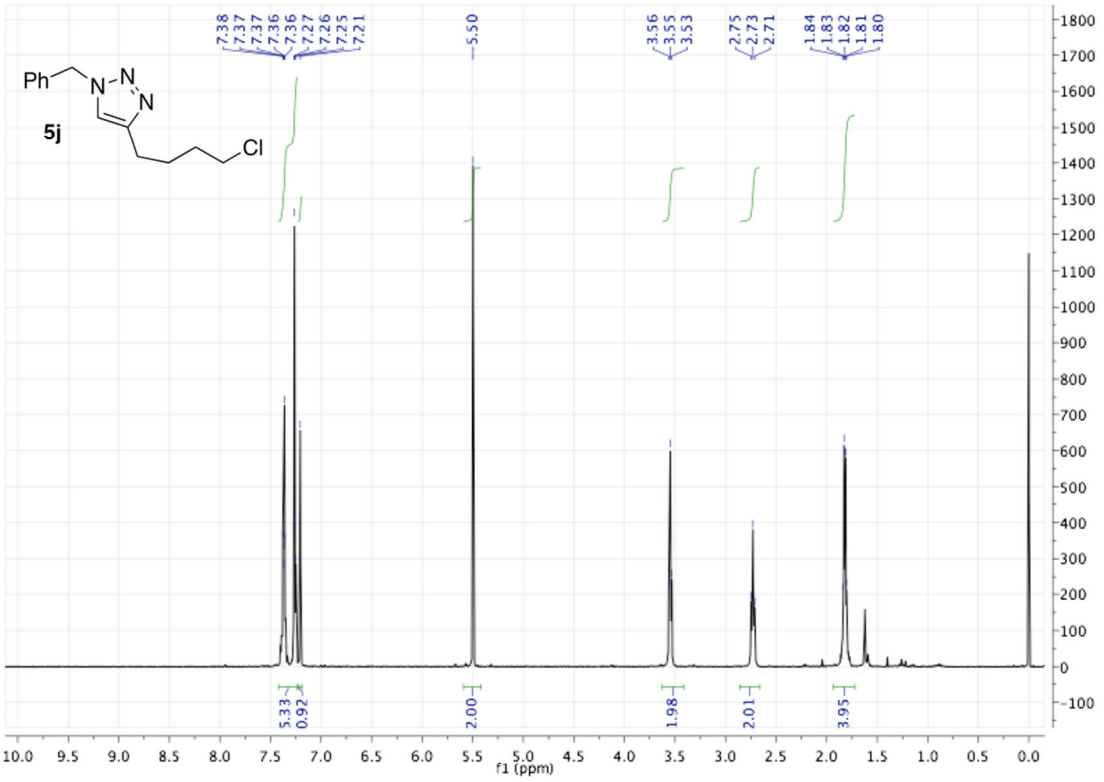
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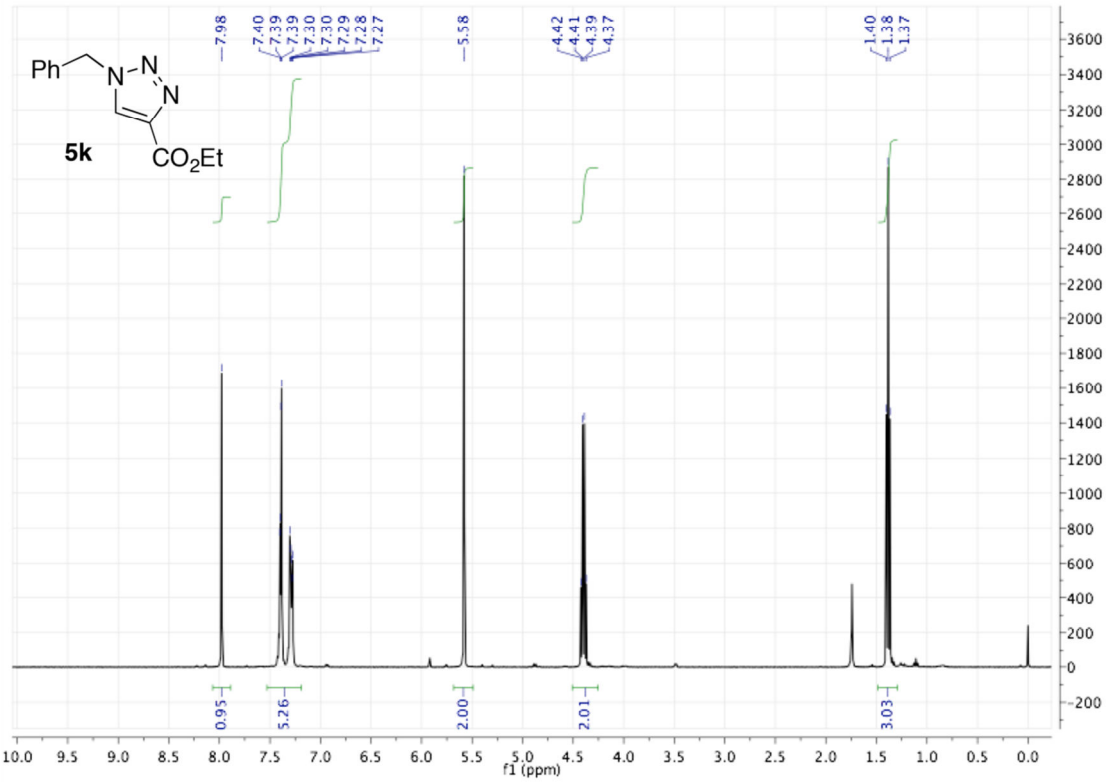
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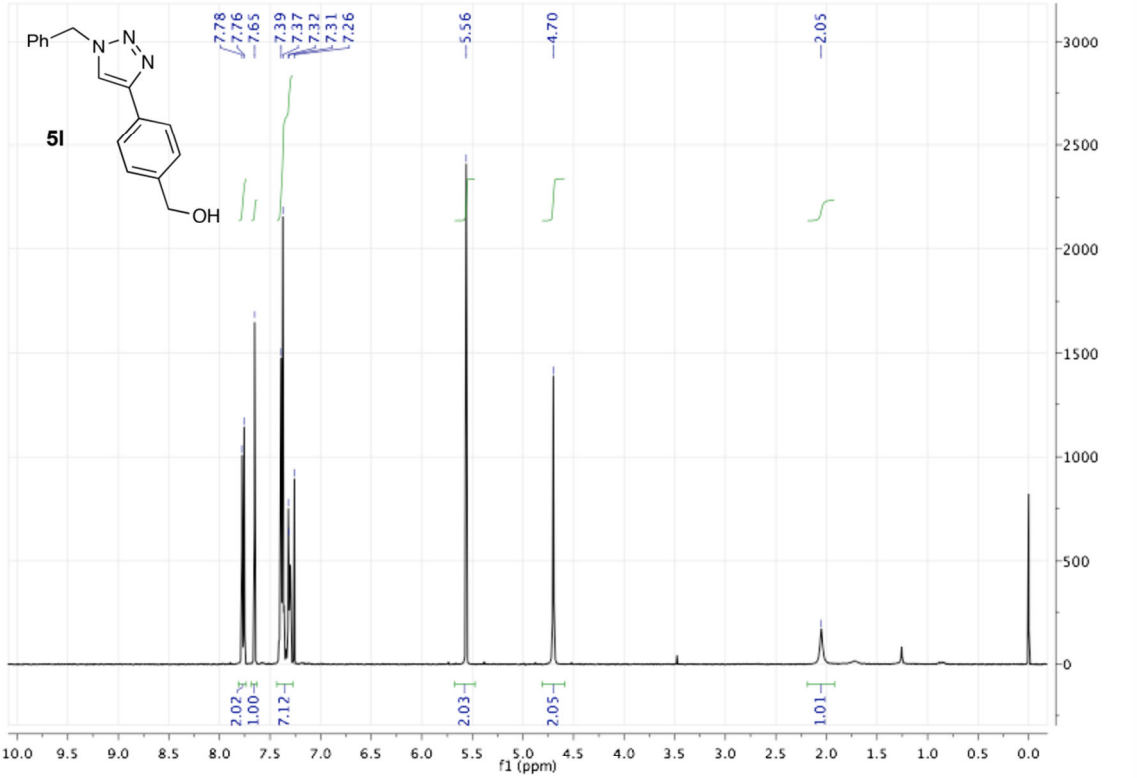
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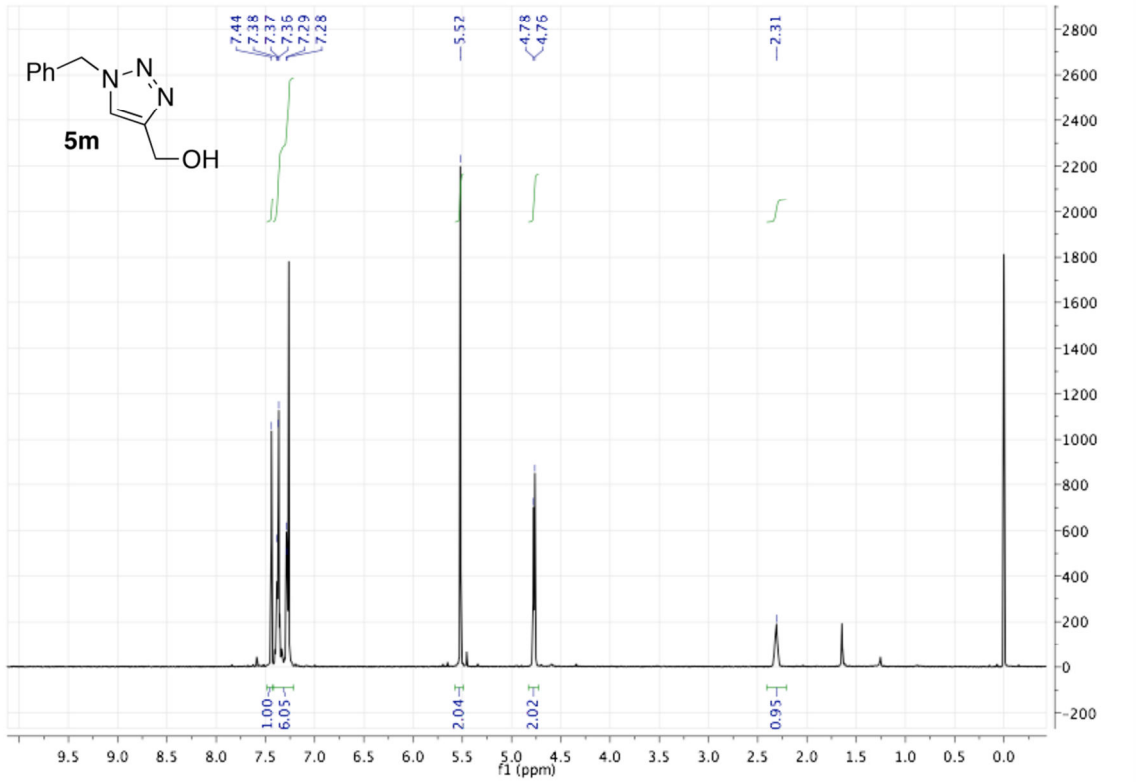
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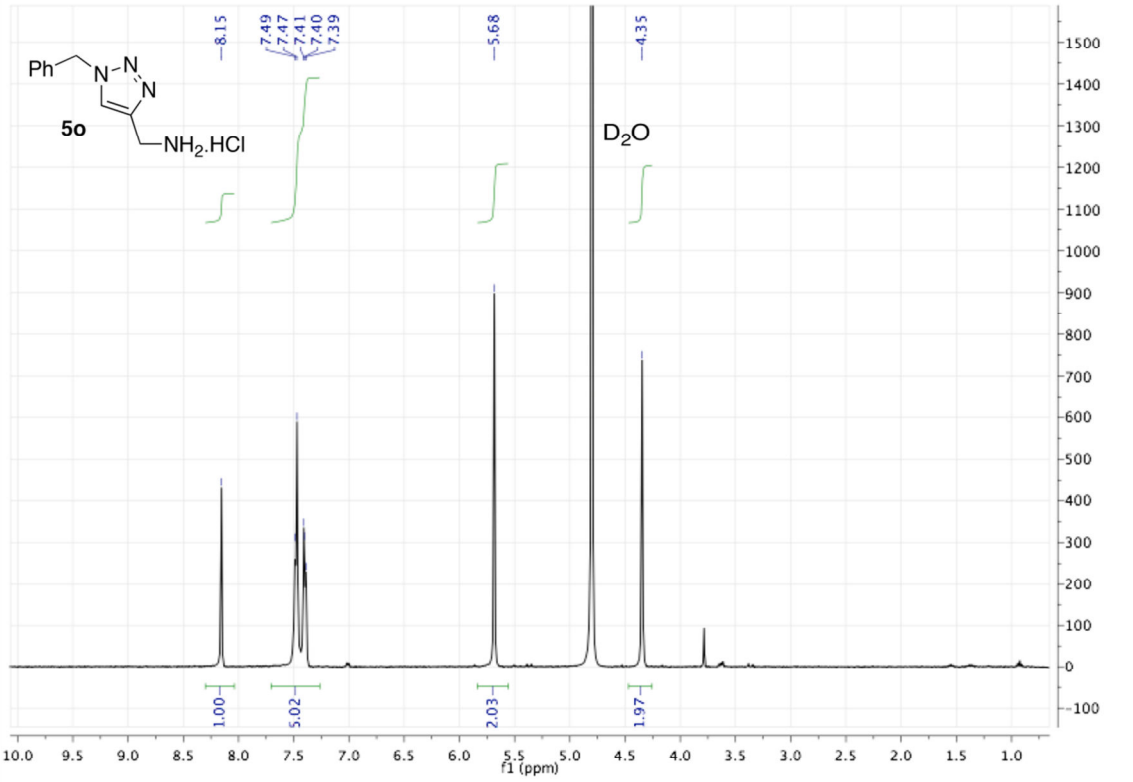
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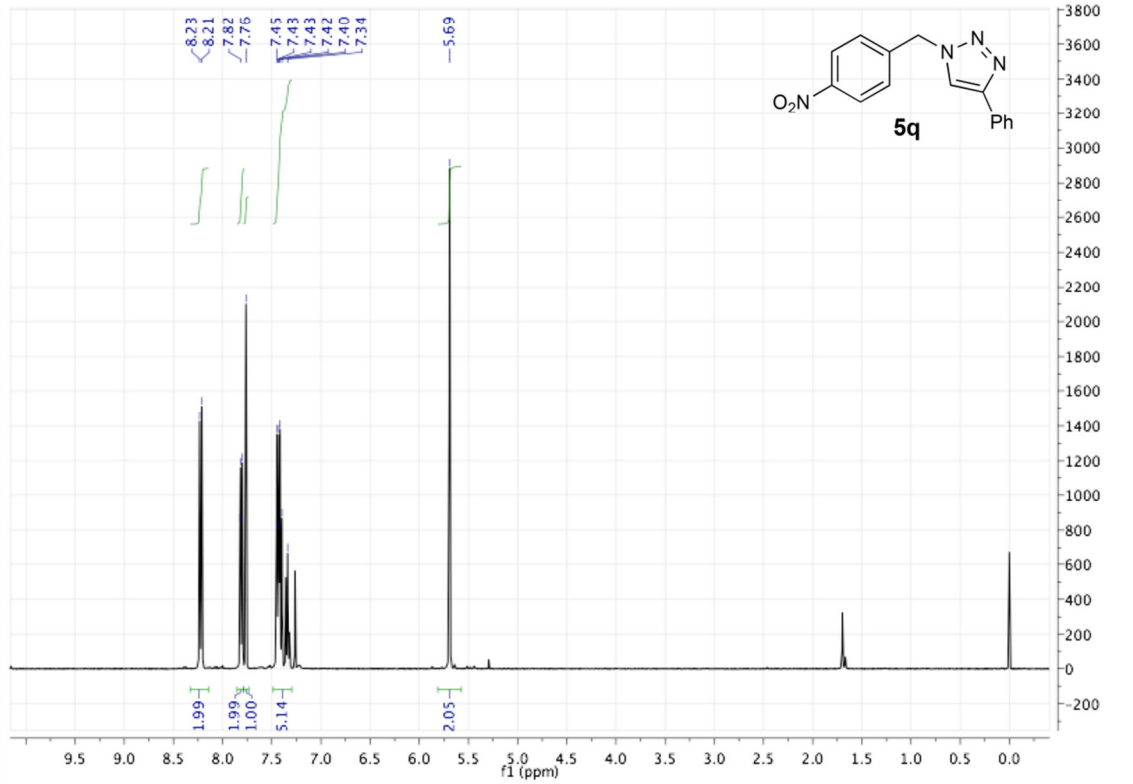
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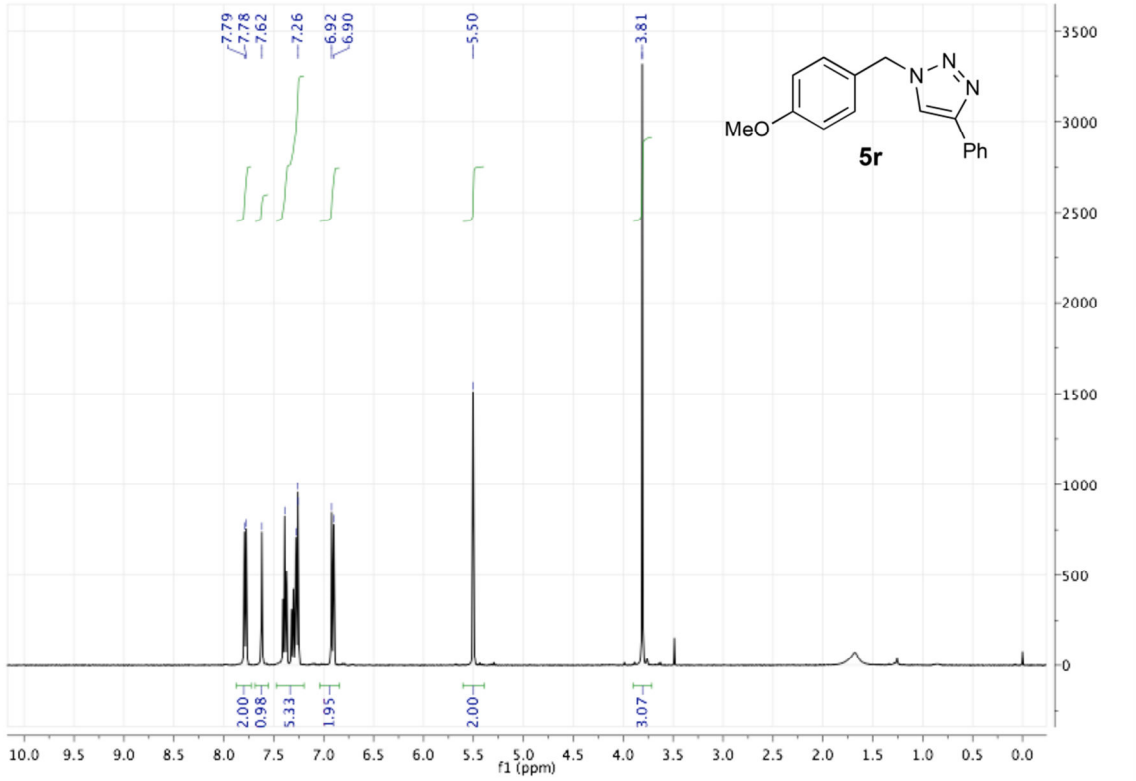

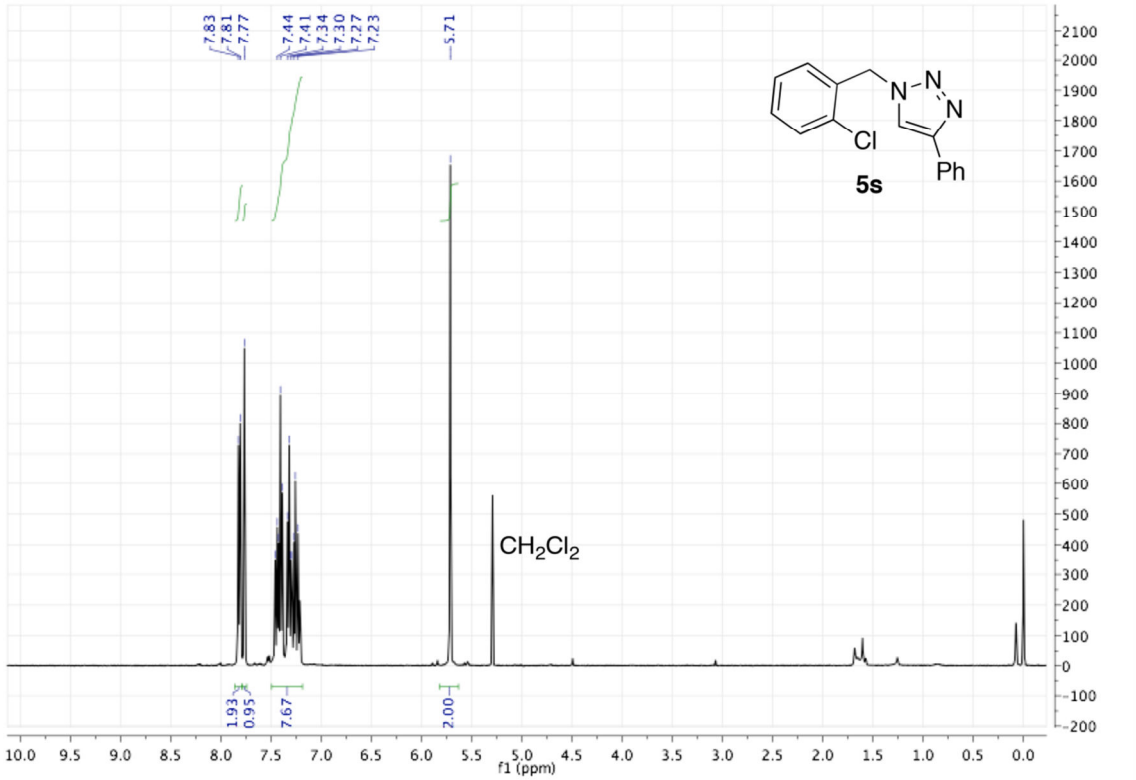

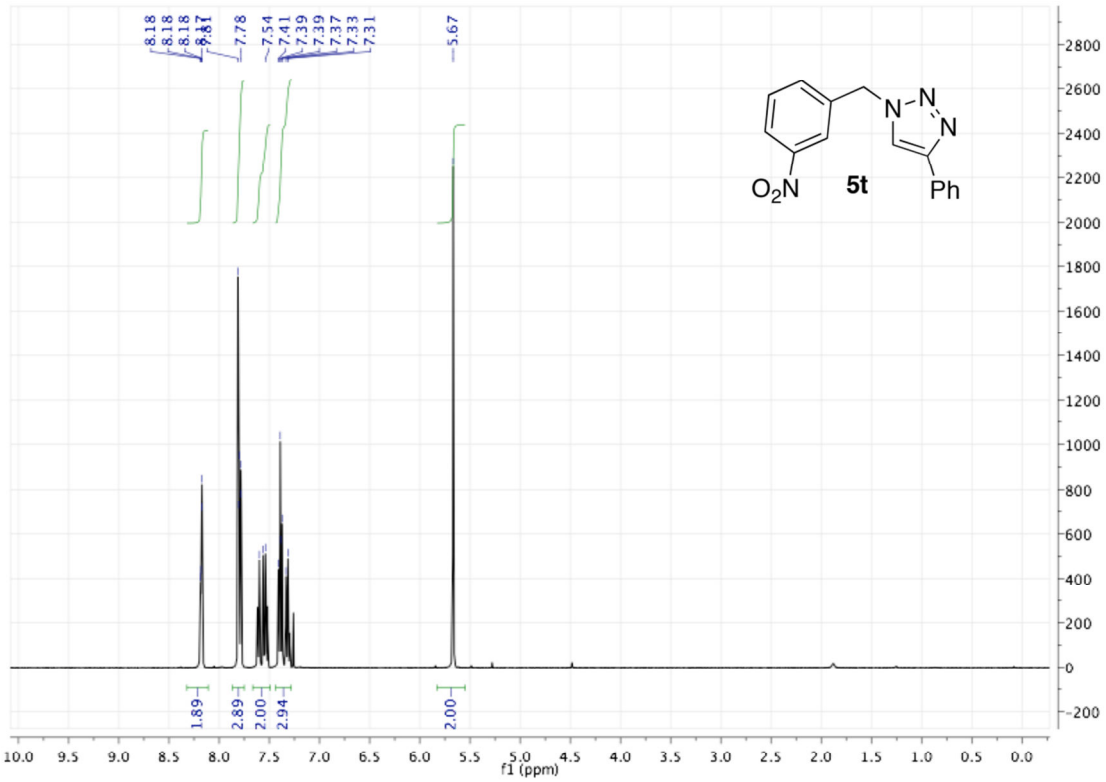

11. Calculated atomic coordinates for tris(pyrazolyl)borate copper(I) chloride.

(B3LYP/LANL2DZ).

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1	5	0	-1.814365	-0.000658	-0.014241
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7	1	0	-3.123111	-0.135122	2.598023
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20	6	0	-1.113083	3.303662	-1.685596

21	1	0	-1.343094	4.245563	-2.161951
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23	1	0	1.152977	3.161351	-1.606217
24	7	0	0.061773	-1.461790	-0.951143
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27	29	0	1.361147	0.001766	0.005551
28	17	0	3.678233	0.002186	0.022670

12. CALCULATED ATOMIC COORDINATES FOR TRIS(TRIAZOLYL)METHANE COPPER(I) CHLORIDE. (B3LYP/LANL2DZ).

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10	6	0	-2.018470	-1.108401	2.398369
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13	1	0	-1.107681	-1.933915	4.183587
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18	7	0	0.034807	1.703982	-0.154539
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20	7	0	0.232676	-1.747139	-2.477322
21	7	0	0.033530	-0.985619	-1.397851
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24	29	0	1.398420	-0.000126	-0.000596
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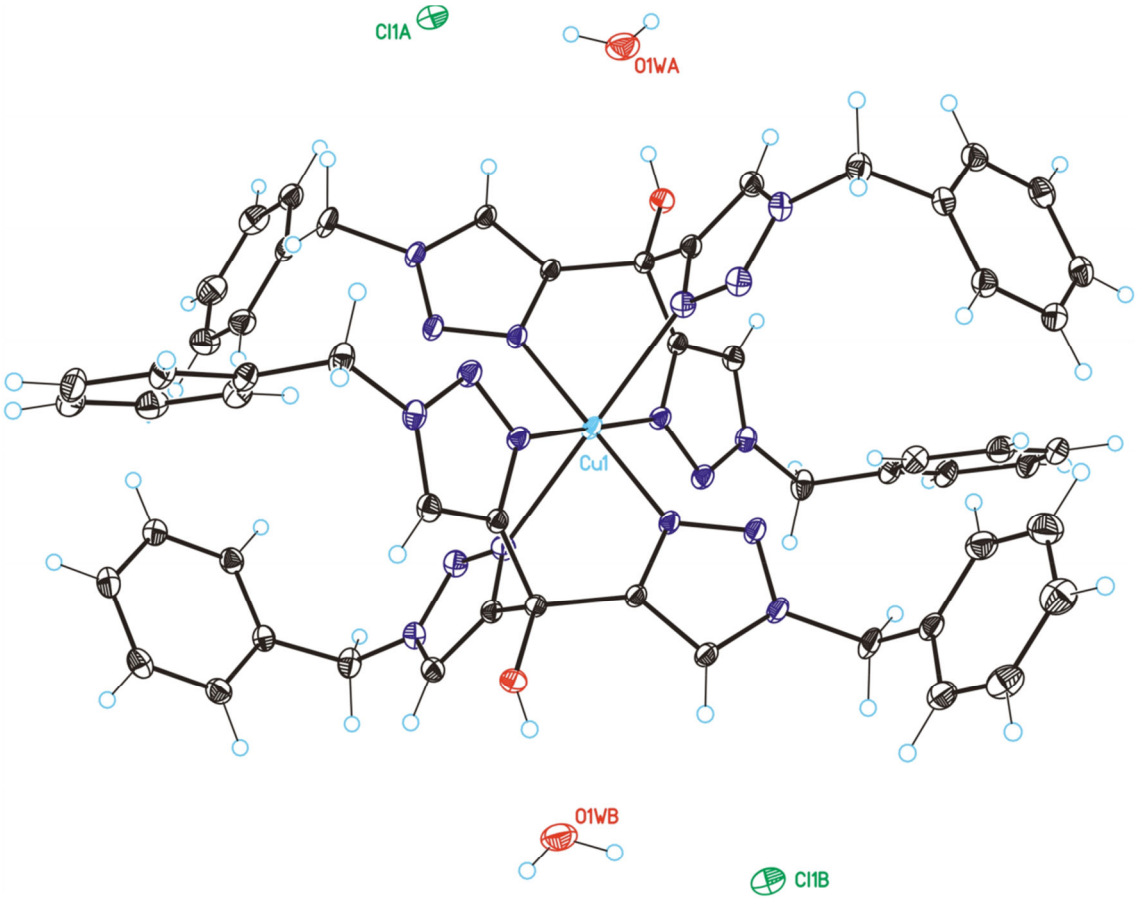
13. ORTEP DRAWING OF $3_2.CuCl_2.(H_2O)_2$:



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PAPER B

Fine-Tunable Tris(triazolyl)methane Ligands for Copper(I)-Catalyzed Azide-Alkyne Cycloaddition Reactions

Submitted to Advance Synthesis & Catalysis

Paper B – Large-scale syntheses of ligands were optimized by Dr. Fernando Bravo (CSOL) and Dr. Alessandro Ferrali (CSOL) at ICIQ. The rest of the experimental work was performed together with Patricia Llanes in Prof. M. A. Pericàs Group at ICIQ.

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Fine-Tunable Tris(triazolyl)methane Ligands for Copper(I)-Catalyzed Azide-Alkyne Cycloaddition Reactions

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[b] Catalyst Selection and Optimization Laboratory (CSOL), ICIQ, Av. Països Catalans, 16. 43007 Tarragona (Spain),
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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The preparation of a small library of modular tris(triazolyl)methane ligands for copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions is reported. The synthesis of the first generation ligand, tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol (**1a**), suitable for work in aqueous systems, is reported at the (50-100 mmol) scale through a one-stage, environmentally benign procedure. One-stage procedures for the synthesis of tris(aryltriazolyl)methanol structures (**1b**, phenyl; **1c**, *p*-trifluoromethylphenyl; **1d**, *p*-methoxyphenyl) designed for electronic fine-tuning of catalytic properties, and of **1a**-derived ethers **2c** (OBn) and **2d** (OMe), designed for CuAAC reactions in organic solvents, are also reported.
The complete set of ligands (**1a-d**, **2c-d**) has been tested in the reaction of phenylacetylene with benzyl azide in six different solvents (water, hexane, toluene, dichloromethane, tetrahydrofuran, and acetonitrile), and this has allowed the identification of **1b**, **1c** and **2c** as the ligands depicting the highest tolerance to changes in solvent polarity within the considered family.
The comparative performance of ligands **1b-d** and **2c** in the cycloaddition of a small family of alkynes with benzyl azide in two very different reaction media (1:1 ^{t}BuOH/H_2O and toluene) has been studied as a guide for catalyst selection in specific applications. The applicability of **1c** in CuAAC reactions involving functional substrates in toluene has been explored under thermal and microwave-accelerated (tandem azide formation plus CuAAC reaction) reaction conditions.

Keywords: Copper; Azides; Alkynes; Click Chemistry; Cycloaddition

Introduction

In the short period of time following its discovery,[1,2] the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has evolved into one of the most employed connective strategies in organic chemistry[3] and has found application in many different fields.[4]

Initial reaction conditions for CuAAC reactions involved the *in situ* reduction of a Cu(II) salt such as $CuSO_4$, used at rather high loading, with ascorbic acid to generate in the reaction media the catalytically active Cu(I) species.[2] However, it was later realized that polydentate nitrogen ligands were able to stabilize Cu(I) intermediates[5] could also accelerate the catalytic process,[6] and this allowed the direct use of Cu(I) salts as catalysts in CuAAC reactions at highly reduced loadings. Tris(triazolylmethyl)amines **I**,[5a],[6a,6c],[7] tetraamino ligands **II**,[8] *N*-heterocyclic carbenes **III**[9] (Figure 1), as well as various copper-coordinating species[10] have been found to be excellent ligands for this chemistry.

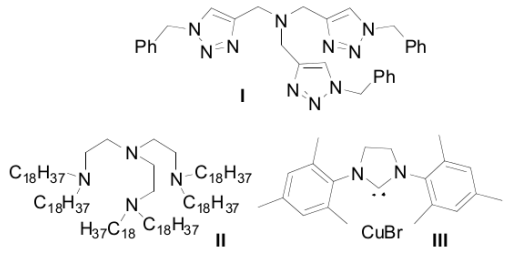


Figure 1. Cu(I) ligands for CuAAC reactions.

In this context, we have recently introduced tris(triazolyl)methanol **1a** (Figure 2) as an effective ligand for CuCl, and have shown that the corresponding neutral complex (**1a**·**CuCl**) is a very efficient catalyst for the azide-alkyne [3+2] cycloaddition reaction in aqueous systems.[11] We

have subsequently immobilized **1a** onto polystyrene resins by using different ligation methods, and have shown that the CuCl complexes of the functional resins **2a-b** behave as highly active and recyclable catalysts for azide-alkyne cycloadditions in a variety of solvents.[12]

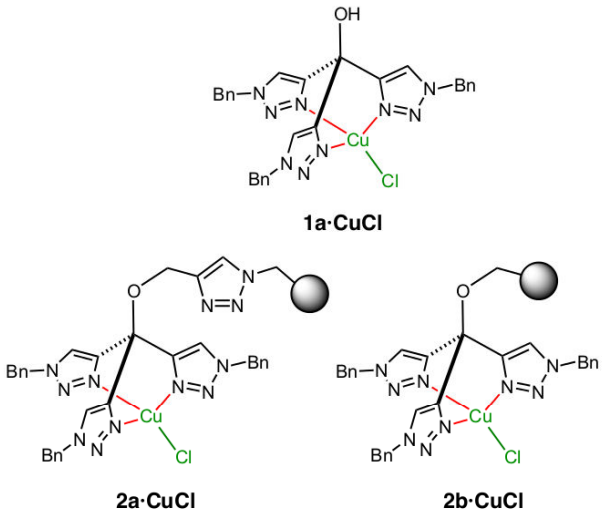
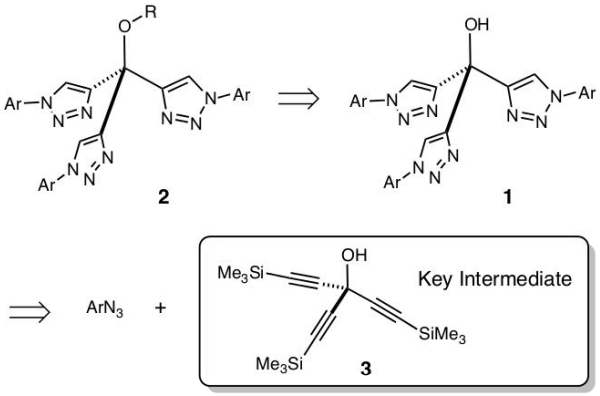


Figure 2. Homogeneous (**1a·CuCl**) and heterogenized (**2a·CuCl** and **2b·CuCl**) catalysts for CuAAC with the tris(triazolyl)methanol (**TTM**) structure.

The structural characteristics of catalysts **1a·CuCl**, **2a·CuCl**,[12] and **2b·CuCl**[12] confer interesting properties to these materials. Thus, the three-point binding provided by the triazole units notably increases the stability of the CuCl complexes and allows their catalytic use at very low loadings even with substrates with high affinity for Cu, such as thioethers and primary and secondary amines.[11-13]

Tris(triazolyl)methanol (TTM) derivatives such as **1** and **2** are modularly constructed from a simple, readily available tris(alkynyl)methanol derivative **3**.[11] If the development of a general purpose catalyst library for CuAAC reactions based on this structure is considered, it can be readily envisioned that parameters such as solubility in aqueous or organic solvents can be controlled by simple etherification of the hydroxy group in **1** leading to **2**, while the use of diversely substituted aryl azides in the synthesis of the TTM structure can allow the modulation of electron density at the triazole unit and, consequently, at the copper atom in the corresponding CuCl complexes.

To make this useful ligand fully available, we wish to report here a large-scale (50-100 mmol) preparation of **1a** through a one-stage process optimized to avoid potentially hazardous solvents or reagents, and not requiring any chromatographic separation. We also report the preparation of a small library of tris(triazolyl)methanol derivatives (**1b-d**, **2c-d**) according to Scheme 1 and involving safe and scalable procedures. Derivatives **1b-d** are tris(aryltriazolyl)methanols designed to modulate electron density at a complexed Cu atom and to study the effect of this modulation on catalytic activity. Derivatives **2c-d** are tris(aryltriazolyl)methanol ethers designed to expand the range of solvents where the corresponding CuCl complexes can be used in catalysis.



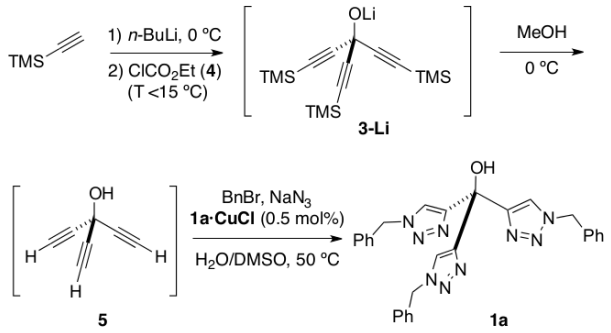
Scheme 1. Retrosynthetic analysis of TTM ligands **1** and **2**.

Results and Discussion

Implementation of a scalable procedure for the preparation of 1a.

The initially reported procedure for the preparation of **1a**[11] involved several chromatographic purifications and made use of relatively expensive and potentially hazardous benzyl azide. In view of the interest of this ligand, whose activity and performance compare very favorably with those of highly priced, commercially available analogs, we aimed at developing an optimized procedure for the preparation of this material fulfilling the following requirements: i) avoiding the isolation or purification of intermediates, ii) using available reagents and environmentally convenient solvents, iii) avoiding the use of benzyl azide, and iv) avoiding the use of chromatography for the final purification of **1a**.

After extensive experimentation, the process represented in Scheme 2 was developed. In the optimized procedure, trimethylsilylacetylene (*ca.* 330 mmol) in anhydrous THF is converted to its Li salt by treatment with a solution of *n*-butyllithium in hexanes with strict temperature control (≤ 15 °C), and the generated acetylide is reacted with ethyl chloroformatate (**4**, *ca.* 90 mmol; limiting reagent) in anhydrous THF, again with strict temperature control. The intermediate lithium salt arising from the double addition-elimination plus addition sequence (**3-Li**), obtained in THF solution does not need to be isolated for the preparation of **1a**. If desired, however, the stable tris(trimethylsilylethynyl)carbynol **3** can be easily isolated from this solution after neutralization and used as a convenient, advanced precursor for the synthesis of different TTM ligands.



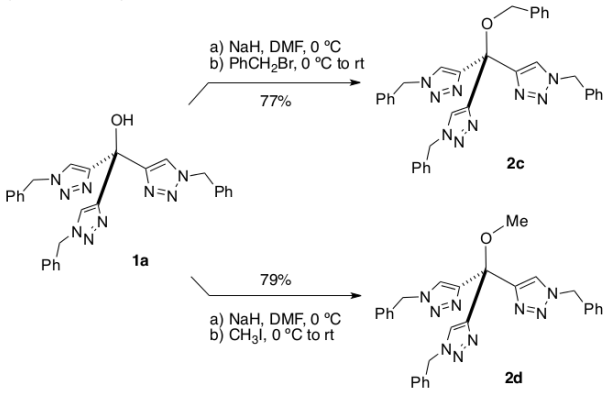
Scheme 2. Optimized procedure for the large-scale production of **1a**.

Addition of excess MeOH to the THF solution of **3-Li** (≤ 15 °C) followed by 2 h stirring at *ca.* 5 °C provokes complete protodesilylation of **3** and generates a light brown solution of **5**. Evaporation under vacuum to a final volume of 50 mL, followed by water addition (300 mL), evaporation of residual THF, and addition of a small volume of DMSO (10 mL) delivers a solution of **5** suitable for the triple CuAAC reaction leading to **1a**. This is performed by addition to the solution of **5** of benzyl bromide (310 mmol), sodium azide (330 mmol) and **1a·CuCl** (*ca.* 0.50 mmol). In this manner, benzyl azide reacts with **5** (or with its partially cycloadded derivatives) as it forms, and accumulation in the reaction media of this potentially hazardous reagent is avoided. Crude **1a**, which precipitates as the reactions proceed, can be purified to a white powder by recrystallization from acetonitrile-ethyl acetate-cyclohexane (1:1:2). In this manner, 30 g of **1a** (64% yield) are obtained in a single batch, the whole process not involving a single purification by column chromatography. At this scale, the preparation of **1a** can be performed in a 1 L flask and involves the use of environmentally benign solvents and conventional reaction conditions. As we will see later in this manuscript, the process can also be adapted for the one-pot preparation of aryl-substituted TTM ligands without isolation of the involved aryl azides.

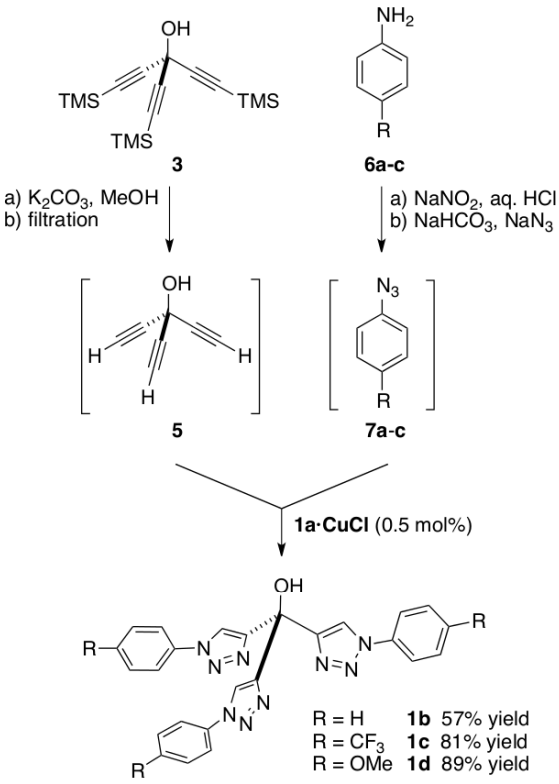
Synthesis of modular tris(triazolyl)methane derivatives.

As we have already mentioned, the immobilization of **1a** on polystyrene matrices, using its hydroxy group as the anchoring point, allowed the preparation of complexes **2a·CuCl** and **2b·CuCl**, which performed as efficient and highly recyclable catalysts for CuAAC reactions in a variety of organic solvents. In view of this behavior, we decided to prepare simple monomeric ethers of **1a** in order to expand the use of their copper complexes to organic solvents covering a broad range of polarity. This can be of particular importance when the product triazoles need to be kept in solution as, for example, in processes involving multiple consecutive reactions.

The benzyl ether (**2c**) and the methyl ether (**2d**) were selected for this purpose and were readily prepared in high yield by simple etherification (Scheme 3).



Scheme 3. Etherification of **1a** leading to **2c-d**.



Scheme 4. One-stage preparation of **1b-d**.

The preparation of analogs of **1a** bearing aryl substituents at the triazole rings was also undertaken. In this manner, the electronic characteristics exerted by substituents at the aryl groups could be transmitted to the copper atom upon complexation, thus modulating the catalytic behavior of the complexes. As shown in Scheme 4, derivatives **1b** (R = H), **1c** (R = CF_3), and **1d** (R = OCH_3) were prepared with this purpose. The synthetic procedures for the preparation of **1b-d** were optimized in view of potential scale-up,

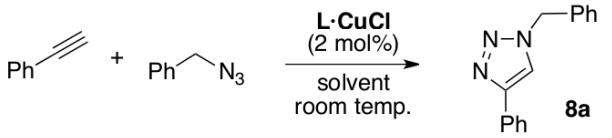
and involved the use of benign solvents and reaction conditions, while avoiding manipulation and storage of aryl azides.

Tris(ethynyl)carbynol **5** was readily prepared in methanol solution from the stable and readily available alcohol **3** (see above) by protodesilylation with methanol in the presence of K_2CO_3 followed by filtration to remove solid materials. Aryl azides **7a-c**, in turn, were prepared in aqueous solution from the corresponding amines **6a-c** by treatment with HNO_2, neutralization, and reaction with sodium azide. Then, combination of the two solutions in the presence of **1a·CuCl** (0.5 mol%) and a small amount of DMSO (1% v/v) at room temperature led to the target TTM derivatives **1b-d** in 57-89% yield. Noteworthy, the preparation of these materials does not involve any chromatographic purification, and only a final recrystallization may be required.

Performance of the CuCl complexes of modular tris(triazolyl)methane derivatives 1a-d and 2c-d in CuAAC reactions.

With the aim of determining the applicability of the prepared TTM ligands in CuAAC reactions, the cycloaddition between phenylacetylene and benzyl azide was first performed in different solvents in the presence of **1a-d** and **2c-d**. The same amount of catalyst (2 mol%) was used in all cases and, for each particular solvent, the same reaction time was used with the whole set of ligands to facilitate comparison. The outcome of this study has been summarized in Table 1, where results for the optimal ligand/solvent combinations are in boldface and highlighted in grey.

Table 1. Comparative performance[a] of catalysts **1a-d** and **2c-d** in the reaction of phenylacetylene with benzyl azide leading to **8a** in different solvents.



8a

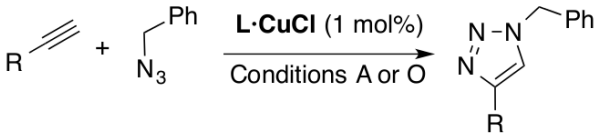
L	H_2O[b] 4h	C_6H_{14} 6h	$PhCH_3$ 6h	CH_2Cl_2 6h	THF 16h	CH_3CN 16h
1a	**98**	5	75	25	90	21
1b	**99**	**99**	**98**	**95**	**78**	**86**
1c	**82**	**99**[c]	**99**[d]	**99**	**80**	**50**
1d	**99**	14	2	22	3	10
2c	**99**	43	26	**98**	**92**	**96**
2d	**56**	27	69	**99**	**60**	**89**

[a]Conversion in [%]. [b]0.5 mol% catalyst was used in this solvent. [c]Conversion was 99% after 3 h and 73% after 1 h. With 1 mol% catalyst, conversion was 99% in 4 h. With 0.5 mol% catalyst, conversion was 73% after 4 h. [d]Conversion was 95% after 3 h.

Several trends observed in this study deserve a comment. First, with the exception of **2d**, all the members of the considered family of catalysts perform very well in water (column 1), the reactions taking place in a short time with only 0.5 mol% catalyst loading. Second, and according to our expectations, ligands **2c** and **2d**, resulting from the etherification of the hydroxy group in **1a**, behave well in aprotic solvent of medium polarity (CH_2Cl_2, THF, CH_3CN). Third, among the tris(aryltriazolyl)methanols **1b-d**, both **1b** (R = H) and the electron poor **1c** (R = CF_3) give high conversions in all the studied solvents at the specified reaction times; by the contrary, ligand **1d** bearing the electron-rich 4-methoxyphenyl substituents originates a very poor catalyst in all solvents but in water.

Next, to determine if the catalytic behavior of the different ligands was correlated to the nature of the reactants, we decided to compare the performance of ligands **1b-d** and **2c** in four cycloadditions involving in all cases benzyl azide and representative alkynes bearing different functionalities. The reactions were performed with 1 mol% catalyst loading, in two different solvent systems covering a wide range in polarity: 1:1 *tert*-butyl alcohol:water and toluene. Results of this study are summarized in Table 2, where results for optimal ligands and reaction conditions are are in boldface and highlighted in grey.

Table 2. Comparative performance[a] of ligands **1b**, **1c**, **1d**, and **2c** in the CuAAC reactions[b] of benzyl azide with representative alkynes.



8a-d

Product	1b A	1b O	1c A	1c O	1d A	1d O	2c A	2c O[g]
8a[c]	**90**	99	99	**99**	64	4	80	21(68)
8b[d]	**99**	88	76	**85**	88	79	90	82(75)
8c[e]	**99**	63	99	**84**	79	69	88	99(82)
8d	**99**	63	95[f]	**72**[f]	66	59	73	67(70)

[a]Yields in [%]. [b]Aqueous conditions (**A**): (1:1) ^{t}BuOH/H_2O, 4h, rt; organic conditions (**O**): Toluene, 4h, rt. [c]Reactions in conditions **O** performed with 2 mol% catalyst for 6h. [d]Reactions leading to this adduct performed with 2 mol% catalyst for 16h. [e]Reactions leading to this adduct in conditions **O** performed under Ar. [f]2 mol% catalyst was used. [g]Yields in parentheses correspond to reactions in dichloromethane.

To compare these results, it should be first kept in mind that one of the employed alkynes (*i.e.* 2-methyl-3-butyne-2-ol) is much less reactive with benzyl azide than the other three. When reactions in aqueous media are performed, **1b·CuCl** appears as the catalyst of choice. Thus, all four adducts are obtained in excellent yields with this catalyst and reaction conditions (column 1). For reactions in toluene, very good results are achieved with **1c·CuCl** (column 4), especially when the low reactivity of 2-methyl-3-butyne-2-ol is considered.

As we have already mentioned, **2c·CuCl** exhibits optimal catalytic conditions in organic solvents of medium polarity (see Table 1). To more properly assess the merits of this catalyst for the preparation of adducts **8a-d** in non-aqueous media, the reactions in column 8 of Table 2 were repeated in CH_2Cl_2 under otherwise identical conditions. Very gratifyingly, uniform yields (in parentheses) were obtained under these conditions for all four studied substrates. Thus, in preparative experiments a simple extension of reaction time will ensure very high yields of the corresponding adducts irrespectively of the nature of the involved alkyne.

In view of the good performance exhibited by **1c·CuCl** for reactions in toluene leading to **8a-d** (mean yield: 85%), some additional experiments including especially challenging substrates, like primary amines, or problematic adducts, like those exhibiting good chelating characteristics for copper were performed in this solvent (Table 3). It is important to point out that CuAAC reactions involving these substrates normally fail, and this can be attributed to the formation of catalytically inactive Cu complexes involving either the reactants or the cycloadducts. According to the observed behavior of **1a·CuCl** in aqueous media, we reasoned that the efficient three-point metal binding in **1c·CuCl** would preserve its catalytic activity in toluene.

As it can be seen, **1c·CuCl** behaves as a very general and active catalyst for CuAAC reactions in this media. Proline derivatives depicting azido groups in different positions (entries 1-3) were efficiently converted into triazoles **8e-g**, which are advanced intermediates for organocatalytic prolines and pyrrolidines.[14] As already mentioned, functional group tolerance in the alkyne component is also very broad (entries 4-7) and alcohols, primary amines and esters lead to the corresponding adducts in high yield. In the same way, alkyl azides (entries 8-11) afford the corresponding cycloadducts in essentially quantitative yield. Very gratifyingly, 1,3,5-tris(azidomethyl)-2,4,6-triethyl-benzene, an important precursor for supramolecular systems,[15] readily underwent triple CuAAC reactions mediated by **1c·CuCl** in toluene to afford the corresponding adducts **8p-q** in very high yields (entries 12-13).

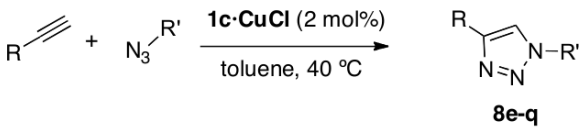
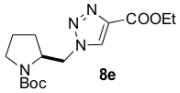
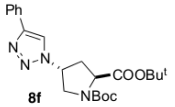
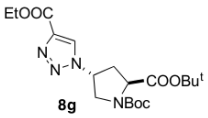
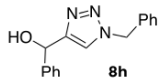
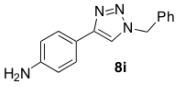
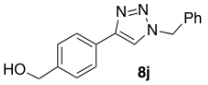
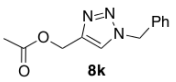
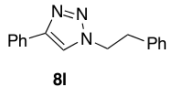
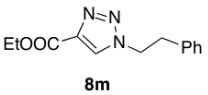
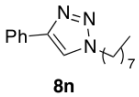
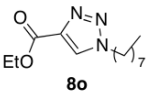
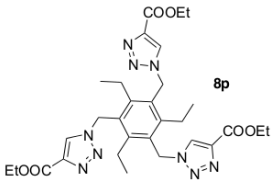
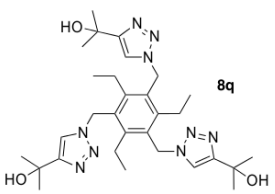


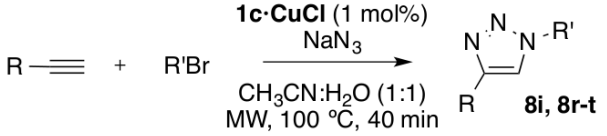
Table 3. CuAAC reactions mediated by **1c·CuCl** in toluene.

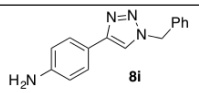
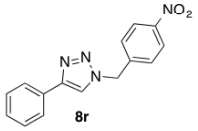
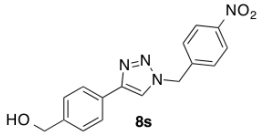
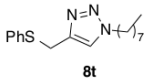
	Product	Time (h)	Yield[a]
1	 **8e**	2	95
2	 **8f**	22	99
3	 **8g**	3	99
4[b]	 **8h**	9	95
5	 **8i**	13	74
6	 **8j**	7	80
7[c]	 **8k**	10	99
8	 **8l**	22	99
9	 **8m**	2	93
10	 **8n**	20	99
11	 **8o**	2	99
12[d]	 **8p**	6	99
13[d]	 **8q**	24	80

[a]Isolated yields as mean value of two experiments. [b]At room temperature. [c]In *t*-BuOH–H_2O (1:1) at 40 ºC. [d]2 mol% catalyst per CuAAC reaction.

Finally, the use of **1c·CuCl** in tandem processes involving azide generation from an organyl bromide and sodium azide and subsequent CuAAC reaction is illustrated by the examples in Table 4. The reactions were performed in acetonitrile/water, at 100 ºC under microwave irradiation in a remarkably short 40 min period.

Table 4. One-pot azide formation plus CuAAC reactions mediated by **1c·CuCl**.



Entry	Product	yield [%][a]
1	 **8i**	51
2	 **8r**	99
3	 **8s**	99
4[b]	 **8t**	54

[a]Isolated yield. [b]Reaction time was 80 min.

Conclusion

The results presented in this study clearly show that modular tris(triazolyl)methanols (**TTM**) are among most useful ligands for copper-catalyzed azide-alkyne cycloaddition reactions. The three-point binding provided by these ligands efficiently stabilizes Cu(I) against oxidation or complexation with amino, hydroxy, and/or thioether groups present in either reactants or reaction products, likewise through favorable self-repair of the catalytic complex. This behavior, not only extends catalyst life and allows very reduced catalyst loadings; it also allows its use with substrates (primary and secondary amines) where most catalysts for CuAAC reactions completely fail.

The first generation catalyst in this family, **1a·CuCl**, tolerates a wide range of functional groups on either the alkyne or the azide reactant, being particularly suitable for work in aqueous media. The fully optimized, environmentally benign preparation of **1a** reported here will make this catalyst available to the chemical community at virtually no cost.

The modification of the first generation catalyst, by simple etherification of the tertiary hydroxy group, provides catalytic species (**2c·CuCl** and **2d·CuCl**) suitable for work in organic solvents that behave particularly well in solvents of medium polarity.

The modular design of the TTM ligands has been exploited for the preparation of a small library of tris(aryltriazolyl)methanol derivatives **1b-d**. While the system involving a *p*-methoxy substituent in the aryl groups (**1d**) has revealed as a mediocre ligand, the parent tris(phenyltriazolyl) derivative (**1b**) and the one involving a *p*-trifluoromethyl substituent (**1c**) behave as very active ligands in a full range of solvents. In particular, **1c** tolerates a wide variety of functional groups on either the alkyne or the azide reactants, and appears as a convenient alternative to **1a** when work in non-aqueous solvents is mandatory.

Experimental Section

General Considerations

All reagents and solvents were used as received. For reactions requiring exclusion of oxygen and moisture, SPS quality THF and DMF were used. Unless otherwise stated, reactions were performed in oven-dried round-bottom flasks fitted with rubber septa and stirring bars, and reactions were conducted under a positive pressure of argon. Syringes or cannulae were used to transfer air- and moisture-sensitive liquids. All copper catalyzed azide-alkyne cycloaddition (CuAAC) reactions were performed in glass vials fitted with stirring bars without any precaution to exclude air and moisture. All flash chromatography purifications were carried out using 60 mesh silica gel and dry-packed columns. For thin layer chromatography (TLC) analysis, pre-coated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used, with UV light and/or phosphomolybdic acid (PMA) or basic aqueous potassium permanganate ($KMnO_4$) as developing agents. Solutions were concentrated under reduced pressure on rotatory evaporators at 30 ºC. Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz or 500 MHz for ^1H and at 100 MHz or 126 MHz for ^{13}C at room temperature. Chemical shifts (δ) are reported in parts per million (ppm) with respect to tetramethylsilane as internal standard, or to the corresponding solvent residual peak ($CDCl_3$: 7.28, 77.16; $(CD_3)_2SO$: 2.50, 39.52; CD_3OD: 3.31, 49.00; D_2O: 4.79 for proton and carbon respectively). The following abbreviations are used for the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br-s, broad signal. Melting points are all uncorrected. IR spectra were recorded on a FT-IR spectrometer operating in ATR mode.

Large scale procedure for the preparation of tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol (1a)[11]

In a flame-dried, 1 L three neck, round bottom flask, provided with magnetic stirrer, addition funnel and thermometer, a solution of trimethylsilylacetylene (47.0 mL, 332.6 mmol) in anhydrous THF (100 mL) is prepared. The solution is cooled with an ice-water bath, and stirred until the internal temperature is *ca.* 5 °C. Then, a solution of BuLi 2.5 M in hexanes (122.0 mL, 305.0 mmol) is slowly added to the solution from the addition funnel (exotherm!), controlling the addition rate in order to keep the internal temperature ≤ 15 °C. In this way, the addition is completed in *ca* 1 h. The addition funnel is rinsed with fresh anhydrous THF (20 mL), which is also added to the reaction mixture. The solution is stirred in the ice-water bath (the internal temperature decreases to *ca.* 5 °C) for 1 h. Then, a solution of ethyl chloroformate (10.0 g, 92.2 mmol) in anhydrous THF (60 mL) is slowly added (exotherm!) through the addition funnel, controlling the addition rate so that the internal temperature is kept below 15 °C. In this way, the addition is completed in *ca.* 30 min.

Afterwards, the addition funnel is rinsed with anhydrous THF (20 mL), which is also added to the reaction mixture. The reaction mixture is then allowed to warm slowly to room temperature (*ca* 23 °C), and is stirred overnight. The solution takes a light brown color as the reaction proceeds. After 14 h at room temperature, TLC analysis of the light brown solution indicates the formation of tris(trimethylsilylethynyl)carbinol (eluent: cyclohexane /ethyl acetate 9:1; R_f: 0.37; stain: phosphomolybdic acid). Next, the reaction mixture is cooled with an ice-water bath until the internal temperature reaches *ca.* 5 °C, and then MeOH (100 mL) is slowly added through the addition funnel (exotherm!), controlling the addition rate in order to keep the internal temperature below 15 °C. This addition is completed in *ca.* 20 min. The reaction mixture is further stirred while cooling with the external ice-water bath (internal temperature stabilizes at *ca.* 5 °C) for 2 h. At this point, the reaction mixture has the aspect of a light brown solution. TLC analysis of this solution indicates formation of tris(ethynyl)carbinol (eluent: cyclohexane/ethyl acetate 9:1; R_f: 0.02; stain: phosphomolybdic acid). The mixture is concentrated under vacuum to a final volume of 50 mL, keeping the bath temperature at 30-35 °C. Water (300 mL) is then added, the solution is concentrated again under vacuum until only water distills, and the distillation is continued for 15-30 more minutes to ensure the removal of rests of organic solvent (bath temperature: 30-35 °C). Finally, enough water is added to adjust the volume of the solution to 300 mL. DMSO (10 mL) is then added, followed by benzyl bromide (37.0 mL, 312.0 mmol), sodium azide (21.5 g, 330.7 mmol) and **1a.CuCl** (0.277 g, 0.460 mmol, 0.5 mol%). The resulting mixture is warmed to 50°C and stirred vigorously overnight at this temperature (CAUTION!!! *Benzyl azide is formed under these conditions; benzyl azide may be explosive!!! Differential scanning calorimetry (DSC) of pure benzyl azide shows an exothermic event starting at about 160 °C, providing a sufficient safety margin*). After 14 h reaction, a brownish solid is abundantly formed, that tends to stick to the walls of the reactor. At this point, the progress of the reaction can be easily monitored by TLC, by taking a sample of the aqueous solution and extracting it with CH_2Cl_2. The absence of the spot corresponding to the starting tris(ethynyl)carbinol is indicative of reaction completion. The aqueous mother liquors are filtered, and all solids remaining in the reactor and in the filter are washed with water (2x100 mL, then 1x200 mL) (CAUTION!!! *the aqueous phase should be disposed with basic aqueous residues; addition of acid may generate hazardous and poisonous hydrazoic acid (HN_3) as a gas!!!*). The brownish solid recovered is partially dried on the filter by passing air through it and, while still wet, it is suspended in a mixture of acetonitrile (80 mL) and ethyl acetate (160 mL), warmed to reflux (internal temperature *ca.* 80 °C) and stirred at that temperature for 1 h. During this process, the solid almost completely dissolves. Cyclohexane (220 mL) is added slowly over 1 h while keeping the mixture under reflux, and then the mixture is cooled to room temperature (*ca.* 23 °C) over 3 h. The resulting slurry is aged overnight at room temperature. The white solid obtained is separated by filtration, then washed 3 times with a 1:1 mixture of ethyl acetate and cyclohexane (3x50 mL). The solid recovered is dried in an oven under vacuum overnight at 65 °C to afford **1a** (29.8 g, 64% yield) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.76 (s, 3H), 7.32 – 7.18 (m, 15H), 5.76 (br-s, 1H), 5.39 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $(CD_3)_2SO$): δ 151.4, 135.2, 127.9, 127.3, 127.2, 122.2, 67.1, 52.4 ppm.

Tris(1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol (1b)

Concentrated aqueous hydrochloric acid solution (37% (v/v), 1.5 mL, 18 mmol) was added dropwise to a suspension of aniline (559 mg, 6.00 mmol) in water at 0 °C. After 15 min, a solution of sodium nitrite (621 mg, 9 mmol) in water (1 mL) was added via syringe. After 15 min, solid sodium bicarbonate was added until pH~7, followed by addition of a solution of sodium azide (702 mg, 10.8 mmol) in water (1.7 mL). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. In a simultaneous manner and in a separate flask, solid potassium carbonate (2.01 g, 14.5 mmol) was added to a solution of tris(trimethyl-silylethynyl)methanol (**3**) (481 mg, 1.5 mmol) in methanol (5 mL) and the mixture was stirred at room temperature for 30 min. The solids were separated by filtration, and the solution was concentrated under reduced pressure to a final volume of *ca.* 3 mL. This solution was added to the mixture containing phenyl azide, followed by the addition of DMSO (0.15 mL) and **1a·CuCl** (9 mg, 0.015 mmol, 1 mol%), and the reaction mixture was stirred overnight at room temperature. After 14 h, a brown precipitate of **1b** was formed; it was separated by filtration and washed with cold diethyl ether (10 mL) to provide essentially pure **1b**. This material can be purified to analytical level by recrystallization from acetonitrile–water (1:2 mixture, 15 mL) to afford **1b** as a pale-yellow solid (394 mg, 57% yield). **mp:** 211 – 212 ºC. **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): δ 8.76 (s, 3H), 7.96 (d, 6H, *J* = 8.3 Hz), 7.60 (t, 6H, *J* = 7.9 Hz), 7.49 (t, 3H, *J* = 8.0 Hz), 7.16 (s, 1H) ppm. **^{13}C NMR** (126 MHz, $(CD_3)_2SO$): δ 152.6, 136.7, 129.9, 128.6, 121.4, 120.1, 68.0 ppm. **FTIR** (neat): ν 3304, 3138, 1597, 1548, 1466, 1235, 1042, 991, 889, 811, 750, 666 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{25}H_{19}N_9ONa$: 484.1614; Found: 484.1610. **Elemental analysis**: Found (calcd. for $C_{25}H_{19}N_9O$): C, 65.06 (65.07); H, 4.27 (4.15); N, 26.87 (27.32).

Tris(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methanol (1c)

Following the above procedure for **1b** and starting from 4-(trifluoromethyl)aniline (967 mg, 6.00 mmol), **1c** was obtained as a pale-yellow solid (808 mg, 81% yield). **mp**: 240 – 241 ºC. **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): δ 8.96 (s, 3H), 8.25 (d, 6H , *J* = 8.5 Hz), 7.99 (d, 6H, *J* = 8.5 Hz), 7.32 (s, 1H) ppm. **^{13}C NMR** (126 MHz, $(CD_3)_2SO$): δ 152.7, 139.4, 128.6 (q, *J* = 32.42 Hz), 127.2 (q, *J* = 3.40 Hz), 124.3 (q, *J* = 274.05 Hz), 122.7, 121.9, 120.5, 67.4 ppm. **^{19}F NMR** (376 MHz, $(CD_3)_2SO$): δ –61.06 ppm. **FTIR** (neat): ν 3258, 1650, 1524,1323, 1161, 1126, 1069, 1044, 895, 840, 594 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{16}F_9N_9ONa$: 688.1232; Found: 688.1212.

Tris(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methanol (1d)

Following the above procedure for **1b** and starting from 4-(methoxy)aniline (741 mg, 6.00 mmol), **1d** was obtained as a pale-yellow solid (736 mg, 89% yield). **mp:** 128 – 130 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.20 (s, 3H), 7.66 (d, 6H, *J*= 9.0 Hz), 7.02 (d, 6H, *J*= 9.0 Hz), 4.98 (s, 1H), 3.88 (s, 9H) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ 159.9, 151.7, 130.4, 122.3, 120.9, 114.7, 68.1, 55.6 ppm. **FTIR** (neat): ν 3141, 2955, 2834, 1514, 1303, 1251, 1108, 1027, 888, 829, 796, 635, 530 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{25}N_9O_4Na$ 574.1927; Found 574.1927.

4,4',4''-((Benzyloxy)methanetriyl)tris(1-benzyl-1*H*-1,2,3-triazole) (2c)

A solution of **1a** (503 mg, 1.0 mmol) in anhydrous DMF (2 mL) was added dropwise via cannula, under a positive pressure of argon, to a stirred suspension of sodium hydride (80 mg, 60% in oil, 2.0 mmol) in anhydrous DMF (2 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature (23 °C). After 2 h, the suspension became a clear solution, which was cooled to 0 °C and benzyl bromide (0.238 mL, 2.0 mmol) was added dropwise via syringe. The reaction mixture was allowed to warm to 23 ºC and was stirred overnight. After 14 h, water (10 mL) was added dropwise and the mixture was extracted with dichloromethane (3×10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Residual DMF can be removed by dissolving the crude product in ethyl

acetate-hexane (4:1, 50 mL) and washing with water (3 × 20 mL). Drying (anhydrous $MgSO_4$) and evaporation under reduced pressure affords crude **2c**, which is further purified by flash column chromatography (silica gel, ethyl acetate). The product was obtained as a white foam (0.456 g, 77% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.84 (s, 3H), 7.32 – 7.28 (m, 9H), 7.24 – 7.19 (m, 6H), 7.19 – 7.11 (m, 5H), 5.44 (s, 6H), 4.41 (s, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 149.0 138.1, 134.3, 128.9, 128.5, 127.9, 127.7, 127.1, 124.4, 72.7, 66.5, 54.0 ppm. **FTIR** (neat): ν 3144, 3064, 2934, 2871, 1496, 1453, 1226, 1130, 1040, 910, 889, 807, 734 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{35}H_{31}N_9ONa$: 616.2549; Found: 616.2546.

4,4',4''-(Methoxymethanetriyl)tris(1-benzyl-1*H*-1,2,3-triazole) (2d)

Following the above procedure for **2c** and using methyl iodide (0.124 mL, 2.0 mmol), **2d** was obtained as a white foam (0.408 g, 79% yield). **mp:** 127 – 129 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.80 (s, 3H), 7.35 – 7.33 (m, 9H), 7.26 – 7.25 (m, 6H), 5.49 (s, 6H), 3.14 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 148.8, 134.3, 129.1, 128.7, 128.1, 124.4, 72.8, 54.2, 52.1 ppm. **FTIR** (neat): ν 3141, 2943, 1605, 1526, 1497, 1232, 1120, 1080, 856, 776 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calctd for $C_{29}H_{27}N_9ONa$: 540.2236; Found: 540.2229. **Elemental analysis:** Found (calcd. for $C_{29}H_{27}N_9O$): C, 66.87 (67.30); H, 5.18 (5.26); N, 24.01 (24.36).

General Procedure for the Preparation of the Copper (I) Complexes of 1a-d and 2c-d

The ligand **L** (x mmol) (**L** = **1a-d**, **2c-d**) and copper(I) chloride (1.05x mmol) in dioxane (10 mL/mmol **L**) were stirred at 60 °C for 6 h. The solvent was then removed under reduced pressure, the green solid residue being redissolved in the minimal amount of dichloromethane (1-2 mL) and precipitated into hexane (20 mL) via dropwise addition of the dichloromethane solution. The solid material was collected by filtration and dried in a vacuum oven at 40 °C for 14 h to afford **L·CuCl**.

Tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol·CuCl (1a·CuCl)

Prepared according to the general procedure for complex formation using **1a** (0.504 g, 1.00 mmol) to afford the desired complex as a light green powder (0.588 g, 98 % yield). **^{1}H NMR** (500 MHz, CD_3OD): δ 7.41 – 7.07 (m, 18H), 5.92 (s, 6H) ppm. **^{13}C NMR** (126MHz, CD_3CN): δ 131.6, 131.2, 130.7, 129.9, 129.5, 101.0, 84.0 ppm. **FTIR (ATR)** (neat): ν 3380, 3111, 3062, 2949, 1718, 1584, 1432, 1142, 1077 cm^{-1}. **HRMS** (MALDI-TOF) *m/z*: $[M +]^+$ calcd for $C_{28}H_{25}N_9OCu$: 566.1478; Found : 566.1536.

Tris(1-phenyl-1*H*-1,2,3-triazol-4-yl)methanol·CuCl (1b·CuCl)

Prepared according to the general procedure for complex formation using **1b** (0.232 g, 0.50 mmol) to afford the desired complex as a light green powder (0.233 g, 83% yield). **^{13}C NMR** (126 MHz, CD_3CN): δ 135.1, 131.0, 130.6, 129.9, 129.5, 126.8, 121.9 ppm. **FTIR (ATR)** (neat): ν 3324, 3136, 1597, 1552, 1465, 1237, 1039, 999, 892, 811, 752, 686 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M +]^+$ calcd for $C_{25}H_{19}N_9OCu$: 524.1003; Found: 524.0997.

Tris(1-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazol-4-yl)methanol·CuCl (1c·CuCl)

Prepared according to the general procedure for complex formation using **1c** (0.333 g, 0.50 mmol) to afford the desired complex as green powder (0.330 g, 86% yield). **^{13}C NMR** (126 MHz, CD_3CN): δ 133.5, 131.1 (d, *J* = 31.5 Hz), 128.6, 126.6 (d, *J* = 52.9 Hz), 124.5 (d, *J* = 49.0 Hz), 122.4 ppm. **FTIR (ATR)** (neat): ν 3085, 1617, 1523, 1323, 1168, 1112, 1069, 1057, 843, 594, 469 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M +]^+$ calcd for $C_{28}H_{16}F_9N_9OCu$: 728.0625; Found: 728.0617.

Tris(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methanol·CuCl (1d·CuCl)

Prepared according to the general procedure for complex formation using **1d** (0.276 g, 0.50 mmol) to afford the desired complex as a light green powder (0.257 g, 79% yield). **^{13}C NMR** (100 MHz, CD_3CN): δ 161.4, 134.7, 133.2, 131.6, 126.1, 123.8, 116.2, 56.8 ppm. **FTIR (ATR)** (neat): ν 3353, 3081, 2936, 2837, 1515, 1306, 1254, 1112, 1028, 830, 799, 613 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M +]^+$ calcd for $C_{28}H_{25}N_9O_4Cu$ 614.1320; Found 614.1309.

4,4',4''-((Benzyloxy)methanetriyl)tris(1-benzyl-1*H*-1,2,3-triazole)·CuCl (2c·CuCl)

Prepared according to the general procedure for complex formation using **2c** (0.297 g, 0.50 mmol) to afford the desired complex as a light green powder (0.300 g, 87% yield). **FTIR (ATR)** (neat): ν 3448, 3115, 3031, 2946, 2870, 1496, 1453, 1227, 1132, 1046, 980, 898, 807, 716 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M +]^+$ calcd for $C_{35}H_{31}N_9OCu$: 656.1942; Found: 656.1928.

4,4',4''-(Methoxymethanetriyl)tris(1-benzyl-1*H*-1,2,3-triazole)·CuCl (2d·CuCl)

Prepared according to the general procedure for complex formation using **2d** (0.259 g, 0.50 mmol) to afford the desired complex as a light green powder (0.278 g, 91% yield). **FTIR (ATR)** (neat): ν 3135, 2935, 1542, 1497, 1226, 1132, 1077, 893, 783, 717 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calctd for $C_{29}H_{27}N_9OCu$: 580.1629; Found: 580.1629.

General Procedure for CuAAC Reactions

In a 3-mL vial, the specified amount of **L·CuCl** (**L** = **1a-d**, **2c-d**) was added to a mixture of the reacting alkyne (1.05 mmol) and the corresponding azide (1.00 mmol) in the specified solvent (1 mL), and the mixture was stirred at 40 ºC for the indicated times or until complete reaction. In reactions with complete conversion providing insoluble compounds, simple filtration afforded the desired CuAAC products with analytical purity. Otherwise, the reaction mixture was diluted with ethyl acetate (10 mL), and the resulting solution was washed with water (5 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. When required, the product was purified by flash column chromatography.

General Procedure for the Tandem Azide Formation and CuAAC Reactions under Microwave Irradiation

In a sealed microwave tube, sodium azide (91 mg, 1.40 mmol) was dissolved in water (1 mL). Acetonitrile (1 mL) was added as co-solvent, followed by the corresponding alkyl or benzyl bromide (1.20 mmol), the alkyne (1.0 mmol), and 1 mol% of catalyst **L.CuCl** (**L** = **1a-d**, **2c-d**). The mixture was heated in the microwave reactor at 100 ºC for 40 minutes (Constant temperature mode, 5 minutes heating ramp, maximum power = 300 W, power max mode kept on; maximum allowed pressure = 300 PSI with stirring on). After cooling to room temperature, the reaction mixture was diluted with ethyl acetate. The solution was washed with water and brine, dried over $MgSO_4$, filtered, and volatiles removed under reduced pressure. If required, the triazole product was purified by flash chromatography on a short silicagel column, or by recrystallization.

1-Benzyl-4-phenyl-1*H*-1,2,3-triazole (8a)[16]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 2. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80 – 7.79 (m, 2H), 7.65 (s, 1H), 7.41 – 7.31 (m, 8H), 5.57 (s, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 148.2, 134.7, 130.5, 129.1, 128.8, 128.14, 128.04, 125.7, 119.4, 54.2 ppm.

Ethyl 1-benzyl-1*H*-1,2,3-triazole-4-carboxylate (8b)[17]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 2. **^{1}H NMR** (400 MHZ, $CDCl_3$): 7.97 (s, 1H), 7.40 – 7.28 (m, 5H), 5.58 (s, 2H), 4.43 – 4.37 (m, 2H), 1.38 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.7, 140.6, 133.7, 129.3, 129.1, 128.2, 127.2, 61.3, 54.4, 14.3 ppm.

1-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-*N*,*N*-dimethylmethanamine (8c)[11]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 2. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.37 – 7.36 (m, 3H), 7.27-7.25 (m, 2H), 5.51 (s, 2H), 3.58 (s, 2H), 2.25 (s, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 145.7, 134.7, 129.1, 128.7, 128.1, 122.3 54.4, 54.1, 45.1 ppm.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-ol (8d)[18]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 2. **^{1}H NMR** (400 MHz, $CDCl_3$): 7.38 – 7.26 (m, 6H), 5.50 (s, 2H), 2.50 (s, 1H), 1.62 (s, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 134.6, 129.1, 128.7, 128.1, 68.3, 54.2, 30.5 ppm.

(*S*)-Ethyl 1-((1-*tert*-butoxycarbonyl)pyrrolidin-2-yl)methyl)-1*H*-1,2,3-triazole-4-carboxylate (8e)[19]

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.103 g, 1.05 mmol) and (*S*)-*tert*-butyl 2-(azidomethyl)pyrrolidine-1-carboxylate (0.226 g, 1mmol) to afford the crude and it was further purified by flash column chromatography (silica gel, hexanes–ethyl acetate (3:1)) to give desired product as white solid (0.308 g, 95% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.05 (br s+s, 1H), 4.75 – 4.45 (m, 2H), 4.44 – 4.39 (m, 2H), 4.13 (br s, 1H), 3.43 – 3.09 (m, 2H), 1.97 – 1.73 (m, 3H), 1.50 (s, 9H), 1.41 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.6, 154.8, 140.3, 128.3,127.8*, 99.9, 80.5*, 80.1, 61.2, 57.0, 52.9*, 51.7, 47.0, 46.8*, 28.4, 28.2*, 23.3, 22.6*, 14.2 ppm (*minor rotamer). **Elemental analysis:** Found (calcd. for $C_{15}H_{24}N_4O_4$): C, 54.88 (55.54); H, 7.07 (7.46); N, 16.93 (17.27).

(2*S*,4*R*)-1,2-di-*tert*-butyl 4-(4-phenyl-1*H*-1,2,3-triazol-1-yl)pyrrolidine-1,2-dicarboxylate (8f)

Prepared according to the general procedure for CuAAC reactions using ethynylbenzene (0.107 g, 1.05 mmol) and (2*S*,4*R*)-di-*tert*-butyl 4-azidopyrrolidine-1,2-dicarboxylate (0.312 g, 1mmol) to afford the desired product as a white solid (0.410 g, 0.99 mmol, 99% yield). **mp**: 148-150 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83 – 7.81 (m, 2H), 7.76 (s, 1H), 7.45 – 7.41 (m, 2H), 7.36 – 7.33 (m, 1H), 5.32 – 5.28 (m, 1H), 4.49 – 4.43 (m, 1H), 4.41 – 4.08 (m, 1H), 3.97 – 3.85 (m, 1H), 2.96 – 2.80 (m, 1H), 2.54 – 2.52 (m, 1H), 1.51 (s, 9H), 1.46 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.3, 153.5, 148.1, 130.3, 128.9, 128.3, 125.7, 118.2*, 118.0, 82.1*, 81.9, 80.9, 58.6*, 58.3, 57.8, 51.9*, 51.7, 36.7*, 35.7, 28.3*, 28.0 ppm (*minor rotamer). **FTIR (ATR)** (neat): ν 2978.1, 1725.4, 1691.1, 1401.3, 1367.1, 1257.7, 1130.4, 1040.7, 1006.4, 912.2, 767.7, 694.1, 512.9 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calctd for $C_{22}H_{30}N_4O_4Na$: 437.2165; Found: 437.2151. **Elemental analysis:** Found (calcd. for $C_{22}H_{30}N_4O_4$): C, 63.55 (63.75); H, 7.00 (7.30); N, 13.66 (13.52). **$[\alpha]_D^{25}$** = -24.9 (c 0.1 in $CHCl_3$).

(2*S*,4*R*)-1,2-di-*tert*-butyl 4-(4-ethoxycarbonyl-1*H*-1,2,3-triazol-1-yl)pyrrolidine-1,2-dicarboxylate (8g)

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.103 g, 1.05 mmol) and (2*S*,4*R*)-di-*tert*-butyl 4-azidopyrrolidine-1,2-dicarboxylate (0.312 g, 1.0 mmol) to afford the desired product as a yellow oil (0.406 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 5.36 – 5.25 (m, 1H), 4.39 – 4.38 (m, 3H), 4.11 – 4.06 (m, 1H), 3.93 – 3.80 (m, 1H), 2.90 – 2.73 (m, 1H), 2.54 – 2.53 (m, 1H), 1.50 – 1.46 (m, 18H), 1.41 (t, J = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 171.1, 160.5, 153.7*, 153.4, 140.6, 126.1, 125.9*, 82.2*, 82.1, 81.0, 61.4, 58.3, 58.1*, 51.8*, 51.6, 36.6*, 35.6, 28.2*, 28.0, 14.3 ppm (*minor rotamer). **FTIR** (neat): ν 2976.9, 1698.6, 1476.8, 1453.3, 1206.2, 1147.1, 1042.4, 844.9, 754.7 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calctd for $C_{19}H_{30}N_4O_6Na$: 433.2058; Found: 433.2063. **$[\alpha]_D^{25}$** = -20.6 (c 0.1 in $CHCl_3$).

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)(phenyl)methanol (8h)[20]

Prepared according to the general procedure for CuAAC reactions using 1-phenylprop-2-yn-1-ol (0.139 g, 1.05 mmol) and benzyl azide (0.133 g, 1.0 mmol) to afford the desired product as a white solid (0.252 g, 95% yield). **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): 7.94 (s, 1H), 7.42 – 7.22 (m, 10H), 5.99 (d, *J* = 4.6 Hz, 1H), 5.83 (d, *J* = 4.6 Hz, 1H), 5.55 (s, 2H) ppm. **^{13}C NMR** (126 MHz, $(CD_3)_2SO$): δ 151.8, 144.0, 136.1, 128.7, 128.1, 128.0, 128.0, 127.0, 126.3, 122.1, 68.0, 52.7 ppm.

4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)aniline (8i)[21]

Prepared according to the general procedure for CuAAC reactions as indicated in Table 3 using 4-ethynylaniline (0.123 g, 1.05 mmol) and benzyl azide (0.133 g, 1.0 mmol) to afford the desired product as a white solid (0.185 g, 74% yield). It was also prepared according to the general procedure for tandem azide formation and CuAAC reaction under microwave irradiation, as indicated in Table 4 using sodium azide (0.091 g, 1.4 mmol), benzyl bromide (0.205 g, 1.2 mmol) and 4-ethynylaniline (0.117 g, 1.0 mmol) to afford the desired product as a white solid (0.127 g, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): 7.60 (d, J = 8.5 Hz, 2H), 7.52 (s, 1H), 7.36 – 7.29 (m, 5H), 6.62 (d, *J* = 8.6 Hz, 2H), 5.58 (s, 2H), 3.76 (br-s, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 134.9, 129.1, 128.7, 128.0, 126.9, 121.1, 118.2, 115.2, 54.1 ppm.

(4-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)phenyl)methanol (8j)[22]

Prepared according to the general procedure for CuAAC reactions using (4-ethynylphenyl)methanol (0.139 g, 1.05 mmol) and benzyl azide (0.133 g, 1.0 mmol) to afford the desired product as a white solid (0.212 g, 80% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): 7.78 (d, J = 8.5 Hz, 2H), 7.65 (s, 1H), 7.40 – 7.31 (m, 7H), 5.57 (s, 2H), 4.70 (s, 2H), 1.90 (t, J = 4.7 Hz, 1H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 148.0, 140.9, 134.6, 129.8, 129.2, 128.8, 128.1, 127.4, 125.8, 119.4, 65.0, 54.2 ppm.

(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl acetate (8k)[23]

Prepared according to the general procedure for CuAAC reactions using prop-2-yn-1-yl acetate (0.102 g, 1.05 mmol) and benzyl azide (0.133 g, 1.0 mmol) to afford the desired product as a colorless oil (0.229 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.39 – 7.27 (m, 5H), 5.52 (s, 2H), 5.18 (s, 2H), 2.05 (s, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 170.5, 142.9, 134.2, 128.8, 128.5, 127.9, 123.4, 57.3, 53.9, 20.6 ppm.

1-Phenethyl-4-phenyl-1*H*-1,2,3-triazole (8l)[18]

Prepared according to the general procedure for CuAAC reactions using ethynylbenzene (0.107 g, 1.05 mmol) and (2-azidoethyl)benzene (0.147 g, 1.0 mmol) to afford the desired product as a white solid (0.247 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.5 Hz, 2H), 7.46 (s, 1H), 7.42 – 7.27 (m, 6H), 7.14 – 7.13 (m, 2H), 4.63 (t, J = 4.7, 2H), 3.25 (t, J = 4.6, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 147.5, 137.1, 128.8, 128.7, 128.7, 128.1, 127.1, 125.7, 119.9, 51.7, 36.8 ppm.

Ethyl 1-phenethyl-1*H*-1,2,3-triazole-4-carboxylate (8m)

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.103 g, 1.05 mmol) and (2-azidoethyl)benzene (0.147 g, 1.0 mmol) to afford the desired product as a white solid (0.228 g, 93% yield). **mp** : 64 – 66 ºC **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.32 - 7.18 (m, 3H), 7.09 – 7.08 (m, 2H), 4.64 (t, *J* = 7.2 Hz, 2H), 4.40 (q, *J* = 6.0 Hz, 2H), 3.23 (t, *J* =7.2 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.6, 139.9, 136.3, 128.8, 128.5, 127.6, 127.2, 61.1, 51.9, 36.4, 26.8, 14.2 ppm. **FTIR (ATR)** (neat): ν 3084, 2973, 1724, 1526, 1201, 1050, 1027, 695 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M]^+$ calctd for $C_{13}H_{16}N_3O_2$: 246.1237; Found: 246.1238. **Elemental analysis:** Found (calcd. for $C_{13}H_{15}N_3O_2$): C, 63.71 (63.66); H, 6.15 (6.16); N, 17.19 (17.12).

4-Octyl-1-phenyl-1*H*-1,2,3-triazole (8n)[24]

Prepared according to the general procedure for CuAAC reactions using ethynylbenzene (0.107 g, 1.05 mmol) and octyl azide (0.155 g, 1.0 mmol) to afford the desired product as a white solid (0.255 g, 99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.84 – 7.83 (m, 2H), 7.74 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 4.39 (t, *J* = 7.3 Hz, 2H), 2.01 – 1.90 (m, 2H), 1.35 – 1.26 (m, 10H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 147.7, 130.7, 128.8, 128.0, 125.7, 119.3, 50.4, 31.7, 30.4, 29.0, 29.0, 26.5, 22.6, 14.0 ppm.

Ethyl 1-octyl-1*H*-1,2,3-triazole-4-carboxylate (8o)[11]

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.103 g, 1.05 mmol) and octyl azide (0.155 g, 1.0 mmol) to afford the desired product as a white solid (0.251 g, 99% yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.07 (s, 1H), 4.45 – 4.39 (m, 4H), 1.94 – 1.90 (m, 2H), 1.42 (t, *J* = 7.1, 3H), 1.31 – 1.28 (m, 10H), 0.88 (t, *J* = 7.1 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.9, 140.5, 127.2, 61.3, 50.7, 31.6, 30.1, 29.0, 28.8, 28.8, 26.3, 22.5, 14.3, 14.0 ppm.

Triethyl 1,1',1''-((2,4,6-triethylbenzene-1,3,5-triyl)tris-(methylene))tris(1*H*-1,2,3-triazole-4-carboxylate) (8p)

Prepared according to the general procedure for CuAAC reactions using ethyl propiolate (0.309 g, 3.15 mmol) and 1,3,5-tris(azidomethyl)-2,4,6-triethyl-benzene (0.327 g, 1.0 mmol) to afford the desired product as thick oil (0.615 g, 99% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.85 (s, 3H), 5.73 (s, 6H), 4.40 (q, *J* = 7.1 Hz, 6H), 2.77 (q, *J* = 7.5 Hz, 6H), 1.39 (t, *J* = 7.1 Hz, 9H), 0.99 (t, *J* = 7.5 Hz, 9H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 160.5, 146.8, 140.4, 129.9, 129.7, 61.4, 48.1, 23.6, 15.3, 14.2 ppm. **FTIR** (neat): ν 3127, 2978, 1720, 1539, 1449, 1375, 1337, 1197, 1036, 840, 772 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calctd for $C_{30}H_{39}N_9O_6Na$: 644.2916; Found: 644.2919.

2,2',2''-(1,1',1''-((2,4,6-Triethylbenzene-1,3,5-triyl)tris-(methylene))tris(1*H*-1,2,3-triazole-4,1-diyl))tris(propan-2-ol) (8q)

Prepared according to the general procedure for CuAAC reactions using 2-methylbut-3-yn-2-ol (0.267 g, 3.15 mmol) and 1,3,5-tris(azidomethyl)-2,4,6-triethyl-benzene (0.327 g, 1.0 mmol) to afford the desired product as a white solid (0.463 g, 80% yield). **mp**: 208 – 209 ºC. **^{1}H NMR** (400 MHz, $(CD_3)_2SO$): 7.66 (s, 3H), 5.60 (s, 6H), 5.09 (s, 6H), 2.84 (q, J = 7.4 Hz, 6H), 1.41 (s, 18H), 0.76 (t, J = 7.4 Hz, 9H) ppm. **^{13}C NMR** (126 MHz, $(CD_3)_2SO$): δ 156.0, 145.5, 130.1, 120.1, 67.2, 47.3, 30.7, 22.9, 14.8 ppm. **FTIR (ATR)** (neat): ν 3328, 2973, 1456, 1370, 1166, 1041, 957 cm^{-1}. **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ calctd for $C_{30}H_{45}N_9O_3Na$: 602.3538; Found: 602.3554.

1-(4-Nitrobenzyl)-4-phenyl-1*H*-1,2,3-triazole (8r)[17]

Prepared according to the general procedure for tandem azide formation and CuAAC reaction under microwave irradiation, as indicated in Table 4. using sodium azide (0.091 g, 1.4 mmol), 1-(bromomethyl)-4-nitrobenzene (0.258 g, 1.2 mmol) and ethynylbenzene (0.102 g, 1.0 mmol) to afford the desired product as white solid (0.277 g, 99% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.6Hz, 2H), 7.81 (d, *J* = 7.2 Hz, 2H), 7.74 (s, 1H), 7.47 – 7.32 (m, 4H), 7.34 (t, *J* = 7.4Hz, 1H), 5.71 (s, 2H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 148.7, 148.0, 141.7, 130.1, 128.9, 128.5, 128.4, 125.7, 124.3, 119.7, 53.2 ppm.

(4-(1-(4-Nitrobenzyl)-1*H*-1,2,3-triazol-4-yl)phenyl)methanol (8s)[11]

Prepared according to the general procedure for tandem azide formation and CuAAC reaction under microwave irradiation, as indicated in Table 4. using sodium azide (0.091 g, 1.4 mmol), 1-(bromomethyl)-4-nitrobenzene (0.258 g, 1.2 mmol) and (4-ethynylphenyl)methanol (0.132 g, 1.0 mmol) to afford the desired product as white solid (0.307 g, 99% yield). **^{1}H NMR** (400 MHZ, CD_3OD): δ 8.39 (s, 1H), 8.25 (d, *J* = 8.6Hz, 2H), 7.79 (d, *J* = 8 Hz, 2H), 7.55 (d, *J* = 8 Hz, 2H), 7.42 (d, *J* = 8 Hz, 2H), 5.80 (s, 2H), 4.63 (s, 2H), 4.56 (s, 1H) ppm. **^{13}C NMR** (126 MHz, CD_3OD): δ 149.4, 144.1,143.3, 130.6, 130.1, 128.6, 126.8, 125.2, 124.9, 122.7, 64.9, 54.1 ppm.

1-Octyl-4-((phenylthio)methyl)-1*H*-1,2,3-triazole (8t)[11]

Prepared according to the general procedure for tandem azide formation and CuAAC reaction under microwave irradiation, as indicated in Table 4. using sodium azide (0.091 g, 1.4 mmol), octyl bromide (0.230 g, 1.2 mmol) and phenyl(prop-2-yn-1-yl)sulfane (0.148 g, 1.0 mmol) to afford the desired product as white solid (0.164 g, 54% yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.34 – 7.25 (m, 5H), 7.20-7.17 (m, 1H), 4.28 – 4.24 (m, 4H), 1.84 – 1.81 (m, 2H), 1.25 (m, 10H), 0.88 (t, *J* = 7.02 Hz, 3H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 144.9, 135.5, 129.5, 128.9, 126.4, 121.2, 99.9, 50.3, 31.7, 30.2, 29.0, 28.9, 28.9, 26.4, 22.6, 14.0 ppm.

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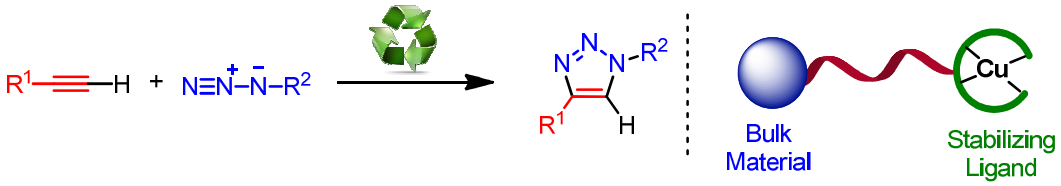
2.3. POLYMER SUPPORTED TRIS(TRIAZOLYL)METHANOL LIGANDS FOR COPPER(I)-CATALYZED AZIDE-ALKYNE CYCLOADDITION

2.3.1. HETEROGENEOUS CuAAC CATALYSTS

Due to the importance and impact of CuAAC reaction, developing a system towards non-toxic, colorless final products and suppressing the costly copper/ligand catalysts is an intersting goal yet to be achieved. There are several reports in the literature using diverse approaches in heterogeneous catalysis: nanofiltration membranes, ligand bearing polymers, metal scavenging iron nanoparticles, copper tubing flow systems and much more.[1] Since our research group was interested in polymer-supported catalysis, an attempt in this direction was developed following the previous efforts (**Scheme 2.11**).



Scheme 2.11. Towards a heterogeneous copper-catalyst system for CuAAC reaction.

Early approaches to heterogeneous CuAAC reaction were done by immobilization of copper(I) species onto Amberlyst A-21.[2] The system was a dimethylaminomethyl grafted PS/DVB resin where the tertiary amine group acted as a ligand and base. However, the system was leaching copper out of the limit of practical concerns, which represents dead end for the nature of heterogeneous catalysis. When this system was adapted to flow conditions, another column for a copper scavenger was required and the leaching was responsible for the decreased activity of the catalyst-packed column over time.[3]

Other examples focused on various Merrifield resins with quaternary ammonium salts even though catalysts were prone to leaching. In the best case, the catalyst was recycled up to ten times with sustained catalytic activity.[4] A more recent example of an imidazolium derived Merrifield resin was much less active.[5]

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Fokin and Kina installed a tris(benzyltriazolylmethyl)amine (TBTA)[6] and terpyridine ligand,[7] respectively, onto a Tentagel resin instead of a Merrifield resin. The design of these catalysts stems from the fact that Tentagel swells much better in a wider range of solvents and the ligands are known to be more active than in previous cases. Preparation of TBTA was more tedious than simple amines used before but it worked at low copper loadings up to ten cycles with longer reaction times (**Figure 2.4**).

There were other approaches using tailored polymer synthesis for polymer supported CuAAC catalysts, overall with limited applicability. A method using phenylalkynylcopper(I) ladder polymers showed some potential but it was limited to use of microwave heating for successful transformations.[8]

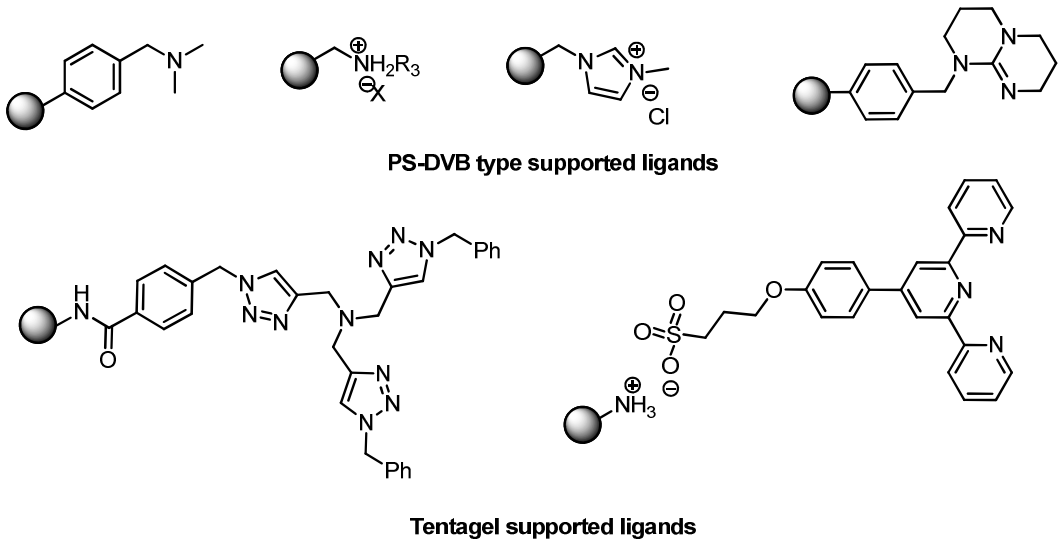

Figure 2.4. General polymer supported ligand/polymer systems.

Another strategy has been the use of biopolymers as supports for cuprous species. Polysaccharides have been particularly investigated since they are readily available from nature in large amounts, they contain different functional groups to link catalyst systems and are biodegradable. In the first example, the carboxylate groups of alginate were subjected to complexation with copper(II) species (catalytically active copper(I) species generated via reduction by other functional groups on the polymer backbone). Even though acceptable results were obtained in the test reaction conditions, the scope was limited for polar compounds due to leaching of copper.[9] Later, in a similar approach, chitosan was modified via imine formation to install a different ligand to its backbone. The results were highly substrate dependent, albeit various systems could be easily

[6] Chan, T. R.; Fokin, V. V. *QSAR Comb. Sci.* **2007**, *26*, 1274.
[7] Suzuka, T.; Ooshiro, K.; Kina, K. y. *Heterocycles* **2010**, *81*.
[8] Buckley, B. R.; Dann, S. E.; Harris, D. P.; Heaney, H.; Stubbs, E. C. *Chem. Commun.* **2010**, *46*, 2274.
[9] Reddy, K. R.; Rajgopal, K.; Kantam, M. L. *Catal. Lett.* **2007**, *114*, 36.

generated.[10] Finally, cross-linked chitosan derivatives prepared by using hexamethylenediisocyanate made possible repeating urea moiety for the complexation of copper(I) species and they turned out to be the most successful approach in all polysaccharide backbones with high activity and scope.[11] In general, biodegradable backbones are interesting because the catalyst loadings are generally quite low, although such bio-molecules are not chemically inert.

Other carbon-based bulk materials tested as supports for CuAAC reaction have been charcoal, activated carbon and carbon nanotubes. A copper-charcoal matrix was developed and the reaction took place at room temperature but slowly.[12] Microwave irradiation greatly reduced the time of the reaction. However, once more, recycling was not optimal due to copper leaching. The system was extended to the use of continuous flow operation and to avoid copper in the final product an additional copper scavenger step/column was necessary. In another example, copper nanoparticles on activated carbon were prepared with very good conversion and activity.[13] However, centrifugal separation was necessary and it generated problems in isolation and recycling procedures. In the same direction, modified multi-walled carbon nanotubes were used to immobilize copper species.[14] High catalytic activity in water was obtained. Nevertheless, separation techniques were based on centrifugation and decantation, which renders the process impractical.

For inorganic solid supports, most of the time, silica was used to immobilize some amine bearing ligands parallel to polymer supported ligands. In all cases, no further improvements were possible to the polymeric systems and in addition, these systems are more laborious in preparation.[15] Moreover, silica coated iron oxide particles were not successful in CuAAC reaction. Other inorganic supports have been developed with alumina, titanium dioxide and zeolites in combination with different copper species. However, none of them improved the results of polymer supported systems either requiring harsh reaction conditions and/or having higher amount of leaching and/or limited recyclability (**Figure 2.5**).

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[10] Chtchigrovsky, M.; Primo, A.; Gonzalez, P.; Molvinger, K.; Robitzer, M.; Quignard, F.; Taran, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5916.
[11] Martina, K.; Leonhardt, S. E. S.; Ondruschka, B.; Curini, M.; Binello, A.; Cravotto, G. *J. Mol. Catal. A: Chem.* **2011**, *334*, 60.
[12] Lipshutz, B. H.; Taft, B. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 8235.
[13] Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Adv. Synth. Catal.* **2010**, *352*, 3208.
[14] Sharghi, H.; Beyzavi, M. H.; Safavi, A.; Doroodmand, M. M.; Khalifeh, R. *Adv. Synth. Catal.* **2009**, *351*, 2391.
[15] (a) Li, P.; Wang, L.; Zhang, Y. *Tetrahedron* **2008**, *64*, 10825. (b) Miao, T.; Wang, L. *Synthesis* **2008**, *2008*, 363. (c) Coelho, A.; Diz, P.; Caamaño, O.; Sotelo, E. *Adv. Synth. Catal.* **2010**, *352*, 1179 (d) Shamim, T.; Paul, S. *Catal. Lett.* **2010**, *136*, 260.

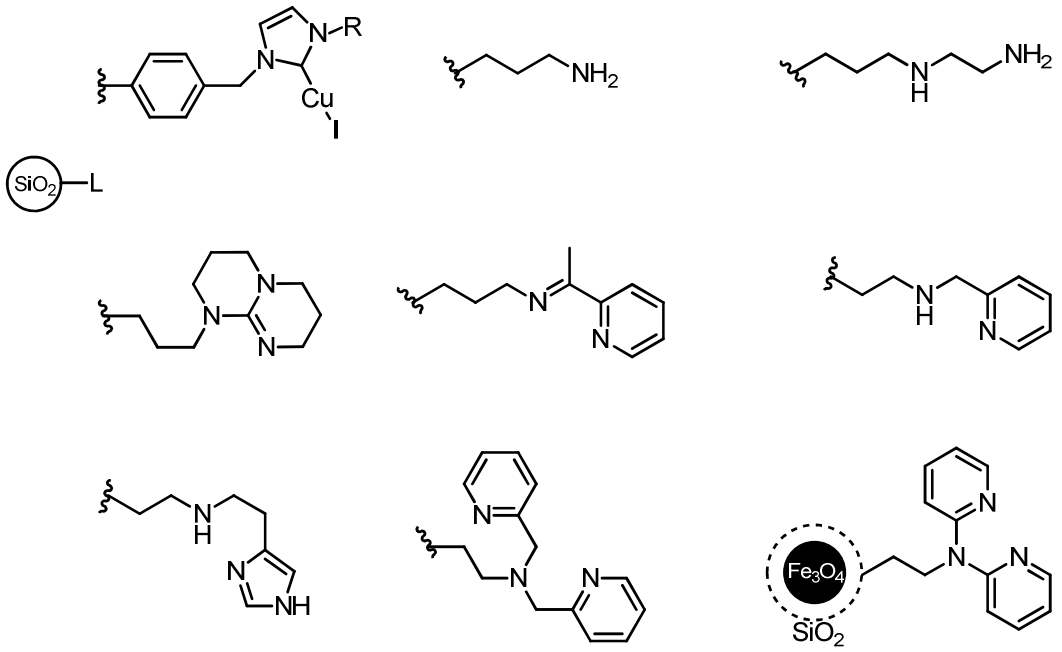

Figure 2.5. Silica and silica coated magnetic nanoparticle supported ligands.

Furthermore, *in situ* oxidized elemental copper sources were also investigated as heterogeneous copper(I) species. Interestingly, copper wire can be used to catalyze the reaction but either a sacrificial oxidizer/stabilizer or very high reaction temperatures with laborious experimental set-ups were necessary.[16]

Finally, the most interesting application of a heterogeneous copper source was the use of a copper-coated AFM tip. By the ability of controlling the movement of the catalytic species with the tip, a surface modified with azide groups can be *clicked* very precisely to generate different patterns of interest via "direct-writing coupling of molecules" with CuAAC reaction.[17]

In summary, despite all the developments, the generation of an optimal heterogeneous catalytic system for CuAAC reaction remains unmet. Even though almost all of the immobilization strategies were investigated, high catalyst loadings, harsh reaction conditions, long reaction times, or metal leaching limit the use of each individual system. One of the systems should be chosen depending on the requirements and applications. The limitation and complexity of satisfactory heterogeneous systems are mostly because the cycloaddition product also complexates with copper species and the leaching of the system is very hard to avoid.

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[17] Paxton, W. F.; Spruell, J. M.; Stoddart, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 6692.

PAPER C

Covalently Immobilized Tris(Triazolyl)Methanol–Cu(I) Complexes: Highly Active and Recyclable Catalysts for CuAAC Reactions

Catal. Sci. Technol., **2012**, *2*, 195-200

Publication Date (Web): 27 Oct 2011

PAPER C - The experimental work on the synthesis of polymer-supported ligand via azido-Merrifield resin and recycling attempt of this derivative in CuAAC reaction were performed by Dr. Salih Özçubukçu in Prof. M. A. Pericàs Group at ICIQ.

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PAPER

Covalently immobilized tris(triazolyl)methanol–Cu(I) complexes: highly active and recyclable catalysts for CuAAC reactions†

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Tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol (**3**), a highly efficient ligand for CuAAC reactions, has been immobilized onto Merrifield resins through different strategies. The S_N2-supported Cu complex (**8**) is stable in water and under air; it is active at low catalyst loadings (1 mol%) and at low concentration (down to 0.125 M) in both aqueous and purely organic media. Resin **8** can be repeatedly reused in 1 : 1 MeOH–water for short reaction times (4 h) with the only precaution of Cu(I) reloading every five cycles.

Introduction

The concept of click chemistry[1] is closely linked to the development of the almost universally applicable copper-catalyzed alkyne–azide cycloaddition (CuAAC).[2,3] Applications of this reaction span from materials science to biological systems, including medicinal chemistry and drug discovery.[4,5] If a criticism can be made to the original CuAAC procedures, it would be related to the fact that fairly high amounts of copper catalyst must be used. This can lead to product contamination, which is unacceptable in electronics, or can lead to toxicity in biomedical applications.[5] To overcome this problem, ligand stabilized Cu(I) species have been developed. In particular, tris(triazoles),[6,7] tetramines,[8] and *N*-heterocyclic carbenes[9] have been successfully used under ambient conditions and at very low catalyst loadings.

The covalent immobilization of such Cu(I) complexes onto solid supports adds further advantages, since catalyst separation can be achieved by simple filtration with an according reduction in copper contamination of reaction products, and (in principle) the catalyst can be recycled and reused with a subsequent improvement of the sustainable characteristics of the overall process.[10]

Up to now, however, the known covalently immobilized catalysts for CuAAC reactions have involved rather lengthy preparations,[10a–e] or have made use of commercial functional polymers involving polyamino appends. In these cases, catalytic use involves either over-stoichiometric amounts of catalytic resin (2 equiv.),[10f] or high copper loadings.[10g] We wish to report herein the development of a readily available and highly active polymer-supported catalyst for CuAAC reactions, whose immobilization takes advantage from the design of the corresponding homogeneous ligand.[7,11]

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1cy00297j

Results and discussion

Determination of the optimal supporting strategy

Complex **1** (Fig. 1), developed as a catalyst for CuAAC reactions,[7] exhibits a notable stability even in the presence of free amino groups in the reacting molecules and has proved to be particularly efficient to catalyze CuAAC reactions on polymers.[12] The free hydroxyl group present in its structure, arising from the Grignard approach used for its synthesis, offers a good opportunity for polymer supporting. Moreover, according to the topology of the system, the supporting process should not perturb the catalytic function of the assembly.

In our initial approach, the CuAAC reaction was selected for the supporting process through the intermediacy of an *O*-propargyl derivative. Thus, treatment of tris(triazole) **3** with

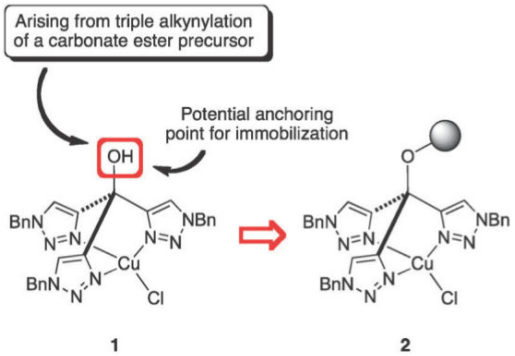
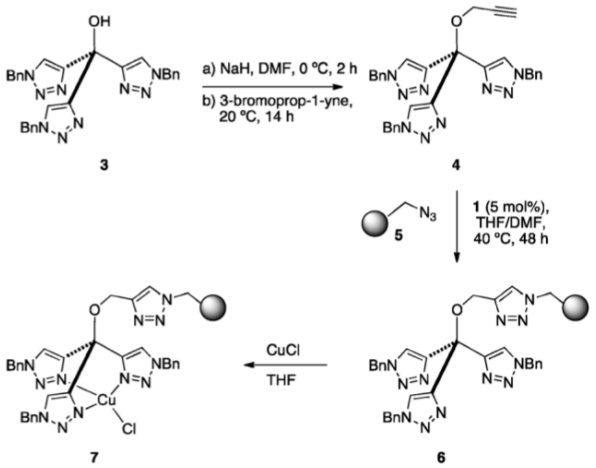


Fig. 1 Immobilization strategy for complex **1**, using a hydroxy group resulting from the synthetic design of the homogeneous ligand.

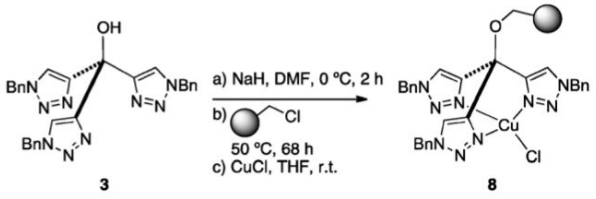


Scheme 1 Synthesis of the immobilized tris(triazolyl)methanol copper(I) complex **7**.

NaH in DMF at 0 °C and reaction with propargyl bromide (Scheme 1) afforded **4** in good yield (82%). For polymer supporting, the commercially available Merrifield resin (1% DVB; f = 1.1 mmol g^{-1}) was first converted to azide **5** by treatment with sodium azide. The CuAAC reaction between **4** and **5** was performed in THF : DMF (1 : 1) at 40 °C for 48 h (IR monitoring) in the presence of 5 mol% of complex **1**.[7] The resulting functional resin **6** (f = 0.56 mmol g^{-1}) was finally converted to its Cu(I) complex **7** by shaking with a stoichiometric amount of CuCl in THF at rt for 15 h.

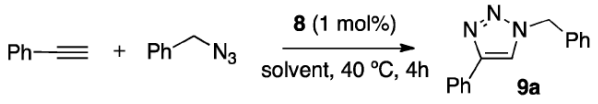
To our delight, when the CuAAC reaction between benzyl azide and phenylacetylene was performed in the presence of 1 mol% of **7** in water at 40 °C, the desired 1,2,3-triazole was obtained in 94% yield after only 3 h. However, when the direct recycling of **7** was attempted, a significant decrease in its catalytic activity was observed. On the other hand, **7** could be recycled and reused for 5 times without any loss of activity with the simple precaution of a short re-conditioning with CuCl in THF after each cycle. This behavior was indicative of Cu leaching from resin **7**, possibly arising from a less geometrically favourable coordination of copper (in addition to the one depicted in Scheme 1) involving the participation of the additional triazole unit present on the linker.

To circumvent this difficulty, a second-generation supported catalyst **8** lacking the triazole linker (Scheme 2) was prepared by alkylation of a Merrifield resin (1% DVB; f = 1.1 mmol g^{-1}) with **3** and complexation with CuCl (1.05 eq). From the elemental analysis of the intermediate metal-free resin, a functionalization f = 0.46 mmol g^{-1} can be calculated for **8**.



Scheme 2 Synthesis of the copper(I) complex of polymer-supported tris(triazolyl)methanol **8**.

Table 1 Solvent screening and recyclability of resin **8**



		Yield[a] (%)				
Entry	Solvent	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
1	H_2O	90	85	15[b]	86[c]	90
2	THF : H_2O (1 : 1)	85	7[b]	79[c]	—	—
3	THF	80	5[b]	50[c]	—	—
4	Toluene[d]	87	—	—	—	—
5	CH_2Cl_2[e]	86	—	—	—	—
6	EtOAc[d]	90	—	—	—	—
7[f]	MeOH : H_2O (1 : 1)	99	99	96	95	79[g]
8[f,h]	MeOH : H_2O (1 : 1)	99	96	94	95	65

[a] Isolated yield. [b] Yield determined by ^{1}H NMR. [c] After resin re-conditioning with CuCl. [d] Complete conversion required 16 h at 40 °C. [e] Complete conversion required 16 h at rt. [f] All yields determined by average of two independent runs. [g] Conversion was complete in 6 h. Isolated yield was 95%. [h] Reactions performed at rt for 8 h.

Optimization of reaction conditions for use in catalysis and recycling of resin 8

Using as a test the reaction of phenylacetylene with benzyl azide, a variety of solvents were screened both for exploring their suitability as reaction media and for determining the limits of recyclability of **8** (Table 1). Unless otherwise specified, the reactions were performed at 40 °C for 4 h.

The catalytic resin **8** performed well in water, but became deactivated after the 2nd run (entry 1); as expected, catalytic activity was fully recovered when the polymer was reconditioned with CuCl (see cycles 4 and 5 in entry 1). A 1 : 1 THF–water mixture (entry 2) or THF alone (entry 3) gave promising results but, again, inter-cycle reconditioning was required. Other organic solvents were also tested (entries 4–6). In all these media, the cycloaddition took place at a lower reaction rate, requiring 16 h for complete conversion. Finally, a 1 : 1 methanol–water mixture was revealed to be the optimal solvent for the reaction (entries 7 and 8). Under these conditions, very high catalytic activity was recorded for four consecutive runs, whereas a slight decrease in yield was observed in the fifth one when the standard reaction time (4 h) was maintained. In fact, conversion for cycle #5 was complete in 6 h (95% yield). It is worth noting here that other covalently supported ligands for CuAAC for whom recycling data are available require, at identical catalyst loading (1%), reaction cycles of 24[10a,10e] or 48 h.[10d] In view of practical application, the achievement of complete conversion in short reaction times is very important. For this reason, we decided to introduce a reconditioning treatment after the fifth cycle. Thus, the sample of **8** used in the five cycles in entry 7 was treated with CuCl and used for five additional cycles, where a completely parallel activity pattern was observed (mean yield for cycles 6 to 10: 92%). After a second reconditioning with CuCl, the yield in cycle 11 was still 91%. Another set of experiments in 1 : 1 methanol–water was performed at room temperature, with 8 h as the reaction time for individual runs (entry 8). The behavior of **8** under these conditions almost exactly reproduced that recorded at 40 °C; slight de-activation

became apparent after the fourth cycle, and reactivation with CuCl led to a complete recovery of catalytic activity.

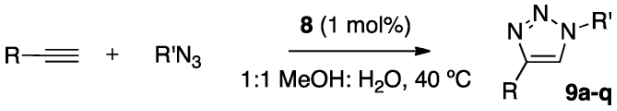
To discard the possibility that the polymeric network could simply act as a copper chloride trap, and that catalysis was simply due to CuCl slowly released into solution, a control experiment was performed by treating a Merrifield resin (1% DVB; $f = 1.1$ mmol g^{-1}) with a large excess (5.0 eq.) of CuCl and using this resin to promote the CuAAC reaction between phenylacetylene and benzyl azide. For comparison purposes, the amount of Merrifield resin/CuCl mixture employed in catalytic experiments corresponded to the weight of **8** used in experiments performed at the same scale. As anticipated, and in spite of its much higher copper content, the Merrifield resin/CuCl mixture behaved as a rather poor catalyst in comparison with **8**. For reactions conducted at 40 °C for 4 h, conversion was 22% in the first cycle, and only 10% in the second one. When the Merrifield resin was mixed with 1.05 eq. CuCl, to mimic in a more realistic manner the copper content of **8**, conversion in the model CuAAC reaction was <5% after 4 h at 40 °C. These results are a clear indication that polymer-bound complex **8** is the actual catalytic species in the process.

Scope of applicability of resin 8

The applicability of the supported catalyst **8** was next explored under the optimized conditions (MeOH : water 1 : 1, 40 °C, 1 mol% catalyst loading). The results have been summarized in Table 2.

Reaction of benzyl azide with several acetylenic alcohols yielded the expected products **9b–e** in high yields (entries 2–5) and short reaction times. As indicated by the formation of **9f** (entry 6), the corresponding esters exhibit a similar behavior. Even propiolic acid, a normally difficult substrate for CuAAC, leads to triazole formation in high yield, although a longer reaction time is required (**9g**, entry 7). With respect to acetylenic amines, *N*,*N*-dimethylpropargylamine afforded the triazole product **9h** in very high yield (entry 8) and even substrates featuring free amino groups, like 4-aminophenylacetylene (entry 9) or a propargyloxypyrrolidine derivative (entry 10), that represent more stringent tests for the reaction given the known tendency of free amino groups to form Cu(I) complexes with deactivation of the catalyst, lead to the corresponding cycloadducts **9i** and **9j** in high yield. The CuAAC reaction of aliphatic alkynes (exemplified by 1-octyne) worked equally well, but required somewhat longer reaction times (16 h) for complete conversion (entries 11 and 13). The reaction with other alkyl azides also took place uneventfully, as seen in entries 12–14. As a particular case, the reaction leading to **9n** (entry 14) was performed in a tandem manner from 1-bromooctane, sodium azide, and phenyl propargyl thioether under microwave irradiation at 100 °C. Under these conditions, triazole **9n** could be isolated in 60% yield after one hour reaction time. Aryl azides were also tested (entries 15 and 16), the corresponding triazoles **9o** and **9p** being obtained in excellent yields after short reaction times. Finally, functional azides and functional alkynes could be combined for the preparation of difunctional triazoles, as in the example of entry 17. The formation of **9q**, which involved the tandem assembly of the azide and the CuAAC reaction in essentially quantitative yield illustrates this possibility.

Table 2 CuAAC reactions catalyzed by **8**[a]



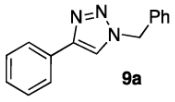
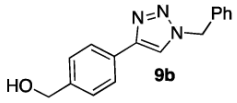
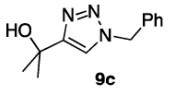
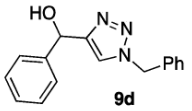
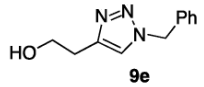
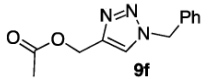
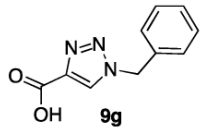
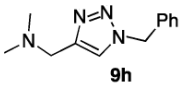
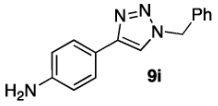
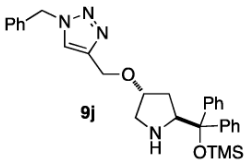
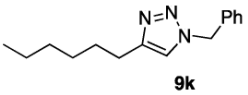
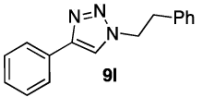
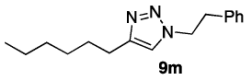
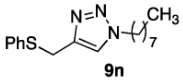
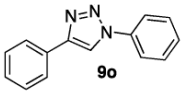
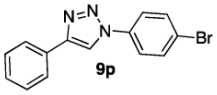
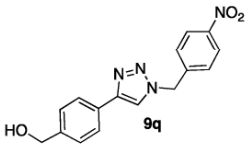
Entry	Product	Time/h	Yield[b] (%)
1	 **9a**	4	99
2	 **9b**	4	98
3	 **9c**	4	98
4	 **9d**	5	99
5	 **9e**	6	99 (94)[c]
6	 **9f**	5	99
7	 **9g**	18	92
8	 **9h**	5	93 (95)[c]
9	 **9i**	6	91[d]
10	 **9j**	4	96
11	 **9k**	16	97
12	 **9l**	5	99

Table 2 (*continued*)

Entry	Product	Time/h	Yield[b] (%)
13	 **9m**	16	99
14	 **9n**	1	60[e,f]
15	 **9o**	5	95
16	 **9p**	5	94
17	 **9q**	8	99[f]

[a] Samples of **8** with loadings of 0.34 mmol g^{-1} and 0.46 mmol g^{-1} were indistinctly used in these experiments. [b] Isolated yield. [c] In water. [d] 3 mol% **8**, rt. [e] Microwave irradiation in *n*-BuOH : water 1 : 1 at 100 °C. [f] *In situ* formation of the azide from the corresponding bromide and sodium azide.

From a practical perspective, the use of **8** is simple and advantageous, allowing ample variation of reaction parameters. Reaction temperatures in the range 20–50 °C can be used at convenience, although in our hands 40 °C represents in most cases an optimal value. Reagent concentration can also be widely varied. While examples in Table 2 have been performed at *ca.* 0.5 M concentration, reactions at 0.125 M concentration worked equally well. As a general rule, examples in Table 2 showing complete conversion in <4 h[13] require 5 h at 0.125 M concentration for completion of the reaction. From the point of view of product isolation, the separation of the triazole products (**9**) from **8** is simply performed by addition of ethyl acetate (to dissolve **9**) and filtration (to recover **8**). After solvent removal *in vacuo*, the triazole products are generally isolated in pure form.[14]

The high recyclability exhibited by **8** (see above) is indicative of very reduced leaching of Cu into aqueous methanol solutions. This fact, together with the low catalyst loading required for reaction, suggested that copper contamination in triazoles **9** should be very low. To confirm this, the amount of copper present in crude triazole **9a** was repeatedly tested: several batches were analyzed by UV-Vis spectroscopy,[15] Cu concentration being in all cases below 250 ppm (mean value: 195 ppm). If required, the remaining Cu traces can be removed with Cu-scavenging resins.[16]

Conclusions

In summary, a tris(triazolyl)methanol ligand has been successfully immobilized in one step onto a polystyrene resin and converted into a Cu(I) complex. Probably due to the protecting cage formed around the metal center[6] and to its particular functional groups arrangement, catalyst **8** behaves as a very active promoter of the CuAAC reaction, as it has been demonstrated with a broad variety of substrates (including free amines and thioethers), and exhibits excellent recycling characteristics.

Experimental section

Synthesis of 3-[tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-propyne (4)

To a flame dried flask containing a suspension of NaH (80 mg, 60% in oil, 2.0 mmol) in DMF (2 mL), a solution of **3** (503 mg, 1.0 mmol) in DMF (2 mL) was added dropwise at 0 °C. After stirring for 2 h at room temperature, the suspension became a clean solution, which was cooled again to 0 °C. Then, a commercial solution of propargyl bromide in toluene (0.220 mL, 80% solution in toluene, 2.0 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 14 h. Water (10 mL) was added to the reaction mixture, which was then extracted with dichloromethane (3 × 10 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Traces of DMF were removed by dissolving the crude product in an ethyl acetate : hexane (4 : 1) mixture (40 mL) and washing the solution with water (3 × 20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to afford crude **4**, which was further purified by flash column chromatography using ethyl acetate as the eluent. The product was obtained as a thick orange oil (0.444 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 3H), 7.34–7.24 (m, 15H), 5.47 (s, 6H), 4.11 (d, J = 2.4 Hz, 2H), 2.05 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 134.3, 129.1, 128.7, 128.2, 124.7, 80.0, 73.6, 73.1, 54.2, 53.0; IR(ATR): 3293, 3147, 3089, 2983, 2244, 1536, 1496, 1266, 1042 cm^{-1}. HRMS calcd. for $C_{31}H_{27}N_9ONa$: 564.2236. Found: 564.2253 ($[M + Na]^+$).

Preparation of the first generation PS-supported catalyst 7

An azido-functionalized Merrifield resin (100 mg, f = 0.94 mmol g^{-1}) was added to a solution of **4** (510 mg, 0.94 mmol) in a 1 : 1 mixture of DMF : THF (5 mL). A sample of **7** (5.6 mg, 0.0094 mmol) was added to the mixture, and the system was shaken for 48 h at 40 °C. The progress of the reaction was monitored by IR spectroscopy, and the process was interrupted after the disappearance of the azide band around 2100 cm^{-1}. Solvents were separated by filtration for the recovery of excess **4**. The resulting resin was washed with water, THF and methanol, respectively, and then dried at 50 °C overnight. Functionalization (f = 0.56 mmol g^{-1}) was calculated at this point by elemental analysis of nitrogen (found: N 9.38%).[16] The functional resin was then suspended in THF (5 mL) and shaken for 15 h with CuCl (9.7 mg, 0.1 mmol) at room temperature. The resulting light-green resin was washed with THF, dried, and stored for use.

Preparation of the second generation PS-supported catalyst 8

To a flame dried flask containing a suspension of NaH (16.8 mg, 95%, 0.7 mmol, stored and weighed in a glove box)

in DMF (2 mL), a solution of **3**[7] (252 mg, 0.5 mmol) in DMF (2 mL) was added dropwise at 0 °C under N_2. After stirring for 2 h at room temperature, the suspension became a clean solution, which was cooled again to 0 °C and added *via* cannula to a pre-swollen sample (DMF, >30 min) of commercial Merrifield resin (1% DVB, 1.1 mmol g^{-1}; 0.327 g, 0.36 mmol) in DMF (4 mL). The reaction mixture was allowed to warm to room temperature, then heated to 50 °C and shaken at that temperature for 96 h. After the reaction mixture cooled down to room temperature, the resin was separated by vacuum filtration and successively washed with DMF–H_2O, H_2O, THF, THF–MeOH (1 : 1), MeOH, and THF. The resulting polymer was dried in a vacuum drying oven at 40 °C overnight. The functionalization of the resin (f = 0.46 mmol g^{-1}) was calculated from the results of elemental analysis of nitrogen (found: N 5.76%).[17] A mixture of CuCl (8.4 mg, 0.084 mmol, 1.05 eq.) and the PS-supported tris(triazolyl)methoxy ligand (262 mg) in THF (10 mL) was shaken at room temperature for 16 h. The colour of the resin turned into green as the complexation proceeded. The CuCl-loaded resin was successively washed with THF (100 mL), H_2O (100 mL), and THF (100 mL), then dried overnight under vacuum and stored for use.

General procedure for CuAAC reaction catalyzed by 8

Preparation of 9a. To a vial containing phenylacetylene (107 mg, 1.05 mmol), benzyl azide (133 mg, 1.00 mmol), water (1 mL), and methanol (1 mL), catalyst **8** (22.5 mg, 0.01 mmol Cu) was added and the mixture shaken in an orbital shaker for 4 h at 40 °C. When TLC analysis revealed that the reaction was complete, the reaction mixture was diluted with ethyl acetate or dichloromethane (10 mL), and the resin was filtered-off and washed with EtOAc or CH_2Cl_2 (20 mL). The combined organic phases were dried, and solvents were removed by evaporation under reduced pressure to afford pure **9a** (232 mg, 99%). The resin was dried overnight under vacuum at 40 °C. In recycling experiments, it was used for the subsequent CuAAC reaction directly.

Reconditioning of resin 8 in recycling experiments

Whenever a catalyst sample used in recycling experiments showed decreased activity (*i.e.*; complete conversion was not achieved under the standard reaction conditions for the particular combination of reagents), the employed catalyst was separated by vacuum filtration at the end of the reaction, transferred to a vial and shaken overnight with 1 eq. of CuCl in THF at room temperature. Then, the catalytic resin was washed with excess THF, H_2O, and THF, and dried under vacuum at 40 °C. A full recovery of the original activity was observed in the next reaction cycle. For extended use of catalytic resin samples, it is convenient repeating the reconditioning process every five reaction cycles.

Analysis of the Cu content in triazole adducts

A modified version of the UV-VIS spectroscopic procedure of Brenner and Harris was used for the analyses.[14] For calibration, two solutions (A and B) have to be prepared. Solution A: a 100 mL aqueous solution of 120 μM bicinchoninic acid was prepared by adding bicinchoninic acid disodium salt hydrate (4.7 mg, 0.012 mmol) (BCA) and sodium ascorbate (39.6 mg , 0.2 mmol) (NaAsc) with 0.1 M sodium phosphate buffer at pH 7. Solution B: Solution A plus Cu(II)$SO_4 \cdot 5H_2O$ (1.5 mg, 0.006 mmol). The solutions were prepared separately. Different volumes of each solution A and B were mixed together to plot the calibration curve (see ESI†). For the determination of the Cu content in adducts **9**, the following representative procedure was followed: to a 5.00 mg sample of the triazole product to be controlled (separated by filtration and only submitted to evaporation of volatiles) in a vial, 5 mL of solution **A** were added and the mixture was vigorously stirred for 15 minutes at RT. Then, the resulting almost colourless solution was filtered through a HPLC filter to a quartz UV cuvette, and its measured absorbance at 354.5 nm was used for the calculation of the copper content either graphically or with the calibration equation.

Acknowledgements

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14 In no case the presence in the reaction product of the regioisomeric 1,5-disubstituted 1,2,3-triazoles as minor components could be detected by NMR.

15 Adapted from: (*a*) A. J. Brenner and E. D. Harris, *Anal. Biochem.*, 1995, **226**, 80; (*b*) A. J. Brenner and E. D. Harris, *Anal. Biochem.*, 1995, **230**, 360 (erratum).

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17 The degree of functionalization of a resin can be calculated from the results of elemental analysis with the formulas: $f_N = (0.714/n_N)\%N$, where n_N is the number of nitrogen atoms in the functional unit and %N is the percent of nitrogen provided by the elemental analysis. See: A. Bastero, D. Font and M. A. Pericàs, *J. Org. Chem.*, 2007, **72**, 2460.

Electronic Supplementary Information (ESI)

Covalently immobilized tris(triazolyl)methanol-Cu(I) complexes: Highly active and recyclable catalysts for CuAAC reactions.

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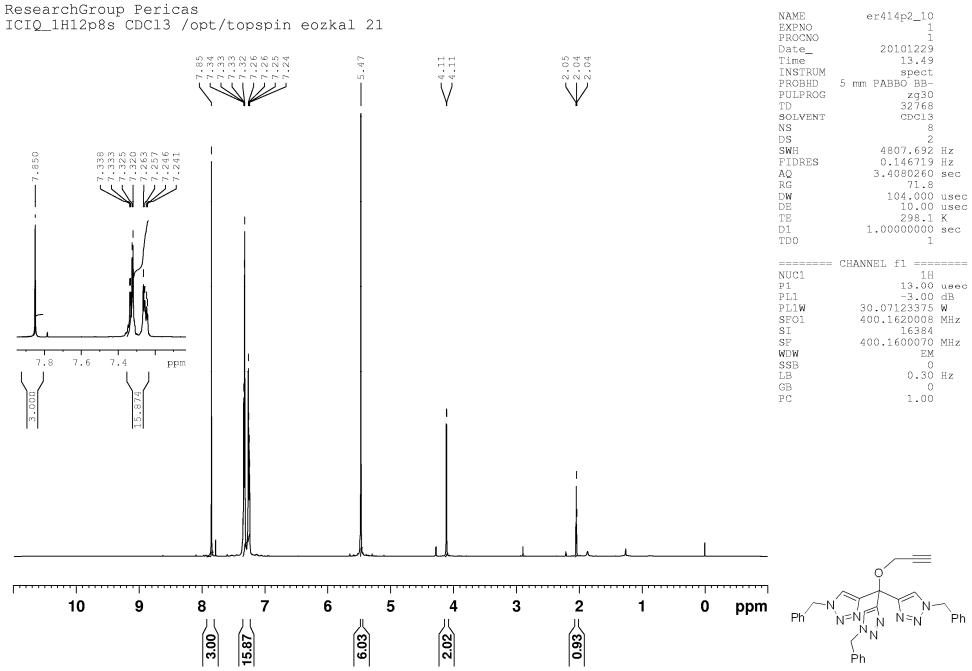
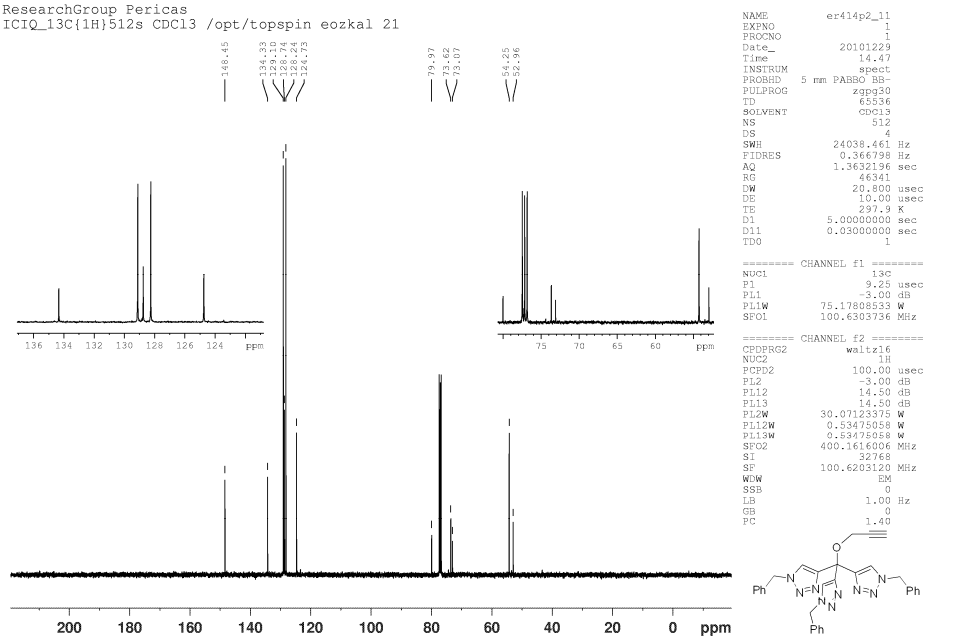
I. General Methods.

All reagents were used as purchased. All reported yields are isolated yields. CuAAC reactions were performed on vials at open air. Merrifield resin (1% DVB, f = 1.1 mmol Cl g^{-1} resin) was obtained from Novabiochem. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. ^{1}H (400.13 MHz) and ^{13}C (100.63 MHz) Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature (unless otherwise stated). Chemical shifts (δ) are reported with respect to tetramethylsilane as internal standard, or to the corresponding solvent residual peak, in ppm. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses made in C.A.I. Microanálisis Elemental, Universidad Complutense de Madrid (Spain). High Resolution Mass Spectra (HRMS) were performed by the High Resolution Mass Spectromety Service at the Institute of Chemical Research of Catalonia. UV spectra were recorded on a Shimadzu UV-1700 spectrophotometer. The optical rotation was recorded on Jasco P-1030 Polarimeter.

II. NMR spectra of 3-[tris(1-benzyl-1H-1,2,3-triazol-4-yl)methoxy]propyne (4).





III. General Procedure for Reconditioning of 8.

Whenever a catalyst sample used in recycling experiments showed decreased activity; the catalyst separated by vacuum filtration at the end of a reaction was transferred to a vial and shaken overnight with 1 eq. of CuCl in THF at room temperature. Then, the catalytic resin was washed with excess THF, H_2O, and THF, and dried under vacuum at 40 ºC. A full recovery of the original activity was observed in the next reaction cycle. For extended use of catalytic resin samples, it is convenient repeating the reconditioning process every five reaction cycles.

IV. Method for UV-Vis Analysis of Cu Content in Triazole 9a:

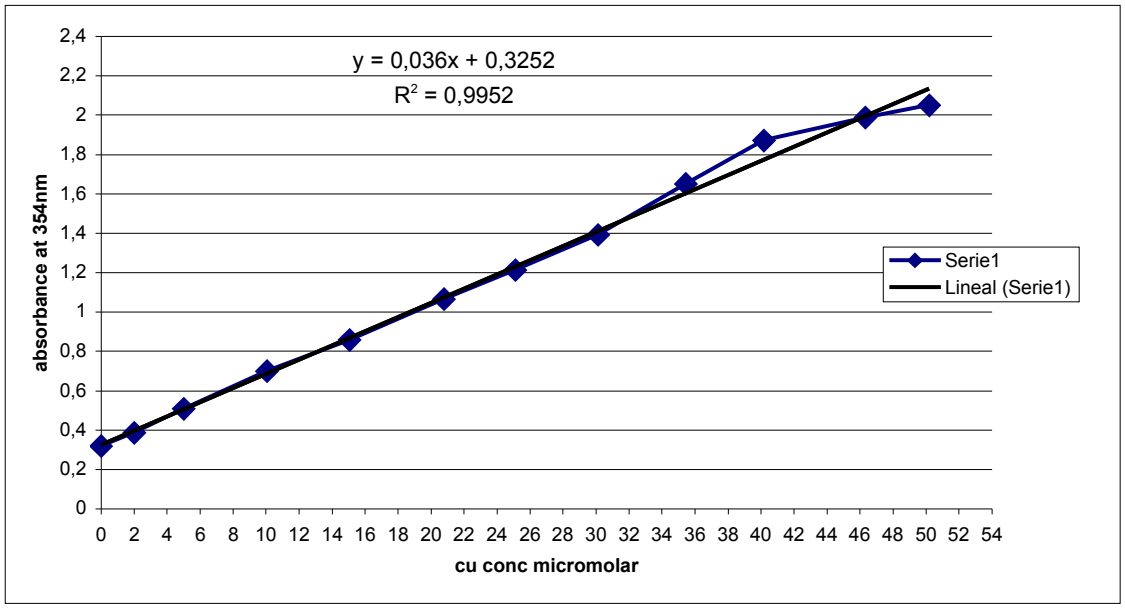
A modified version of the procedure of Brenner and Harris was used for the analyses.[i]

Solution A: A 100 mL aqueous solution of 120 µM bicinchoninic acid was prepared by adding bicinchoninic acid disodium salt hydrate (4.7 mg, 0.012 mmol) (BCA) and sodium ascorbate (39.6 mg ,0.2 mmol) (NaAsc) with 0.1 M sodium phosphate buffer at pH 7.

Solution B: Solution A plus $Cu(II)SO_4.5H_2O$ (1.5 mg, 0.006 mmol) was prepared, separately.

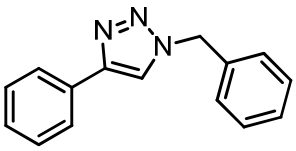
Different volumes of each solution A and B were mixed together to plot the calibration curve with respect to incremental increase in the amount copper. After this calibration, a modified version (see below) of the procedure described in the original paper was used for determination of copper content in the CuAAC reaction products.

Representative procedure for UV analysis: A 5 mg sample of the CuAAC reaction product to be controlled (only purified by filtration and evaporation of volatiles) was weighed in a vial and a 5 mL of solution **A** was added and it was stirred vigorously for 15 minutes at RT. Then, the almost colorless resulting solution was filtered through a HPLC filter to a quartz UV cuvette, and its measured absorbance at 354.5 nm was used for the calculation of the copper content either graphically or with the calibration equation.



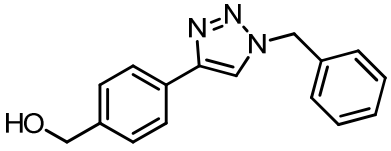
V. ^{1}H and ^{13}C NMR Data/Spectra of 1,2,3-triazoles.

1-benzyl-4-phenyl-1H-1,2,3-triazole (9a):



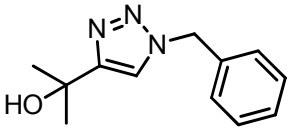
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.77 (m, 2H), 7.66 (s, 1H), 7.41 – 7.29 (m, 8H), 5.57 (s, 2H). **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): δ 147.2, 136.5, 131.2, 129.3, 129.2, 128.6, 128.3, 125.7, 122.0, 53.5. Spectroscopic data matched the literature[2].

(4-(1-benzyl-1H-1,2,3-triazol-4-yl)phenyl)methanol (9b):



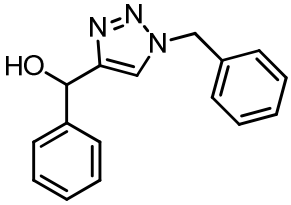
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.61 (s, 1H), 7.82 (s, 2H), 7.40 – 7.37 (m, 7H), 5.64 (s, 2H), 5.24 – 5.22 (m, 1H), 4.53 (s, 2H). **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): δ 147.2, 142.8, 136.5, 129.6, 129.3, 128.6, 128.4, 127.4, 125.4, 121.8, 63.1, 53.5. Spectroscopic data matched the literature[3].

2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-ol (9c):



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 7.25 – 7.15 (m, 5H), 5.36 (s, 2H), 4.09 (br, 1H), 1.51 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 156.3, 133.8, 129.0, 128.5, 128.0, 119.7, 69.4, 53.9, 30.5. Spectroscopic data matched the literature[4].

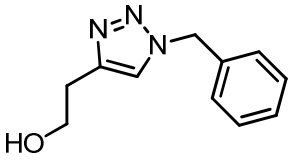
(1-benzyl-1H-1,2,3-triazol-4-yl)(phenyl)methanol (9d):



^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.95 (s, 1H), 7.43 – 7.25 (m, 10H), 5.99 (d, *J* = 4.6 Hz, 1H), 5.84 (d, *J* = 4.6 Hz, 1H), 5.56 (s, 2H).

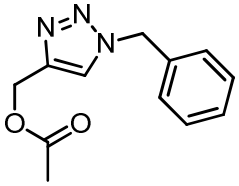
^{13}C NMR (100 MHz, $(CD_3)_2SO$): δ 152.3, 144.5, 136.6, 129.2, 128.6, 128.5, 128.5, 127.5, 126.8, 122.6, 68.5, 53.2. Spectroscopic data matched the literature[5].

2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethanol (9e):



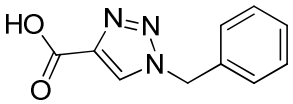
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.89 (s, 1H), 7.38 – 7.29 (m, 5H), 5.54 (s, 2H), 4.67 (t, *J* = 5.3 Hz, 1H), 3.62 (q, *J* = 6.3 Hz, 2H), 2.76 (t, *J* = 4.6 Hz, 2H). **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): δ 145.2, 136.7, 129.2, 128.5, 128.4, 123.0, 60.8, 53.1, 29.6. Spectroscopic data matched the literature[4].

(1-benzyl-1H-1,2,3-triazol-4-yl)methyl acetate (9f):



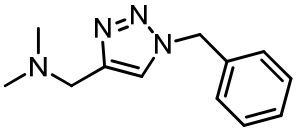
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.33 – 7.22 (m, 5H), 5.47 (s, 2H), 5.13 (s, 2H), 1.99 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.7, 143.1, 134.5, 129.1, 128.8, 128.1, 123.7, 57.6, 54.1, 20.8. Spectroscopic data matched the literature[6].

1-benzyl-1H-1,2,3-triazole-4-carboxylic acid (9g):



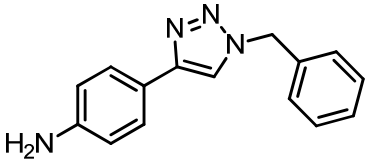
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.77 (s, 1H), 7.38 – 7.34 (m, 5H), 5.64 (s, 2H). Spectroscopic data matched the literature[7].

1-(1-benzyl-1H-1,2,3-triazol-4-yl)-N,N-dimethylmethanamine (9h):



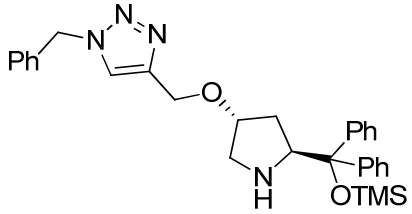
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.25-7.11 (m, 5H) 5.39 (s, 2H), 3.46 (s, 2H), 2.13 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.4, 134.8, 128.9, 128.5, 127.9, 122.5, 54.2, 53.9, 45.0. Spectroscopic data matched the literature[8].

4-(1-benzyl-1H-1,2,3-triazol-4-yl)aniline (9i):



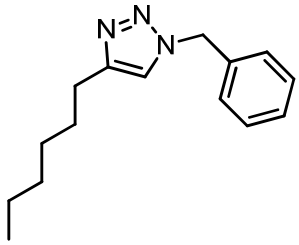
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 8.31 (s, 1H), 7.50 – 7.48 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.33 (m, 5H), 6.61 – 6.58 (d, *J* = 8.6 Hz, 2H), 5.58 (s, 2H), 5.22 (br, 2H). **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): δ 149.1, 136.7, 129.2, 128.5, 128.3, 126.6, 119.7, 118.8, 114.3, 53.3. Spectroscopic data matched the literature[9].

1-benzyl-4-((((3R,5S)-5-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidin-3-yl)oxy)methyl)-1H-1,2,3-triazole (9j):



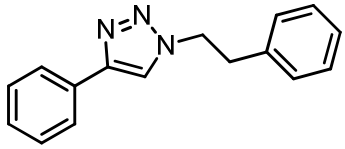
Physical form: thick orange oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.48-7.46 (d, *J* = 7.15 Hz, 2H), 7.38-7.23 (m, 13H), 5.51-5.50 (d, *J* = 2.20 Hz, 2H), 4.53 (d, *J* = 2.15 Hz, 2H), 4.44 (t, *J* = 8.03 Hz, 1H), 3.90 (brs, 1H), 3.08-3.06 (d, *J* = 11.60 Hz, 1H), 2.85-2.82 (dd, *J* = 11.90, 4.70 Hz, 1H), 1.82-1.81 (dd, *J* = 12.15 Hz, 2H), -0.078 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 145.6, 145.5, 134.6, 129.1, 128.7, 128.4, 128.1, 127.9, 127.8, 127.7, 127.3, 127.2, 122.7, 82.6, 78.8, 64.0, 62.5, 54.2, 52.2, 34.3, 2.16. **IR (ATR):** ν = 3306.02, 3054.07, 2953.28, 1592.51, 1404.37, 1343.21, 1131.95, 917.53. **HRMS** calculated for $C_{30}H_{36}N_4O_2SiNa$: 535.2505. Found: 535.2523 ($[M^+Na]^+$). $[\alpha]_D^{26}$ = -2.65 ± 0.693 (c=0.97 in $CHCl_3$).

1-benzyl-4-hexyl-1H-1,2,3-triazole (9k):



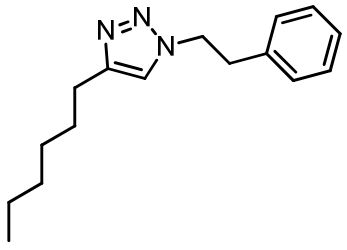
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 7.89 (s, 1H), 7.36 – 7.27 (m, 5H), 5.54 (s, 2H), 2.61 – 2.57 (t, *J* = 7.5 Hz, 2H), 1.59 – 1.55 (t, *J* = 6.8 Hz, 2H), 1.26 (s, 6H), 0.86 – 0.83 (t, *J* = 6.3 Hz, 3H). **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): δ 147.8, 136.8, 129.2, 128.5, 128.2, 122.4, 53.1, 31.4, 29.4, 28.7, 25.5, 22.5, 14.3. Spectroscopic data matched the literature[10].

1-phenethyl-4-phenyl-1H-1,2,3-triazole (9l):



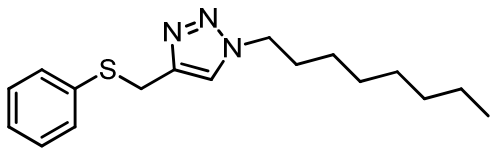
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 – 7.79 (d, *J* = 7.1 Hz, 2H), 7.51 (s, 1H), 7.43 – 7.15 (m, 8H), 4.65 – 4.62 (t, *J* = 7.3 Hz, 2H), 3.28 – 3.25 (t, *J* = 7.3 Hz, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 147.5, 137.1, 130.7, 128.9, 128.8, 128.7, 128.0, 127.1, 125.7, 120.0, 51.7, 36.8. Spectroscopic data matched the literature[4].

4-hexyl-1-phenethyl-1H-1,2,3-triazole (9m):



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 – 7.07 (m, 5H), 7.00 (s, 1H), 4.54 – 4.50 (t, *J* = 7.3 Hz, 2H), 3.18 – 3.15 (t, *J* = 7.3 Hz, 2H), 2.66 – 2.63 (t, *J* = 7.6 Hz, 2H), 1.63 – 1.56 (m, 2H), 1.31 – 1.26 (m, 6H), 0.89 – 0.85 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 148.1, 137.3, 128.7, 128.6, 126.9, 120.9, 51.4, 36.8, 31.6, 29.4, 28.8, 25.6, 22.6, 14.1. Spectroscopic data matched the literature[11].

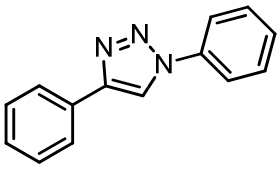
1-octyl-4-((phenylthio)methyl)-1H-1,2,3-triazole (9n)[1]:



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 – 7.14 (m, 6H), 4.24 – 4.19 (m, 4H), 1.80 – 1.77 (m, 2H), 1.22 (s, 10H), 0.87 – 0.84 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 144.7, 135.6, 129.5, 128.9, 126.4,

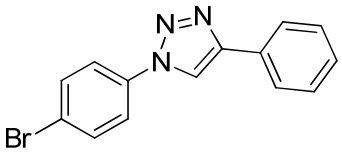
121.9, 50.3, 31.7, 30.2, 29.0, 28.9, 28.9, 26.4, 22.6, 14.1. Spectroscopic data matched the literature[8].

1,4-diphenyl-1H-1,2,3-triazole (9o):



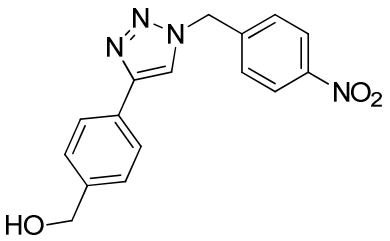
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.92 – 7.26 (m, 10H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 148.4, 137.1, 130.3, 129.8, 129.0, 128.8, 128.4, 125.9, 120.5, 117.6. Spectroscopic data matched the literature[5].

1-(4-bromophenyl)-4-phenyl-1H-1,2,3-triazole (9p):



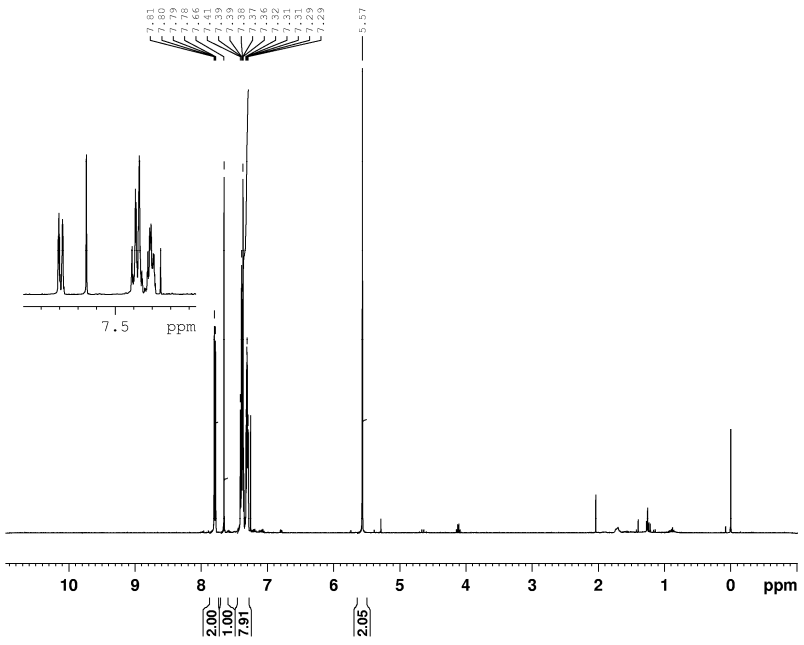
^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ 9.35 (s, 1H), 7.95 – 7.40 (m, 9H). Spectroscopic data matched the literature[7].

(4-(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)phenyl)methanol (9q):



^{1}H NMR (400 MHZ, CD_3OD): δ 8.37 (s, 1H), 7.94 (d, *J* = 8 Hz, 2H), 7.55 (d, *J* = 8 Hz, 2H), 7.29 (d, *J* = 8 Hz, 2H), 7.13 (d, *J* = 8 Hz, 2H), 5.55 (s, 2H), 5.05 (t, *J* = 4 Hz, 1H), 4.27 (d, *J* = 4 Hz ,1H). **^{13}C NMR** (100 MHz, $(CD_3)_2SO$): δ 147.3, 147.0, 143.4, 142.5, 129.1, 129.0, 127.1, 125.2, 124.0, 121.8, 62.8, 52.3. Spectroscopic data matched the literature[8].

er011p12

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PROCNO                  1
Date_            20090116
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INSTRUM             spect
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PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                      8
DS                      2
SWH              4789.272 Hz
FIDRES           0.146157 Hz
AQ               3.4210291 sec
RG                    128
DW                104.400 usec
DE                  6.00 usec
TE                298.0 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                   9.20 usec
PL1                 -4.00 dB
PL1W          37.85744095 W
SFO1          400.1320007 MHz
SI                  16384
SF            400.1300113 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00
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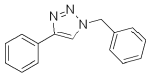
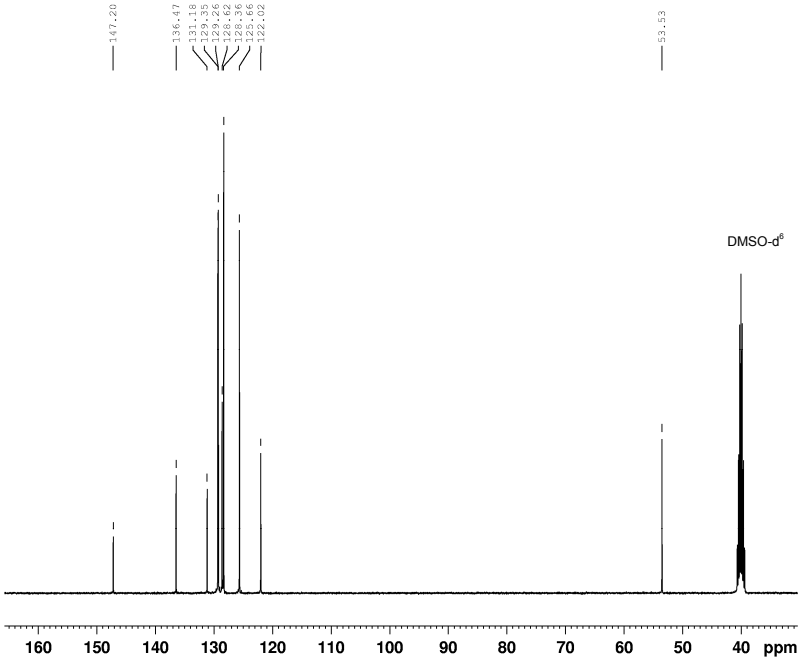


ResearchGroup Pericas
ICIQ_13C{1H}512s DMSO /opt/topspin eozkal 43

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PROCNO                  1
Date_            20101230
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INSTRUM             spect
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PULPROG            zgpg30
TD                  65536
SOLVENT             DMSO
NS                    512
DS                      4
SWH             23980.814 Hz
FIDRES           0.365918 Hz
AQ               1.3664756 sec
RG                 14596.5
DW                 20.850 usec
DE                  6.00 usec
TE                298.0 K
D1             5.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   13C
P1                   7.00 usec
PL1                 -5.00 dB
PL1W         119.14923859 W
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -4.00 dB
PL12                13.89 dB
PL13                13.89 dB
PL2W          37.85744095 W
PL12W          0.61539114 W
PL13W          0.61539114 W
SFO2          400.1316005 MHz
SI                  32768
SF            100.6127690 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
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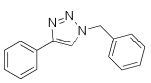
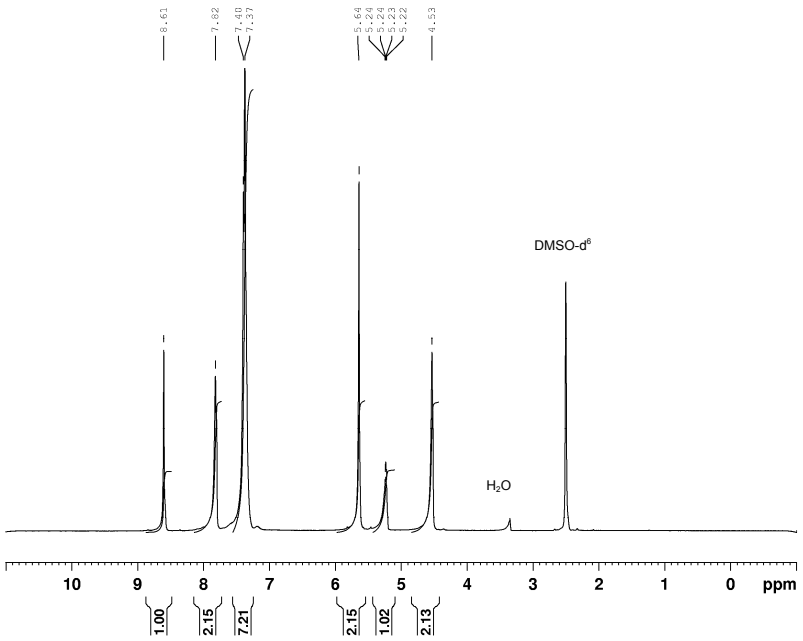


ResearchGroup Pericas
ICIQ_1H12p8s DMSO /opt/topspin eozkal 16

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PROCNO                  1
Date_            20101224
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PULPROG               zg30
TD                   32768
SOLVENT               DMSO
NS                       8
DS                       2
SWH              4807.692 Hz
FIDRES           0.146719 Hz
AQ               3.4080260 sec
RG                    40.3
DW                104.000 usec
DE                 10.00 usec
TE                 298.2 K
D1             1.00000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.00 usec
PL1                 -3.00 dB
PL1W         30.07123375 W
SFO1         400.1620008 MHz
SI                   16384
SF           400.1600000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
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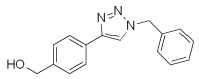
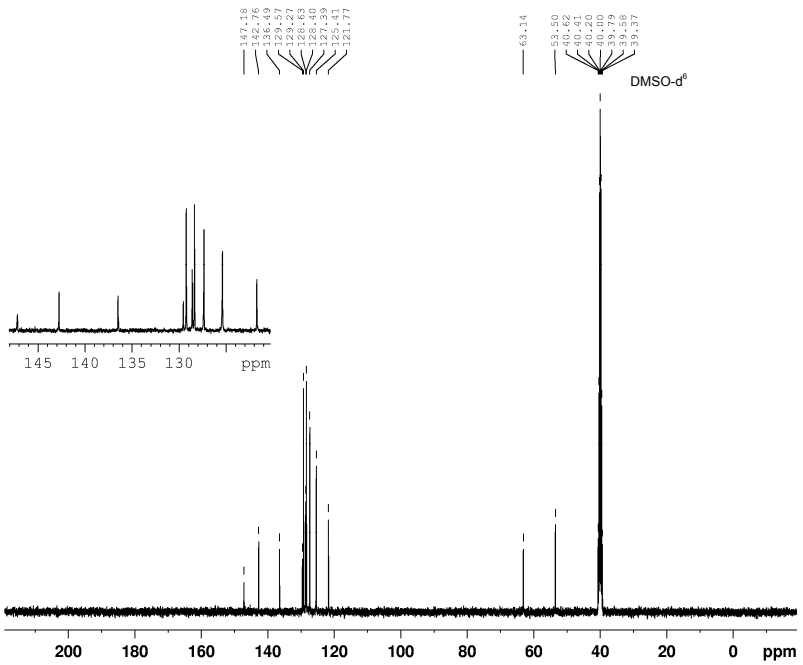


ResearchGroup Pericas
ICIQ_13C{1H}512s DMSO /opt/topspin eozkal 16




```
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EXPNO                   1
PROCNO                  1
Date_            20101224
Time                14.33
INSTRUM             spect
PROBHD    5 mm PABBO BB-
PULPROG            zgpg30
TD                   65536
SOLVENT               DMSO
NS                     512
DS                       4
SWH             24038.461 Hz
FIDRES           0.366798 Hz
AQ               1.3632196 sec
RG                   46341
DW                20.800 usec
DE                 10.00 usec
TE                 298.1 K
D1             5.00000000 sec
D11            0.03000000 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                  13C
P1                   9.25 usec
PL1                 -3.00 dB
PL1W         75.17808533 W
SFO1         100.6303736 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                 -3.00 dB
PL12                14.50 dB
PL13                14.50 dB
PL2W         30.07123375 W
PL12W         0.53475058 W
PL13W         0.53475058 W
SFO2         400.1616006 MHz
SI                   32768
SF           100.6203120 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
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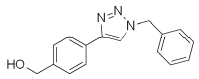

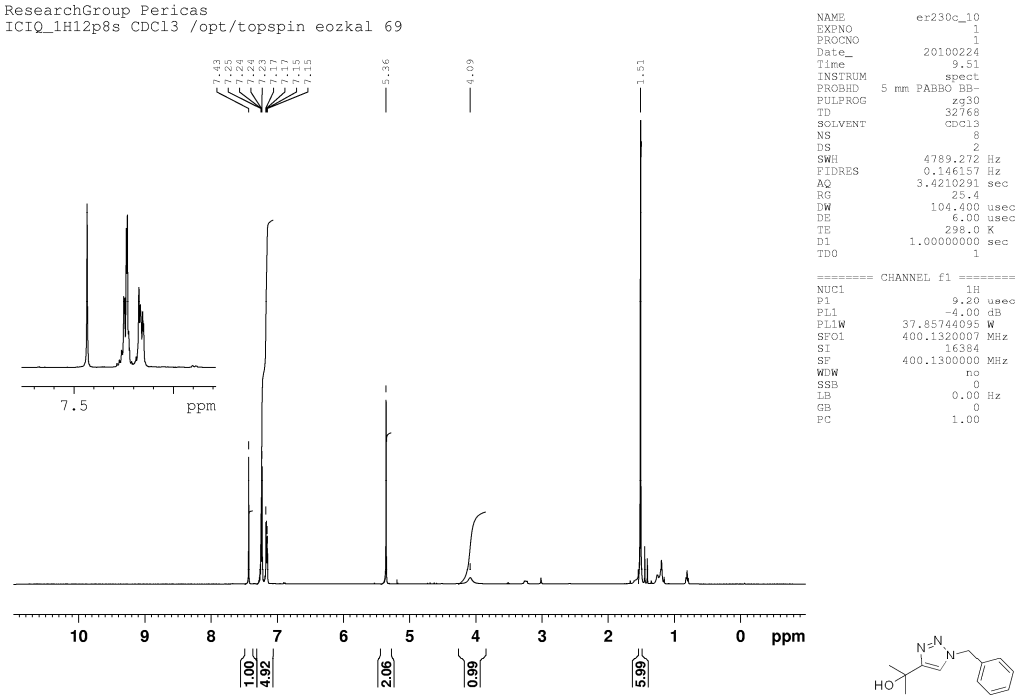
ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin eozkal 69
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7.24
7.23
7.17
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7.15
7.15
5.36
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7.5
ppm
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FIDRES 0.146157 Hz
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RG 25.4
DW 104.400 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
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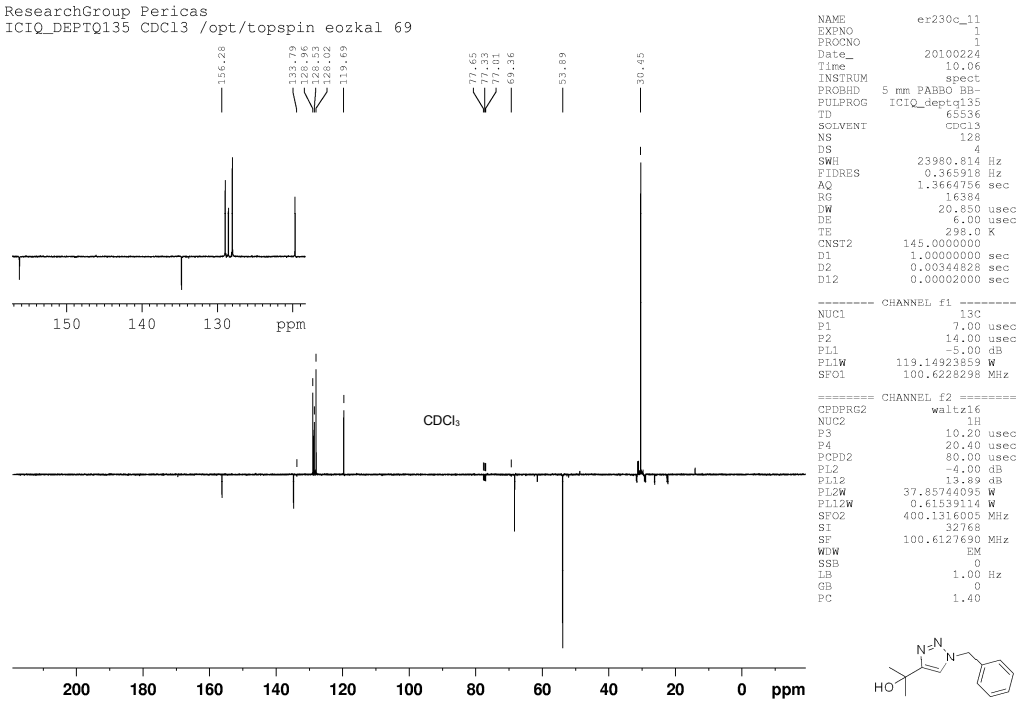
N
N
HO


ResearchGroup Pericas
ICIQ_DEPTQ135 CDCl3 /opt/topspin eozkal 69
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128.53
128.02
119.69
77.65
77.33
77.01
69.36
53.89
30.45
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CDCl3
200 180 160 140 120 100 80 60 40 20 0 ppm
NAME er230c_11
EXPNO 1
PROCNO 1
Date_ 20100224
Time 10.06
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TD 65536
SOLVENT CDCl3
NS 128
DS 4
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FIDRES 0.365918 Hz
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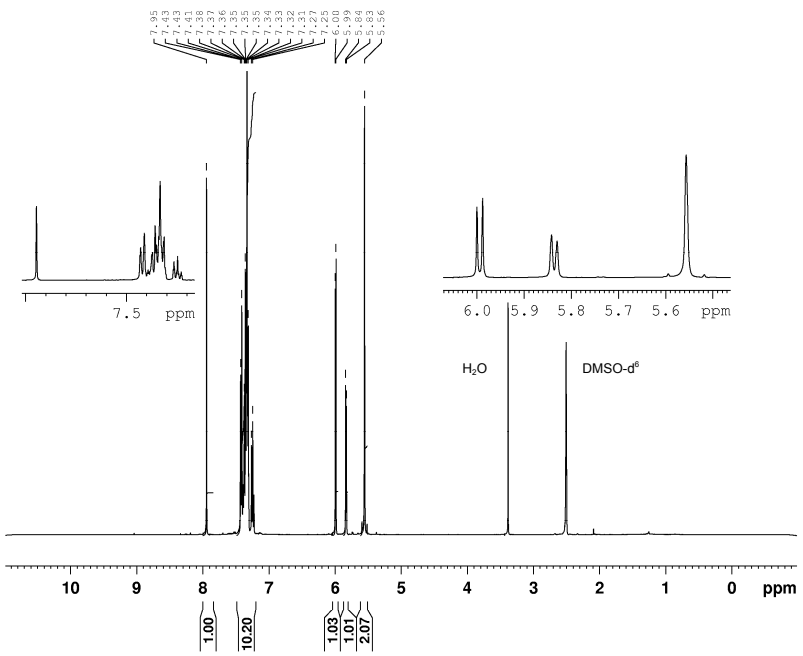
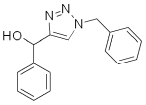
RG 16384
DW 20.850 usec
DE 6.00 usec
TE 298.0 K
CNST2 145.0000000
D1 1.00000000 sec
D2 0.00344828 sec
D12 0.00002000 sec
-------- CHANNEL f1 --------
NUC1 13C
P1 7.00 usec
P2 14.00 usec
PL1 -5.00 dB
PL1W 119.14923859 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
P3 10.20 usec
P4 20.40 usec
PCPD2 80.00 usec
PL2 -4.00 dB
PL12 13.89 dB
PL2W 37.85744095 W
PL12W 0.61539114 W
SFO2 400.1316005 MHz
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
N
N
N
HO

ResearchGroup Pericas
ICIQ_1H12p8s DMSO /opt/topspin eozkal 41



NAME	er231r2p2_10
EXPNO	1
PROCNO	1
Date_	20101229
Time	23.58
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	8
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	71.8
DW	104.400 usec
DE	6.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.20 usec
PL1	-4.00 dB
PL1W	37.85744095 W
SFO1	400.1320007 MHz
SI	16384
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00



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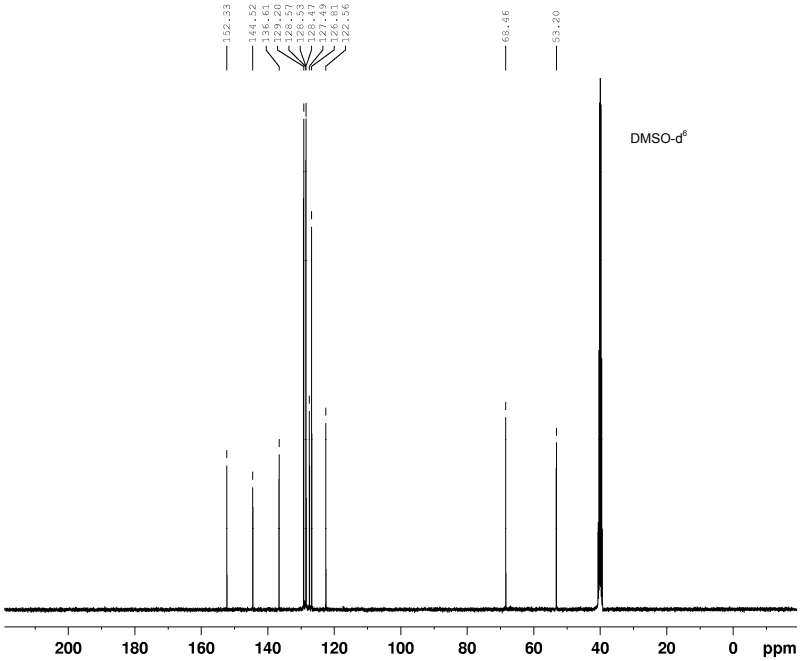
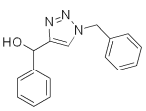
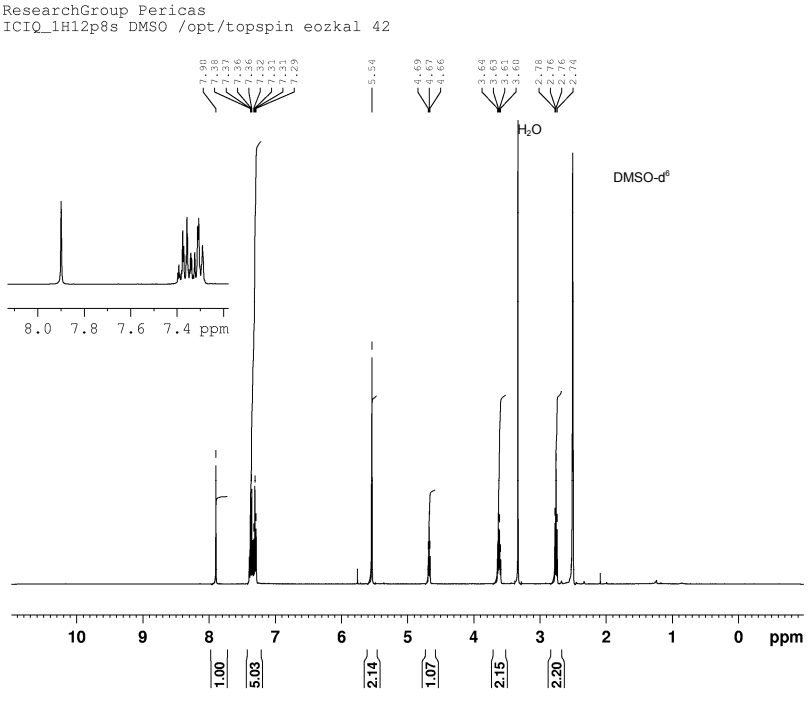
ICIQ_13C{1H}512s DMSO /opt/topspin eozkal 41



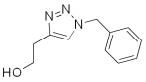
NAME	er231r2p2_11
EXPNO	1
PROCNO	1
Date_	20101230
Time	0.56
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	512
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	14596.5
DW	20.850 usec
DE	6.00 usec
TE	298.0 K
D1	5.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	7.00 usec
PL1	-5.00 dB
PL1W	119.14923859 W
SFO1	100.6228298 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-4.00 dB
PL12	13.89 dB
PL13	13.89 dB
PL2W	37.85744095 W
PL12W	0.61539114 W
PL13W	0.61539114 W
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

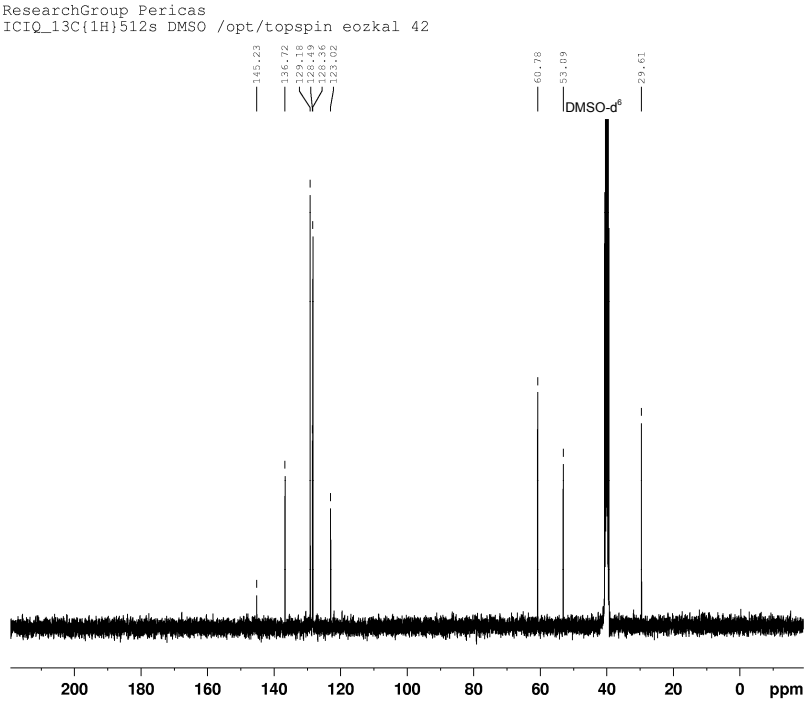




NAME er126r2p2_10
EXPNO 1
PROCNO 1
Date_ 20101230
Time 1.05
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 8
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 181
DW 104.400 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 9.20 usec
PL1 -4.00 dB
PL1W 37.85744095 W
SFO1 400.1320007 MHz
SI 16384
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

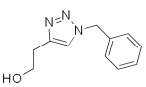




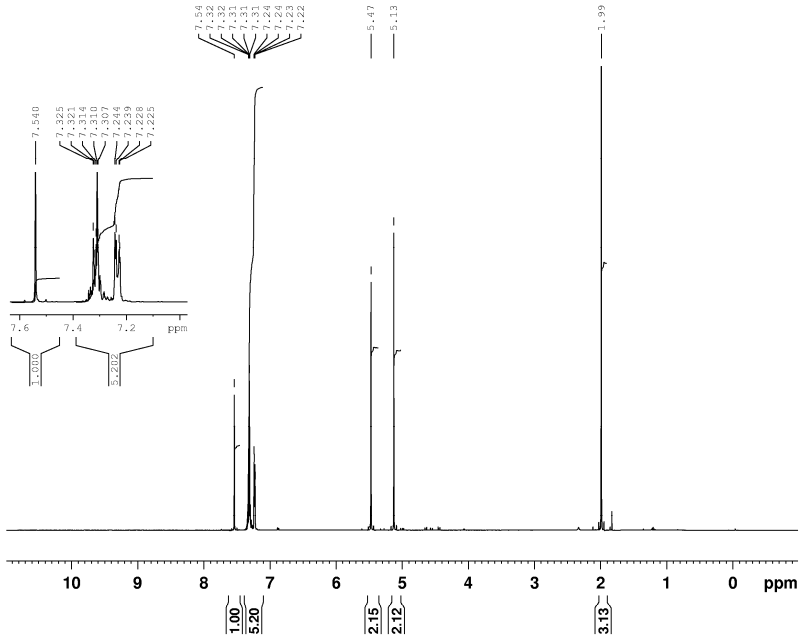
NAME er126r2p2_11
EXPNO 1
PROCNO 1
Date_ 20101230
Time 2.02
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 512
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 23170.5
DW 20.850 usec
DE 6.00 usec
TE 298.1 K
D1 5.00000000 sec
D11 0.03000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 13C
P1 7.00 usec
PL1 -5.00 dB
PL1W 119.14923859 W
SFO1 100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -4.00 dB
PL12 13.89 dB
PL13 13.89 dB
PL2W 37.85744095 W
PL12W 0.61539114 W
PL13W 0.61539114 W
SFO2 400.1316005 MHz
SI 32768
SF 100.6127690 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

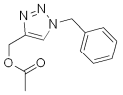


1H experiment

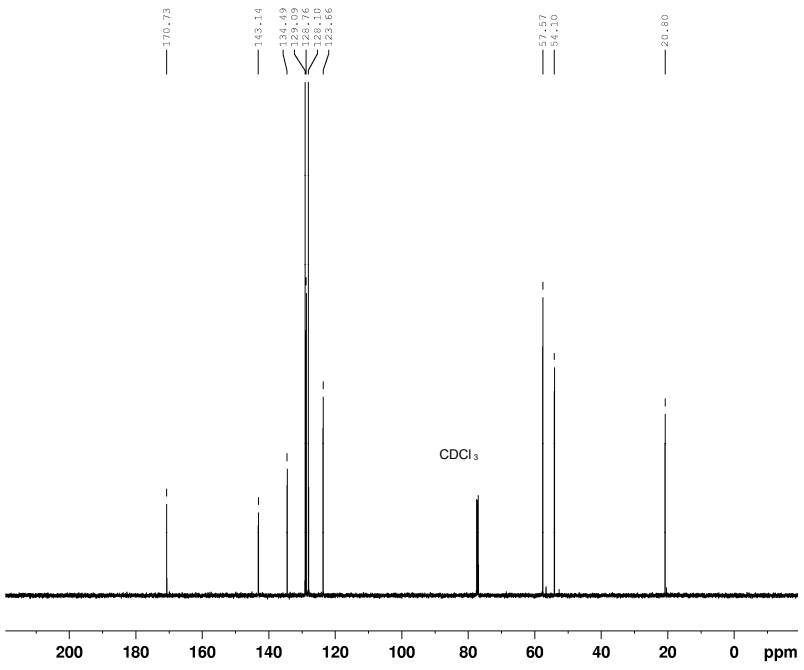



```
NAME          er264p_1_1
EXPNO                  1
PROCNO                 1
Date_           20100505
Time               11.26
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                     8
DS                     2
SWH             6009.615 Hz
FIDRES          0.183399 Hz
AQ              2.7264309 sec
RG                  28.5
DW                83.200 usec
DE                10.00 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.80 usec
PL1                 3.00 dB
PL1W         12.58925438 W
SFO1         500.1325007 MHz
SI                 16384
SF           500.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



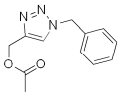
13C{1H} experiment




```
NAME          er264p_2_1
EXPNO                  1
PROCNO                 1
Date_           20100505
Time               11.33
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                    55
DS                     4
SWH            30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0814105 sec
RG                  1820
DW                16.500 usec
DE                10.00 usec
TE                298.1 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                  8.50 usec
PL1                 0.00 dB
PL1W         75.35659027 W
SFO1         125.7703648 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                 3.00 dB
PL12               18.14 dB
PL13               20.39 dB
PL2W         12.58925438 W
PL12W         0.38547841 W
PL13W         0.22961490 W
SFO2         500.1320005 MHz
SI                 32768
SF           125.7577890 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```



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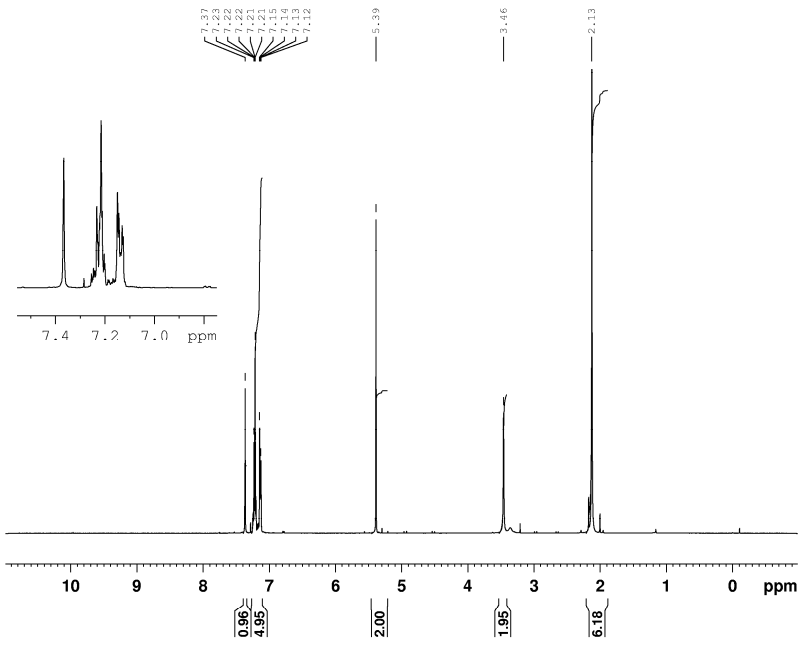
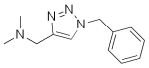


NAME	er124c_10
EXPNO	1
PROCNO	1
Date_	20090717
Time	19.59
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	8
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	32
DW	104.400 usec
DE	6.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	9.20 usec
PL1	-4.00 dB
PL1W	37.85744095 W
SFO1	400.1320007 MHz
SI	16384
SF	400.1300000 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



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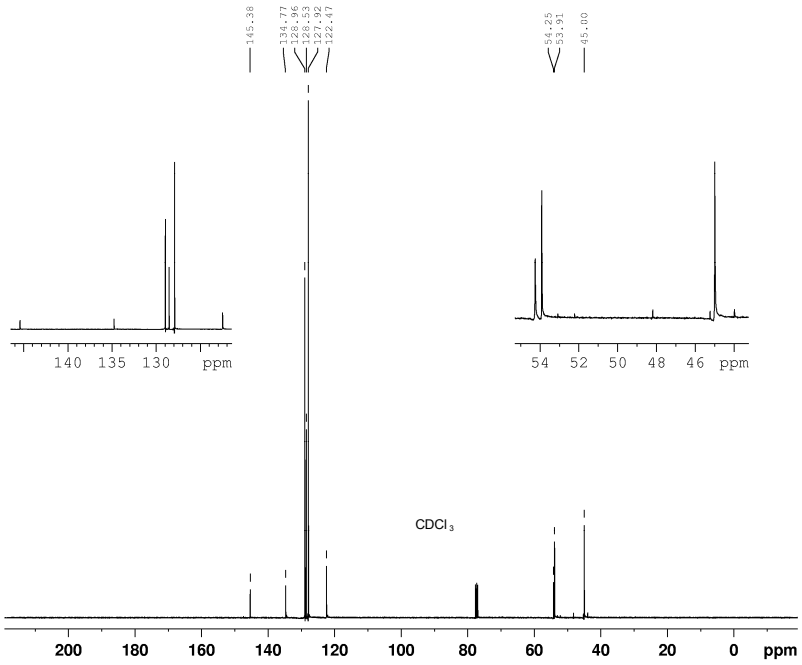
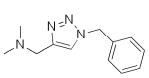
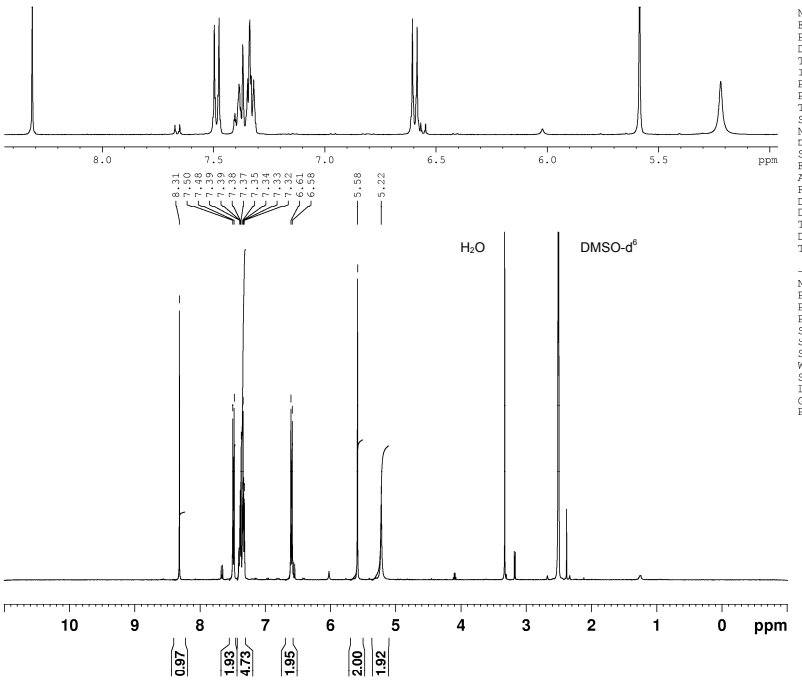
ICIQ_13C{1H}1024s CDCl3 /opt/topspin eozkal 27



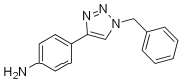
NAME	er124c_11
EXPNO	2
PROCNO	1
Date_	20090717
Time	20.55
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	1024
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	7298.2
DW	20.850 usec
DE	6.00 usec
TE	298.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	7.00 usec
PL1	-5.00 dB
PL1W	119.14923859 W
SFO1	100.6228298 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-4.00 dB
PL12	13.89 dB
PL13	13.89 dB
PL2W	37.85744095 W
PL12W	0.61539114 W
PL13W	0.61539114 W
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

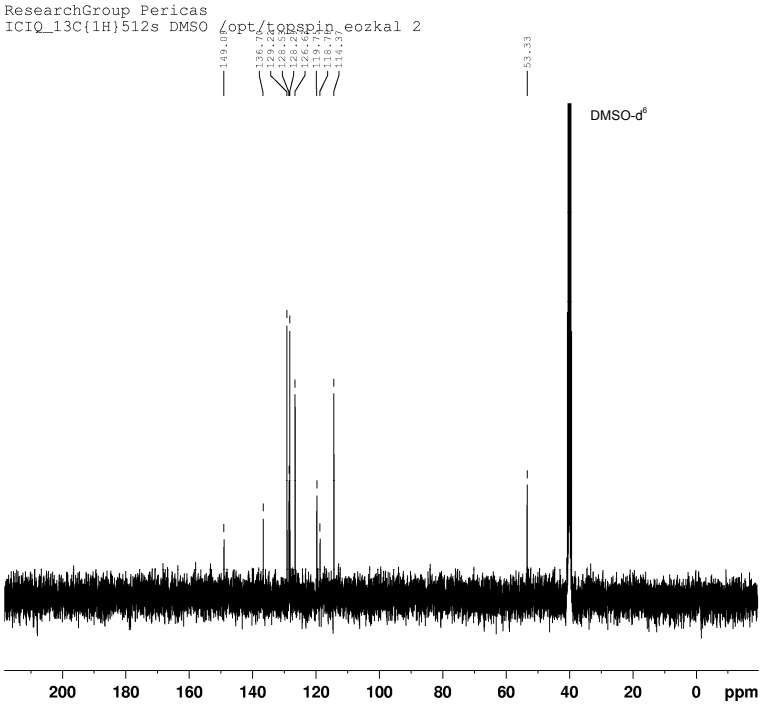





```
NAME            er413c_10
EXPNO                   1
PROCNO                  1
Date_            20101223
Time                10.54
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  32768
SOLVENT              DMSO
NS                      8
DS                      2
SWH              4807.692 Hz
FIDRES          0.146719 Hz
AQ              3.4080260 sec
RG                  322.5
DW                104.000 usec
DE                 10.00 usec
TE                 297.9 K
D1             1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  13.00 usec
PL1                 -3.00 dB
PL1W         30.07123375 W
SFO1         400.1620008 MHz
SI                  16384
SF           400.1600000 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
```

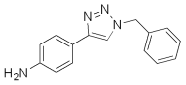





```
NAME            er413c_11
EXPNO                   1
PROCNO                  1
Date_            20101223
Time                11.18
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                  65536
SOLVENT              DMSO
NS                    512
DS                      4
SWH             24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.3632196 sec
RG                  46341
DW                20.800 usec
DE                 10.00 usec
TE                 298.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.25 usec
PL1                 -3.00 dB
PL1W         75.17808533 W
SFO1         100.6303736 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                 -3.00 dB
PL12                14.50 dB
PL13                14.50 dB
PL2W         30.07123375 W
PL12W         0.53475058 W
PL13W         0.53475058 W
SFO2         400.1616006 MHz
SI                  32768
SF           100.6203120 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```



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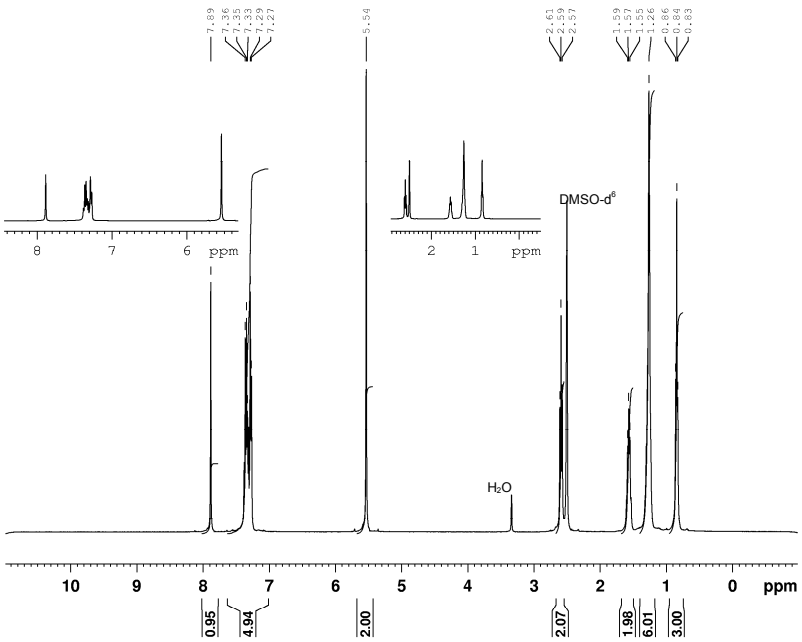
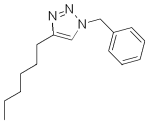
ICIQ_1H12p8s DMSO /opt/topspin eozkal 17

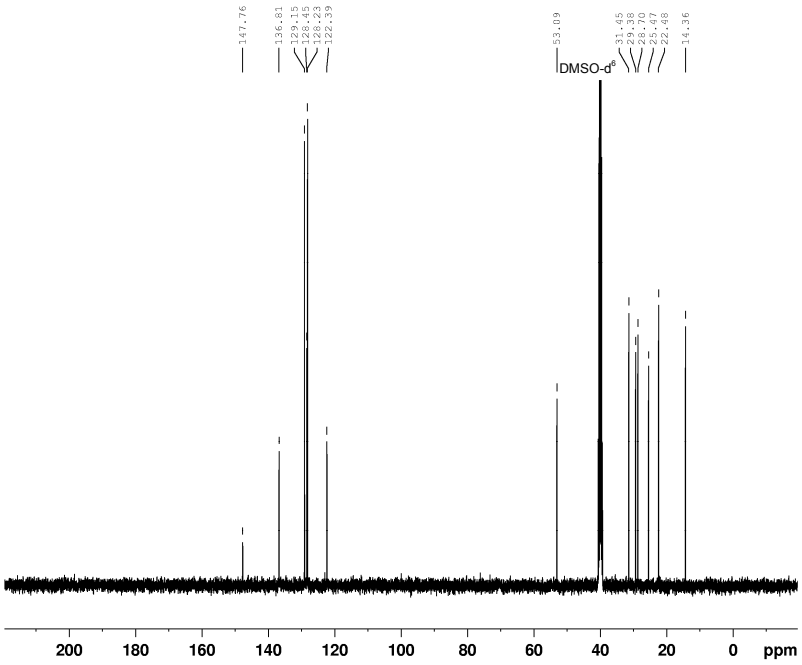



```
NAME            ersa4_10
EXPNO                  1
PROCNO                 1
Date_           20101224
Time               13.28
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG             zg30
TD                 32768
SOLVENT             DMSO
NS                     8
DS                     2
SWH             4807.692 Hz
FIDRES          0.146719 Hz
AQ              3.4080260 sec
RG                  71.8
DW                104.000 usec
DE                 10.00 usec
TE                298.2 K
D1             1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                 13.00 usec
PL1                -3.00 dB
PL1W         30.07123375 W
SFO1         400.1620008 MHz
SI                 16384
SF           400.1600000 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```



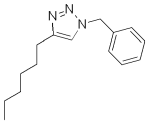
ResearchGroup Pericas
ICIQ_13C{1H}512s DMSO /opt/topspin eozkal 17



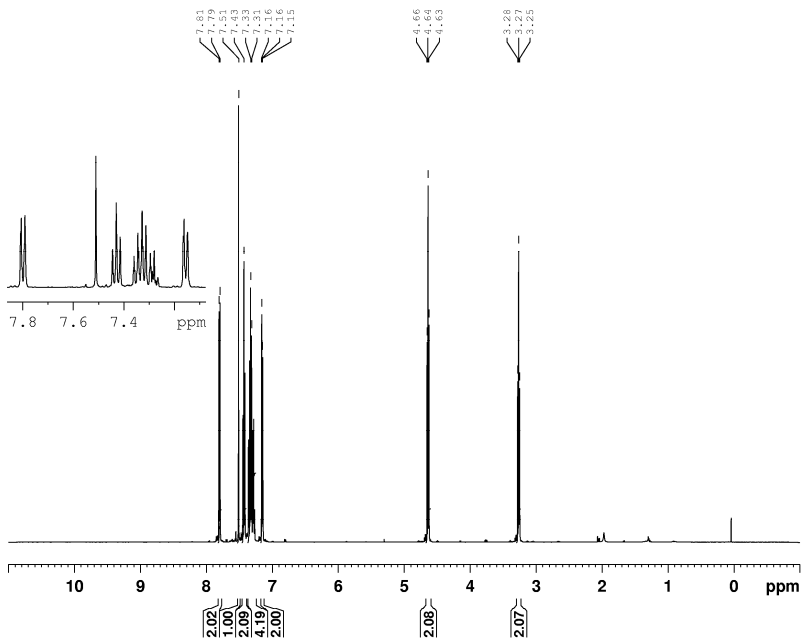

```
NAME            ersa4_11
EXPNO                  1
PROCNO                 1
Date_           20101224
Time               15.35
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                 65536
SOLVENT             DMSO
NS                   512
DS                     4
SWH            24038.461 Hz
FIDRES          0.366798 Hz
AQ              1.36321960 sec
RG                  46341
DW                 20.800 usec
DE                 10.00 usec
TE                298.0 K
D1             5.00000000 sec
D11            0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                  9.25 usec
PL1                -3.00 dB
PL1W         75.17808533 W
SFO1         100.6303736 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                -3.00 dB
PL12               14.50 dB
PL13               14.50 dB
PL2W         30.07123375 W
PL12W         0.53475058 W
PL13W         0.53475058 W
SFO2         400.1616006 MHz
SI                 32768
SF           100.6203120 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
```

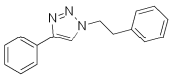


1H experiment

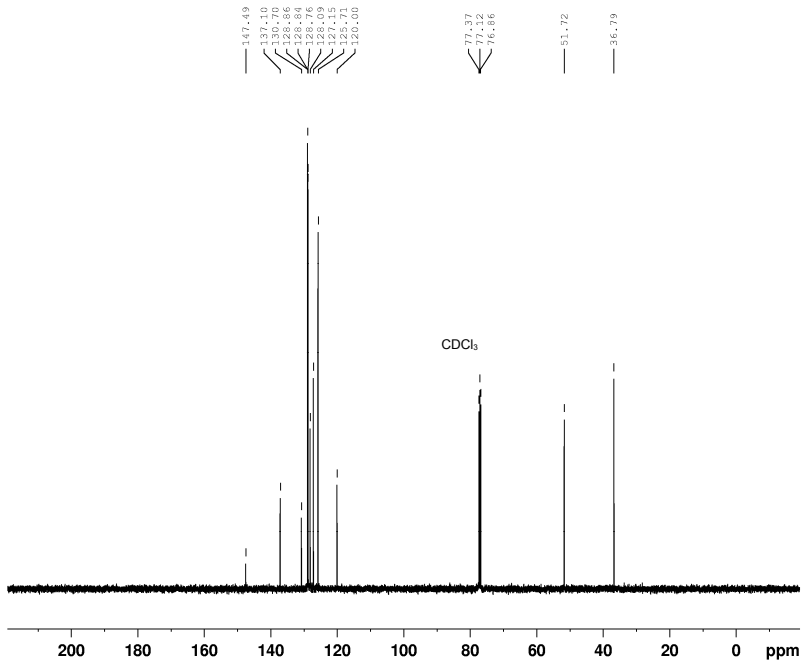



```
NAME      er262c_1_1.topspin
EXPNO                      1
PROCNO                     1
Date_               20100505
Time                   11.11
INSTRUM                spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                        6
DS                        2
SWH                6009.615 Hz
FIDRES            0.183399 Hz
AQ                2.7264309 sec
RG                     50.8
DW                   83.200 usec
DE                   10.00 usec
TE                   298.1 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                      1H
P1                     13.80 usec
PL1                     3.00 dB
PL1W           12.58925438 W
SFO1           500.1325007 MHz
SI                    16384
SF             500.1300000 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```



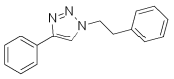
13C {1H} experiment, 1024 scans

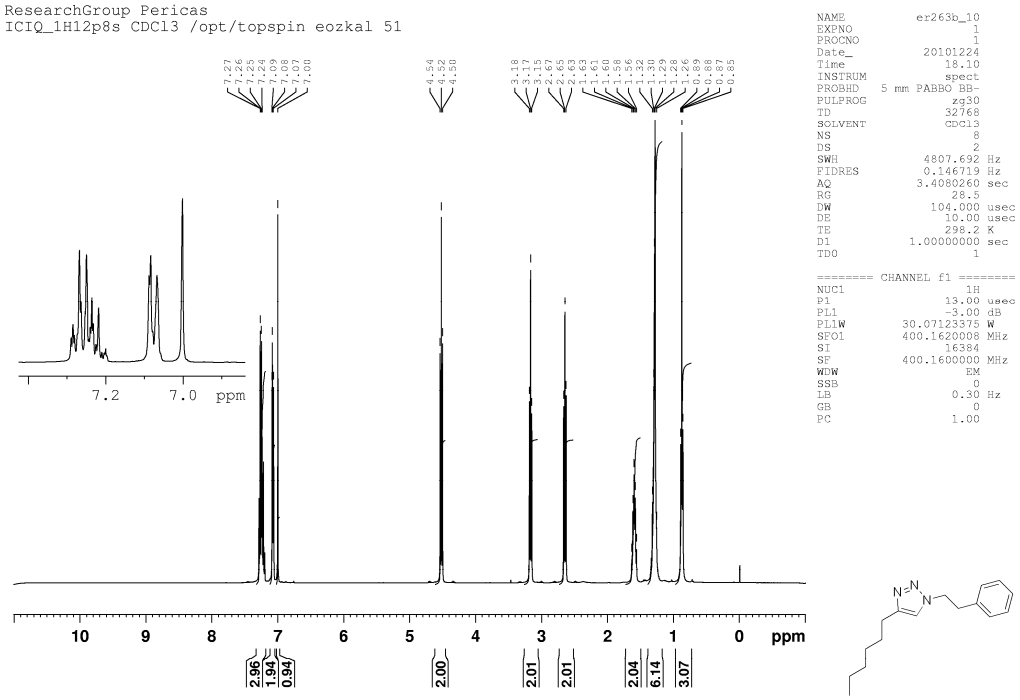


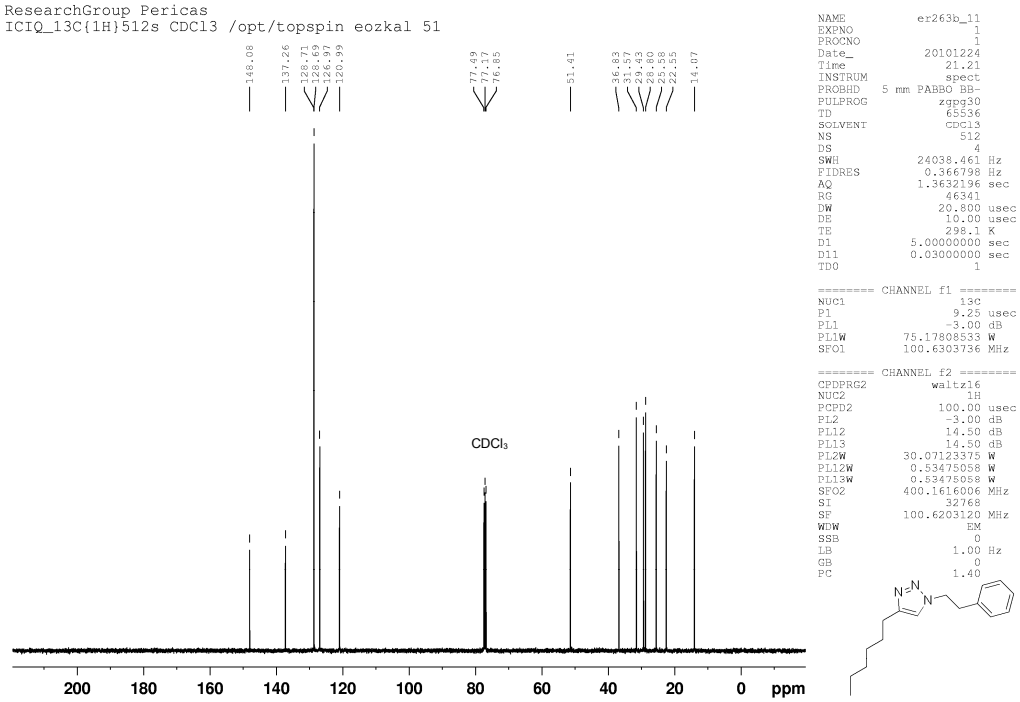

```
NAME          er262c_2_1
EXPNO                   1
PROCNO                  1
Date_            20100505
Time                11.14
INSTRUM             spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                   64
DS                    4
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.0814105 sec
RG                  1820
DW                16.500 usec
DE                10.00 usec
TE                298.1 K
D1          1.00000000 sec
D11         0.03000000 sec
TD0                   1

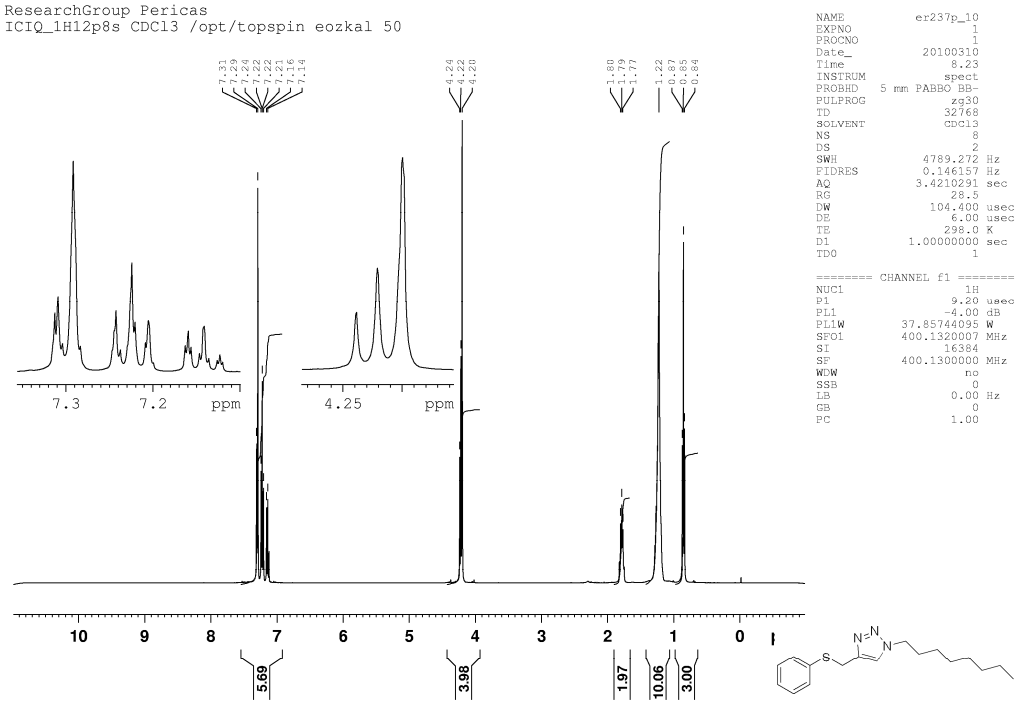
======== CHANNEL f1 ========
NUC1                 13C
P1                  8.50 usec
PL1                 0.00 dB
PL1W       75.35659027 W
SFO1      125.7703648 MHz

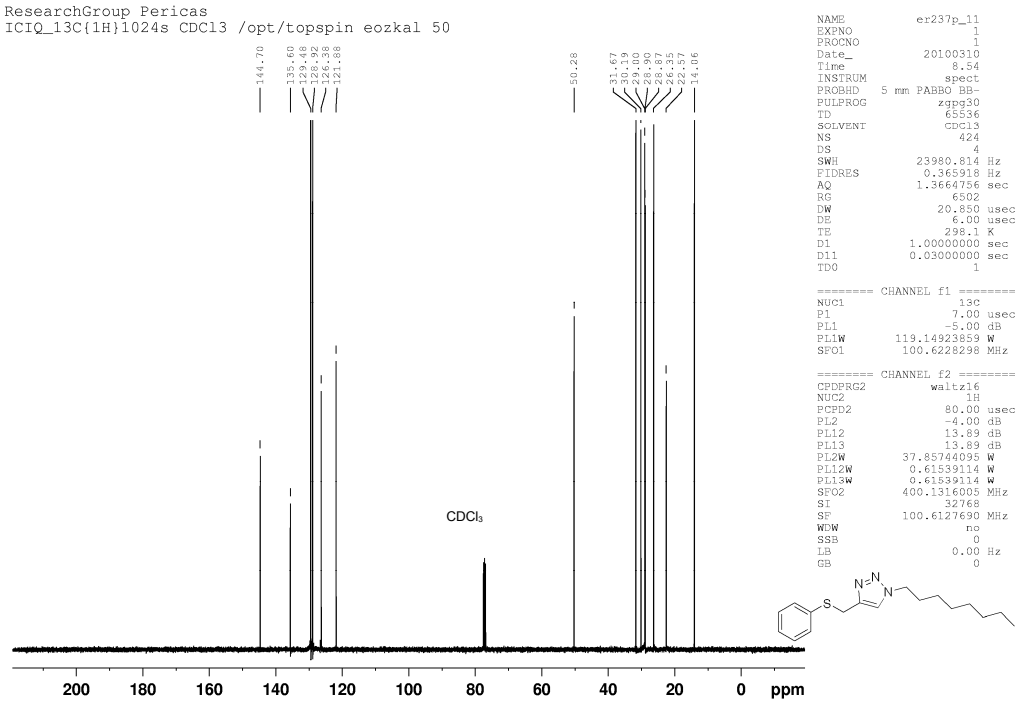
======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                 1H
PCPD2              80.00 usec
PL2                 3.00 dB
PL12               18.14 dB
PL13               20.39 dB
PL2W       12.58925438 W
PL12W       0.38547841 W
PL13W       0.22961490 W
SFO2      500.1320005 MHz
SI                32768
SF        125.7577890 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

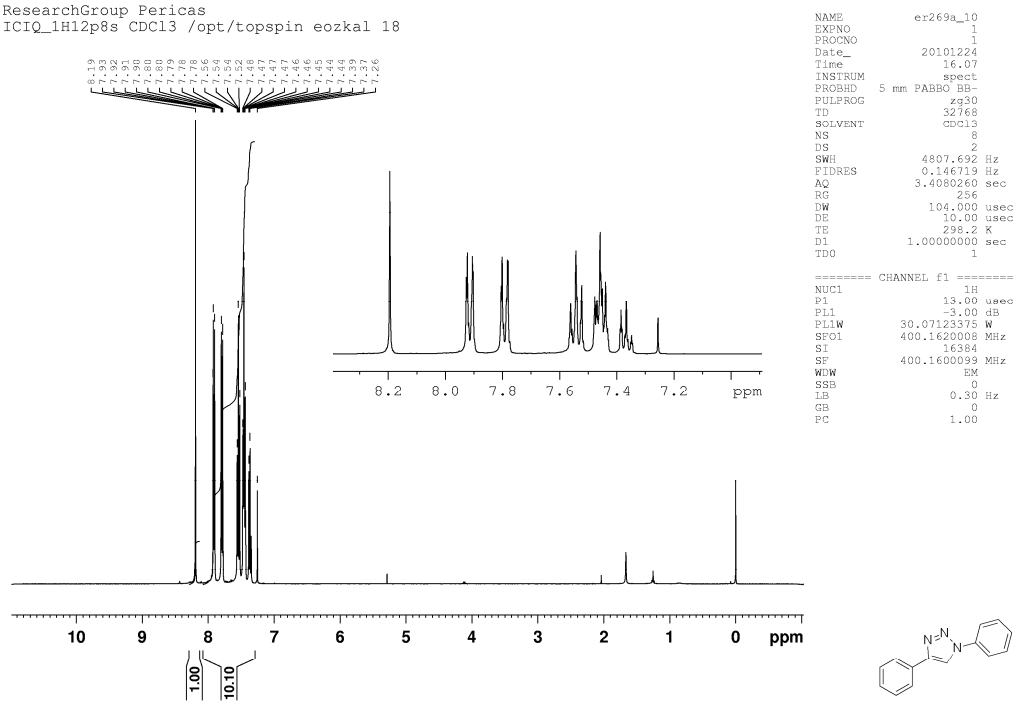


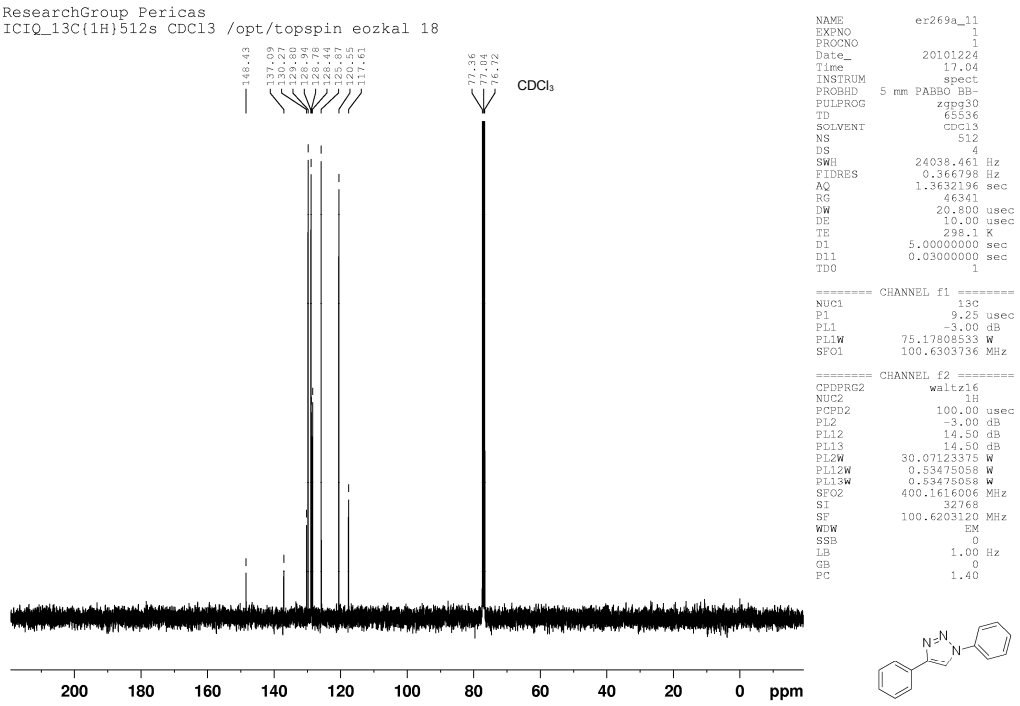

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin eozkal 51
7.27
7.26
7.25
7.24
7.09
7.08
7.07
7.00
4.54
4.52
4.50
3.18
3.17
3.15
2.67
2.65
2.63
1.63
1.61
1.60
1.58
1.56
1.32
1.30
1.29
1.28
1.26
0.89
0.88
0.87
0.85
7.2
7.0
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm
2.96
1.94
0.94
2.00
2.01
2.01
2.04
6.14
3.07
NAME er263b_10
EXPNO 1
PROCNO 1
Date_ 20101224
Time 18.10
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 4807.692 Hz
FIDRES 0.146719 Hz
AQ 3.4080260 sec
RG 28.5
DW 104.000 usec
DE 10.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.00 usec
PL1 -3.00 dB
PL1W 30.07123375 W
SFO1 400.1620008 MHz
SI 16384
SF 400.1600000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

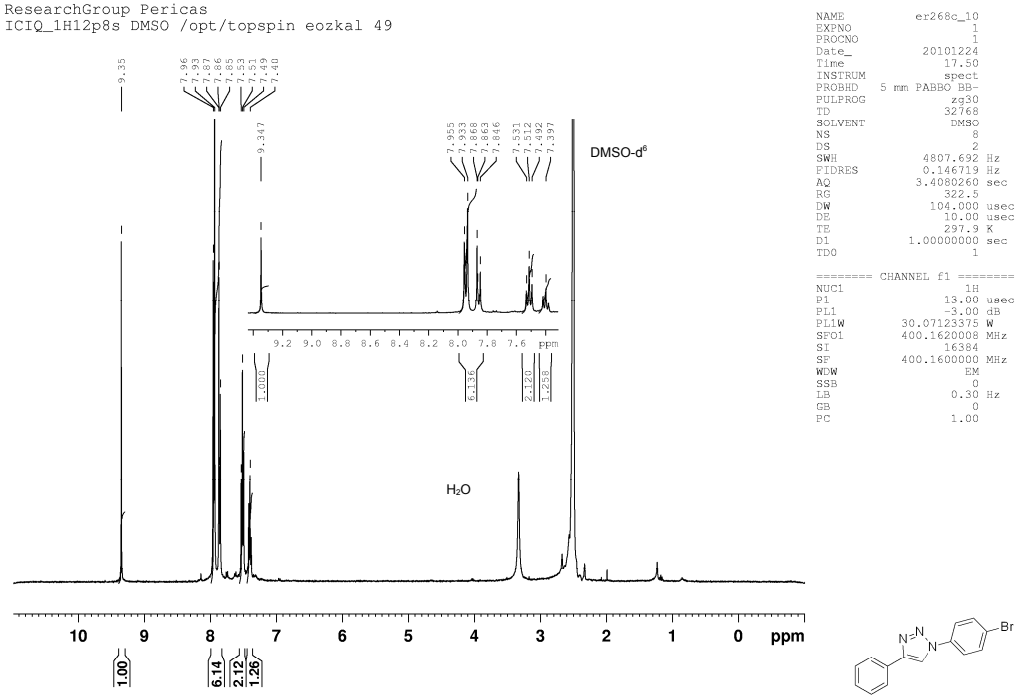

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin eozkal 51
148.08
137.26
128.71
128.69
126.97
120.99
77.49
77.17
76.85
51.41
36.83
31.57
29.43
28.80
25.58
22.55
14.07
CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm
NAME er263b_11
EXPNO 1
PROCNO 1
Date_ 20101224
Time 21.21
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3632196 sec
RG 46341
DW 20.800 usec
DE 10.00 usec
TE 298.1 K
D1 5.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.25 usec
PL1 -3.00 dB
PL1W 75.17808533 W
SFO1 100.6303736 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -3.00 dB
PL12 14.50 dB
PL13 14.50 dB
PL2W 30.07123375 W
PL12W 0.53475058 W
PL13W 0.53475058 W
SFO2 400.1616006 MHz
SI 32768
SF 100.6203120 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40


ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin eozkal 50
7.31
7.29
7.24
7.22
7.22
7.21
7.16
7.14
4.24
4.22
4.20
1.80
1.79
1.77
1.22
0.87
0.85
0.84
7.3
7.2
ppm
4.25
ppm
10
9
8
7
6
5
4
3
2
1
0
5.69
3.98
1.97
10.06
3.00
NAME er237p_10
EXPNO 1
PROCNO 1
Date_ 20100310
Time 8.23
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 28.5
DW 104.400 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.20 usec
PL1 -4.00 dB
PL1W 37.85744095 W
SFO1 400.1320007 MHz
SI 16384
SF 400.1300000 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00


ResearchGroup Pericas
ICIQ_13C{1H}1024s CDCl3 /opt/topspin eozkal 50
144.70
135.60
129.68
128.92
126.38
121.88
50.28
31.67
30.19
29.00
28.90
28.87
26.35
22.57
14.06
CDCl3
200
180
160
140
120
100
80
60
40
20
0
ppm
NAME er237p_11
EXPNO 1
PROCNO 1
Date_ 20100310
Time 8.54
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 424
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 6502
DW 20.850 usec
DE 6.00 usec
TE 298.1 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 7.00 usec
PL1 -5.00 dB
PL1W 119.14923859 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -4.00 dB
PL12 13.89 dB
PL13 13.89 dB
PL2W 37.85744095 W
PL12W 0.61539114 W
PL13W 0.61539114 W
SFO2 400.1316005 MHz
SI 32768
SF 100.6127690 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0

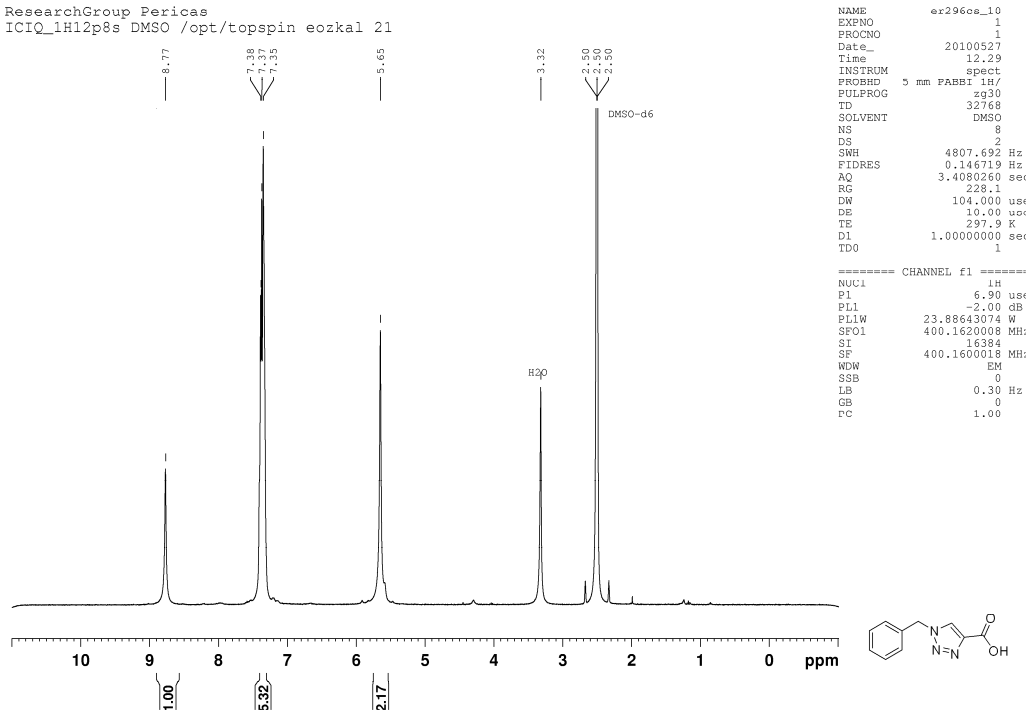

ResearchGroup Pericas
ICIQ_1H12p8s CDCl3 /opt/topspin eozkal 18
8.19 7.93 7.92 7.91 7.91 7.80 7.80 7.79 7.78 7.78 7.56 7.54 7.54 7.52 7.48 7.47 7.47 7.46 7.46 7.45 7.44 7.44 7.39 7.37 7.26
8.2 8.0 7.8 7.6 7.4 7.2 ppm
10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
10.10
NAME er269a_10
EXPNO 1
PROCNO 1
Date_ 20101224
Time 16.07
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 8
DS 2
SWH 4807.692 Hz
FIDRES 0.146719 Hz
AQ 3.4080260 sec
RG 256
DW 104.000 usec
DE 10.00 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 13.00 usec
PL1 -3.00 dB
PL1W 30.07123375 W
SFO1 400.1620008 MHz
SI 16384
SF 400.1600099 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

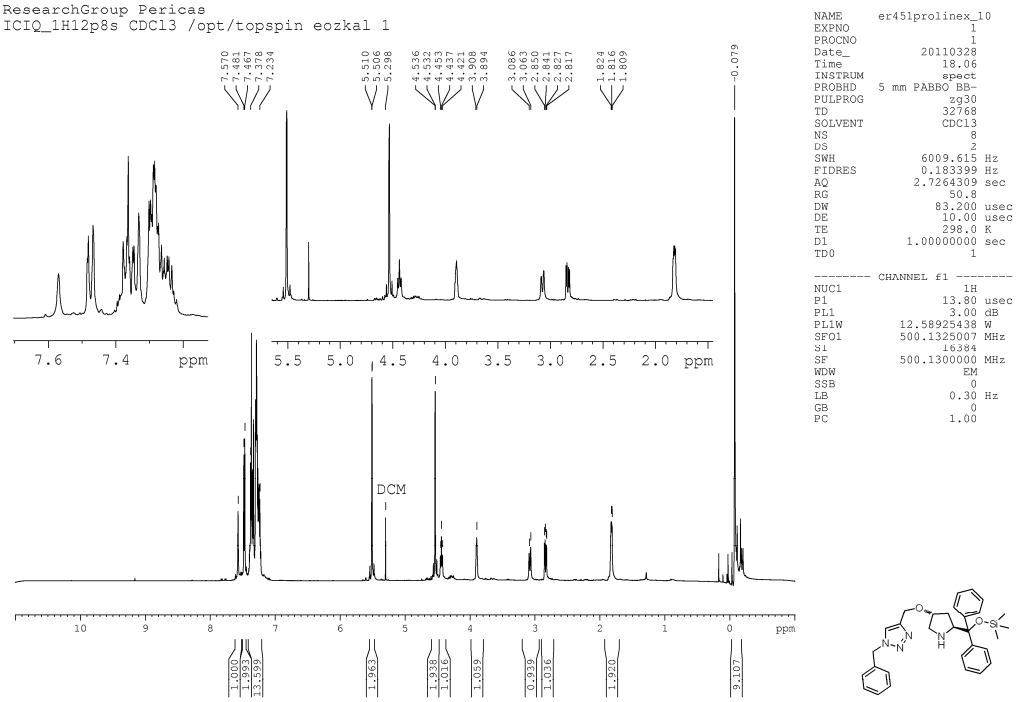

ResearchGroup Pericas
ICIQ_13C{1H}512s CDCl3 /opt/topspin eozkal 18
148.43 137.09 130.27 129.60 128.94 128.78 128.44 125.87 120.55 117.61
77.36 77.04 76.72
CDCl3
200 180 160 140 120 100 80 60 40 20 0 ppm
NAME er269a_11
EXPNO 1
PROCNO 1
Date_ 20101224
Time 17.04
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3632196 sec
RG 46341
DW 20.800 usec
DE 10.00 usec
TE 298.1 K
D1 5.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.25 usec
PL1 -3.00 dB
PL1W 75.17808533 W
SFO1 100.6303736 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 100.00 usec
PL2 -3.00 dB
PL12 14.50 dB
PL13 14.50 dB
PL2W 30.07123375 W
PL12W 0.53475058 W
PL13W 0.53475058 W
SFO2 400.1616006 MHz
SI 32768
SF 100.6203120 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40




```
NAME              er268c_10
EXPNO                     1
PROCNO                    1
Date_              20101224
Time                  17.50
INSTRUM               spect
PROBHD   5 mm PABBO BB-
PULPROG                zg30
TD                    32768
SOLVENT                DMSO
NS                        8
DS                        2
SWH                4807.692 Hz
FIDRES            0.146719 Hz
AQ                3.4080260 sec
RG                    322.5
DW                  104.000 usec
DE                   10.00 usec
TE                   297.9 K
D1                1.00000000 sec
TD0                       1

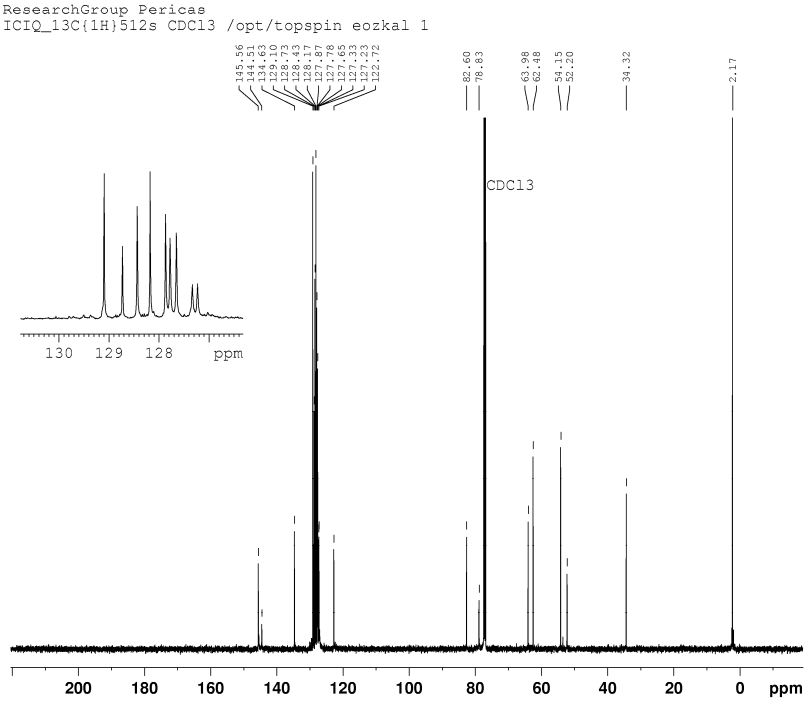
======== CHANNEL f1 ========
NUC1                    1H
P1                   13.00 usec
PL1                  -3.00 dB
PL1W           30.07123375 W
SFO1           400.1620008 MHz
SI                    16384
SF             400.1600000 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.00
```


ResearchGroup Pericas
ICIQ_1H12p8s DMSO /opt/topspin eozkal 21
8.77
7.38
7.37
7.35
5.65
3.32
2.50
2.50
2.50
DMSO-d6
H2O
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
5.32
2.17
NAME er296cs_10
EXPNO 1
PROCNO 1
Date_ 20100527
Time 12.29
INSTRUM spect
PROBHD 5 mm PABBI 1H/
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 8
DS 2
SWH 4807.692 Hz
FIDRES 0.146719 Hz
AQ 3.4080260 se
RG 228.1
DW 104.000 us
DE 10.00 us
TE 297.9 K
D1 1.00000000 se
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 6.90 us
PL1 -2.00 dB
PL1W 23.88643074 W
SFO1 400.1620008 MH
SI 16384
SF 400.1600018 MH
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
N
N=N
O
OH




```
NAME      er451prolinex_10
EXPNO                    1
PROCNO                   1
Date_             20110328
Time                 18.06
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                       8
DS                       2
SWH               6009.615 Hz
FIDRES               0.183399 Hz
AQ                2.7264309 sec
RG                    50.8
DW                  83.200 usec
DE                  10.00 usec
TE                  298.0 K
D1             1.00000000 sec
TD0                      1

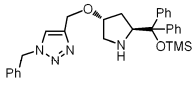
========= CHANNEL f1 =========
NUC1                     1H
P1                   13.80 usec
PL1                   3.00 dB
PL1W           12.58925438 W
SFO1           500.1325007 MHz
SI                   16384
SF             500.1300000 MHz
WDW                     EM
SSB                      0
LB                   0.30 Hz
GB                       0
PC                   1.00
```

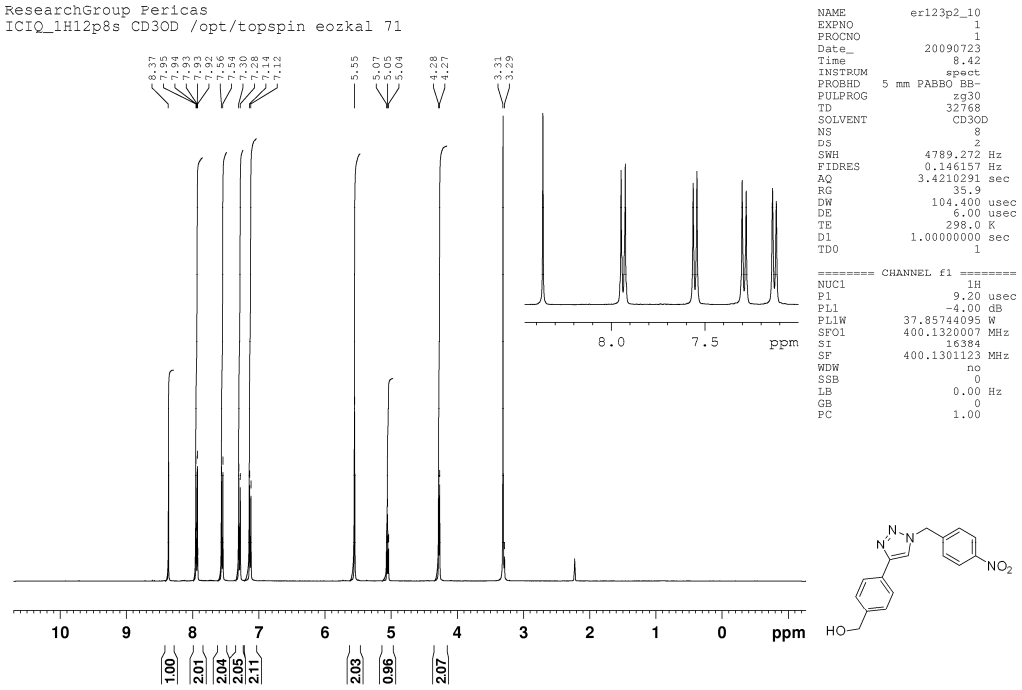



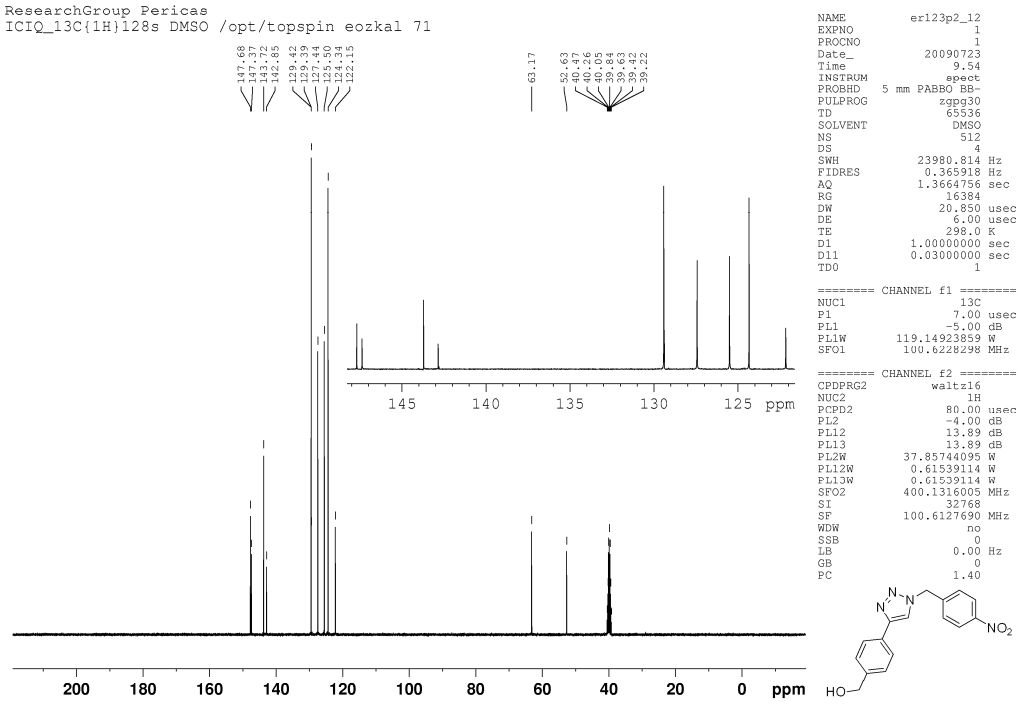

```
NAME      er451prolinex_11
EXPNO                    1
PROCNO                   1
Date_             20110328
Time                 21.42
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG           zgpg30
TD                   65536
SOLVENT              CDCl3
NS                     512
DS                       4
SWH              30303.031 Hz
FIDRES               0.462388 Hz
AQ                1.0814105 sec
RG                    1030
DW                  16.500 usec
DE                  10.00 usec
TE                  297.9 K
D1             3.00000000 sec
D11            0.03000000 sec
TD0                      1

========= CHANNEL f1 =========
NUC1                     13C
P1                    8.50 usec
PL1                   0.00 dB
PL1W          75.35659027 W
SFO1          125.7703648 MHz

========= CHANNEL f2 =========
CPDPRG2              waltz16
NUC2                     1H
PCPD2                80.00 usec
PL2                   3.00 dB
PL12                 18.14 dB
PL13                 20.39 dB
PL2W           12.58925438 W
PL12W           0.38547841 W
PL13W           0.22961490 W
SFO2           500.1320005 MHz
SI                   32768
SF             125.7577890 MHz
WDW                     EM
SSB                      0
LB                   1.00 Hz
GB                       0
PC                   1.40
```




ResearchGroup Pericas
ICIQ_1H12p8s CD3OD /opt/topspin eozkal 71
8.37
7.95
7.94
7.93
7.93
7.92
7.56
7.54
7.30
7.28
7.14
7.12
5.55
5.07
5.05
5.04
4.28
4.27
3.31
3.29
8.0
7.5
ppm
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
2.01
2.04
2.05
2.11
2.03
0.96
2.07
NAME er123p2_10
EXPNO 1
PROCNO 1
Date_ 20090723
Time 8.42
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 32768
SOLVENT CD3OD
NS 8
DS 2
SWH 4789.272 Hz
FIDRES 0.146157 Hz
AQ 3.4210291 sec
RG 35.9
DW 104.400 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.20 usec
PL1 -4.00 dB
PL1W 37.85744095 W
SFO1 400.1320007 MHz
SI 16384
SF 400.1301123 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00
NO2
HO


ResearchGroup Pericas
ICIQ_13C{1H}128s DMSO /opt/topspin eozkal 71
147.68
143.77
143.72
142.85
129.42
129.39
127.44
125.50
124.34
122.15
63.17
52.63
40.47
40.26
40.05
39.84
39.63
39.42
39.22
145
140
135
130
125
ppm
200
180
160
140
120
100
80
60
40
20
0
ppm
NAME er123p2_12
EXPNO 1
PROCNO 1
Date_ 20090723
Time 9.54
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 512
DS 4
SWH 23980.814 Hz
FIDRES 0.365918 Hz
AQ 1.3664756 sec
RG 16384
DW 20.850 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 7.00 usec
PL1 -5.00 dB
PL1W 119.14923859 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 -4.00 dB
PL12 13.89 dB
PL13 13.89 dB
PL2W 37.85744095 W
PL12W 0.61539114 W
PL13W 0.61539114 W
SFO2 400.1316005 MHz
SI 32768
SF 100.6127690 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.40
NO2
HO

VI. References

[1] Adapted from: (a) Brenner, A. J.; Harris, E. D. *Anal. Biochem.* **1995**, *226*, 80. (b) Brenner, A. J.; Harris, E. D. *Anal. Biochem.* **1995**, *230*, 360 (erratum).

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[3] Zhang, Q.; Tacaks, J. M. *Org. Lett.* **2008** *10* (4), 545-548.

[4] Appukkuttan, P.; Dehaen, W.; Fokin, V. V.; Van der Eycken, E. *Org. Lett.* **2004** *6* (23), 4223-4225.

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[8] Özçubukçu, S.; Ozkal, E.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2009**, *11*, 4680.

[9] Lőrincz, K.; Kele, P.; Novák, Z. *Synthesis* **2009,** *20*, 3527-3532.

[10] Alonso, F.; Moglie, Y.; Radivoy, G.; Yus, M. *Eur. J. Org. Chem.* **2010**, 1875–1884.

[11] Feng W.; Hua, F.; Yuyang, J.; Yufen, Z. *Green Chem.* **2008**, *10* (4), 452-456.

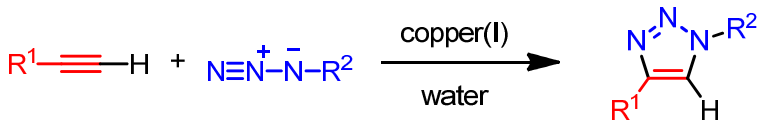
Chapter III

CONTENTS

3. "*CLICK*" LIGANDS FOR ASYMMETRIC METAL-CATALYSIS

3.1. 1,2,3-TRIAZOLE LIGANDS IN METAL-CATALYZED REACTIONS

CuAAC reaction stands out as a proof of concept reaction for click chemistry and triazoles derived from it have been extensively exploited in all research fields related to chemistry (**Scheme 3.1**).



Scheme 3.1. Copper-catalyzed azide-alkyne cycloaddition reaction forming 1,2,3-triazoles.

Most metal complexes of triazoles have been used in inorganic chemistry for chelation studies.[1] In catalysis, the early attempts have been in the direction of insertion of structural complexity to create an easily tunable ligand family. Apart from CuAAC reaction itself (See Chapter 2), Zhang and co-workers designed a triazole based monophosphine ligand (ClickPhos) for palladium-catalyzed amination and Suzuki-Miyaura reactions.[2] The synthesis of these ligands has been carried out through a non-catalytic Grignard strategy of AAC components. Most probably, the ligand has phosphine monodentate coordination to Pd in its catalytic reaction. Later, ClickFerrophos ligands were developed in a similar manner (**Figure 3.1**).[3]

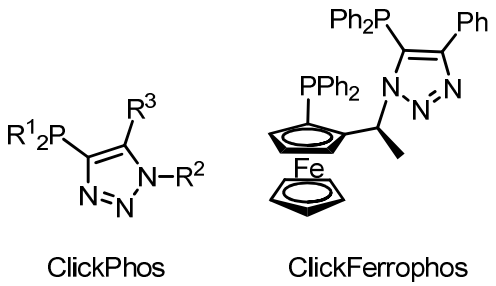


Figure 3.1. Modular ligands using 1,2,3-triazoles from CuAAC reaction.

[1] Struthers, H.; Mindt, T. L.; Schibli, R. *Dalton Trans.* **2010**, *39*, 675.
[2] Liu, D.; Gao, W.; Dai, Q.; Zhang, X. *Org. Lett.* **2005**, *7*, 4907.
[3] Fukuzawa, S.-i.; Oki, H.; Hosaka, M.; Sugasawa, J.; Kikuchi, S. *Org. Lett.* **2007**, *9*, 5557.

Besides adding modularity and ease of derivatization to such ligands, the presence of three nitrogen atoms, two of which bearing a non-bonding electron pair, and the high electron density of the aromatic ring, make triazoles not only a point of diversity but also a useful Lewis base to coordinate with transition metals. We reasoned that these coordination complexes could be used to our interest in metal-catalyzed reactions. Until now, the variety in triazole ligands for transition metal catalysis can be found in phosphine ligands, bidentate *P,N*-chelates, ferrocenyl bisphoshines, pincer ligands and carbenes and their activity was mostly limited to metal catalyzed cross-coupling reactions.[4] The vast majority of developed systems were achiral and the enantioselective cases are scarce.

Van Maarseveen and co-workers used bidentate phosphine-triazole ligands (Clickphine) for palladium-catalyzed allylic alkylation reactions with excellent regioselectivity (**Figure 3.2**, **(a)**).[5] Extensive ^{31}P NMR studies revealed that the active species in catalysis was the monodentate *P*-coordinated complex; although palladium coordination through the N3 nitrogen atom in solution was also observed. Scrivanti and co-workers have synthesized cationic pyridyltriazole palladium complexes which had moderate activity in Suzuki reaction **(b)**.[6] Milani and co-workers also investigated similar palladium complexes, which were moderately active for styrene carbonylation **(c)**.[7] Finally, Chen and co-workers succesfully developed a combination of NHC/triazole bearing ligands that were active catalysts for the Suzuki coupling of aryl bromides and 1,1-dibromo-1-alkenes **(d)**.[8]

Hao, Wang and co-workers showed one of the first tetradentate coordination complexes of triazole bearing ligands using bisaminotriazole ligands. Their complexes were structurally characterized by X-ray and these ligands were used for Mn-catalyzed

[4] Crowley, J. D.; McMorran, D. A. *Top. Heterocycl. Chem.*, **2012**, *28*, 31.
[5] Detz, R. J.; Heras, S. A.; de Gelder, R.; van Leeuwen, P. W. N. M.; Hiemstra, H.; Reek, J. N. H.; van Maarseveen, J. H. *Org. Lett.* **2006**, *8*, 3227.
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[7] D'Amora, A.; Fanfoni, L.; Cozzula, D.; Guidolin, N.; Zangrando, E.; Felluga, F.; Gladiali, S.; Benedetti, F.; Milani, B. *Organometallics* **2010**, *29*, 4472.
[8] Gu, S.; Xu, H.; Zhang, N.; Chen, W. *Chem. Asian J.* **2010**, *5*, 1677.

epoxidation of terminal olefins with peracetic acid. With as low as 0.5 mol% catalyst, conversions of over 90% were observed at 0 °C within minutes **(e)**.[9]

In terms of pincer ligands, a set of "*click*" ligands has been derived from classical pincer complexes. Gandelman and co-workers arranged triazole rings in a way that the aryl group on the classical pincer complexes has been substituted, thus having C5 coordination to Pd by metal insertion to the relatively acidic C5–H bond. These ligands afforded very high activity for Mizoroki-Heck reaction **(f)**.[10]

The use of alkylated triazolium salts to generate C5 complexation from triazoles is a very recent field and such ligands have been used in catalysis only for CuAAC reaction, Pd-catalyzed cross-couplings, enyne cyclizations **(g)**[11] and water oxidation **(h)**.[12]

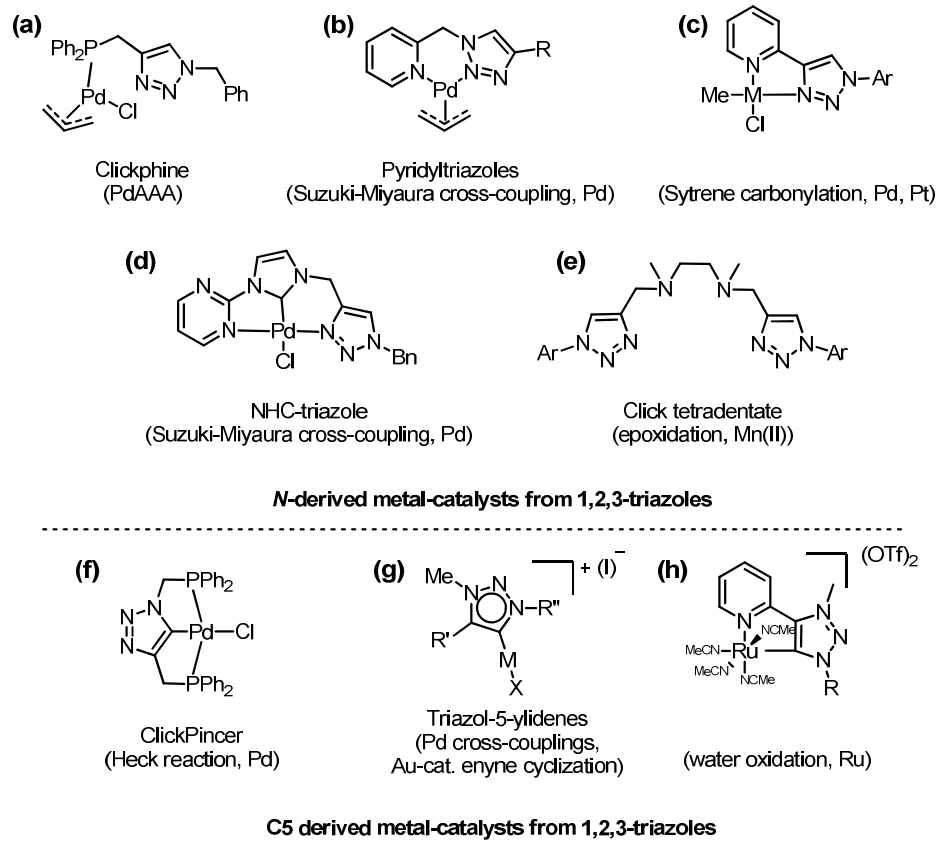

Figure 3.2. Triazole-based metal/ligand complexes for metal-catalyzed reactions.

[9] Hao, E.; Wang, Z.; Jiao, L.; Wang, S. *Dalton Trans.* **2010**, *39*, 2660.
[10] Schuster, E. M.; Botoshansky, M.; Gandelman, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4555.
[11] Kilpin, K. J.; Paul, U. S. D.; Lee, A.-L.; Crowley, J. D. *Chem. Commun.* **2010**, *47*, 328.
[12] Lalrempuia, R.; McDaniel, N. D.; Müller-Bunz, H.; Bernhard, S.; Albrecht, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9765.

In terms of enantioselective catalysis, *P*-chirogenic phosphines (ChiraClick) developed by Kann and co-workers were used in palladium-catalyzed asymmetric allylic alkylation (PdAAA) reactions but gave low enantioselectivity (**Figure 3.3**, **(a)**),[13] and amino acid derived ligands introduced by Adolfsson and Tinnis in Rhodium-catalyzed asymmetric transfer hydrogenation (RhATH) turned out to be active with low catalyst loading and good enantioselectivities for ATH conditions **(b)**.[14]

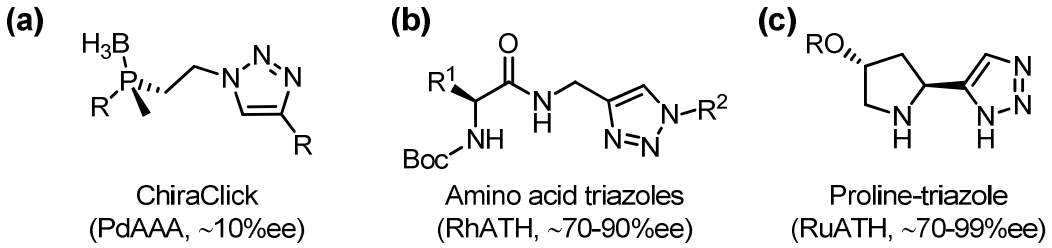

Figure 3.3. "Click" ligands for asymmetric metal-catalysis utilizing triazole binding.

Recently, proline-derived aminotriazoles developed in our research group showed the direct metal-triazole interaction clearly, with good catalytic activity in RuATH **(c)**.[15]

In general, practical examples of enantioselective reactions with triazole-based ligands remain mostly unexplored to our knowledge. Consequently, over the course of this thesis we sought for the expansion of asymmetric catalysis with 1,2,3-triazoles and we envisioned that molybdenum-catalyzed asymmetric allylic alkylation would be the best fit for that objective.

3.2. MOLYBDENUM CATALYZED ASYMMETRIC ALLYLIC ALKYLATION REACTION

Methods for efficient synthesis of optically active compounds have greatly advanced thanks to asymmetric metal-catalyzed reactions. Fundamental advances have been achieved in hydrogenation and oxidation reactions through transfer of oxygen and molecular hydrogen. However, approaches towards the cornerstone of asymmetric synthesis, the asymmetric formation of C–C bond have been scarce. In recent times, there has been a tremendous boost in the field in this direction, primarily by asymmetric Lewis

[13] Dolhem, F.; Johansson, M. J.; Antonsson, T.; Kann, N. *ACS Comb. Sci.* **2007**, *9*, 477.
[14] Tinnis, F.; Adolfsson, H. *Org. Biomol. Chem.* **2010**, *8*, 4536.
[15] Cambeiro, X. C.; Pericàs, M. A. *Adv. Synth. Catal.* **2011**, *353*, 113.

acid-catalyzed reactions, asymmetric phase transfer catalysis and more recently, by organocatalysis.

Among all asymmetric C–C bond formations, metal-catalyzed asymmetric allylic alkylations (AAA) are one of a kind because with the different metals and their mode of action involved, asymmetry can be installed in various ways. Briefly, the reaction starts by oxidative addition of allylic substrate **1** to a low valent metal complex to form π-allyl metal complex **2**. If a soft nucleophile (*e.g.* malonates) attacks to the carbon atom on the complex **2** a carbon–carbon bond is formed and the metal coordinates to the double bond as a π-complex **A**. In the case of a hard nucleophile (*e.g.* Grignard reagents), however, it first attacks to the metal to form π-allyl alkyl metal complex **B**. The final product **3** is liberated, in both pathways, by reductive elimination (**Scheme 3.2**).[16] In addition to C–C bond, a diverse set of carbon-heteroatom bond formation can be generated (C–H, C–O, C–N, C–S, C–P).[17] A wide variety of metals can be utilized in AAA such as palladium,[18] tungsten,[19] iridium,[20] molybdenum,[21] copper,[22] rhodium,[23] ruthenium,[24] gold,[25] and nickel.[26] However, the most studied and versatile of all is palladium in terms of stereo- and regio-selectivity.[27,28]

[16] Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.
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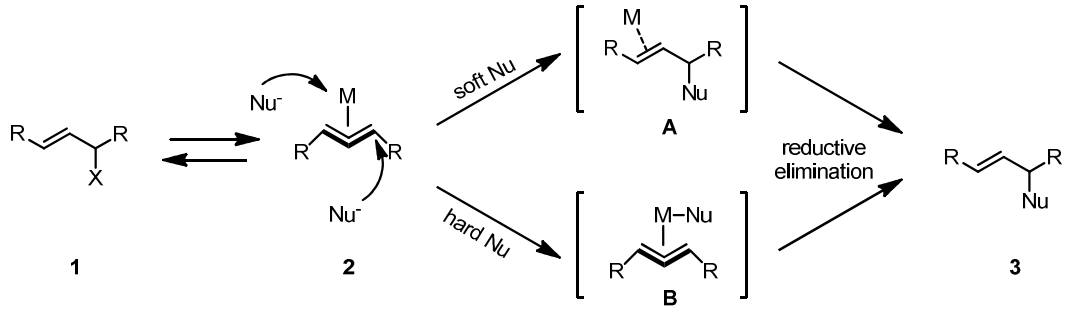
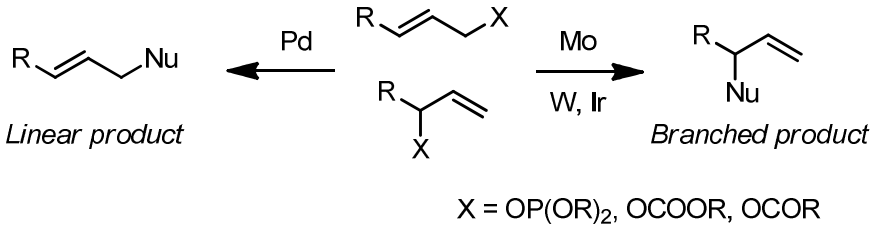
[27] Mori, M. In *Comprehensive Chirality*; Elsevier, Amsterdam, **2012**, 74.
[28] Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.



Scheme 3.2. General reactivity preference for asymmetric allylic alkylation reactions.

To our interest, the complementary counterpart of palladium-catalyzed asymmetric allylic alkylation (PdAAA) in terms of regioselectivity, are the molybdenum – catalyzed asymmetric allylic alkylation (MoAAA), first introducted by Trost and Lautens.[29] In this case, monosubstituted allylic substrates afford branched products in contrast to palladium catalysis (**Scheme 3.3**). However, it took a decade to develop the proper family of chiral catalysts for MoAAA process. The presence of equilibrating allyl complexes leads to similar product distribution regardless of the regio- and stereoisomer of the substrate that is utilized. Therefore, the reaction is a general methodology for enantioselective synthesis of complex molecules that affords high selectivity.[30]

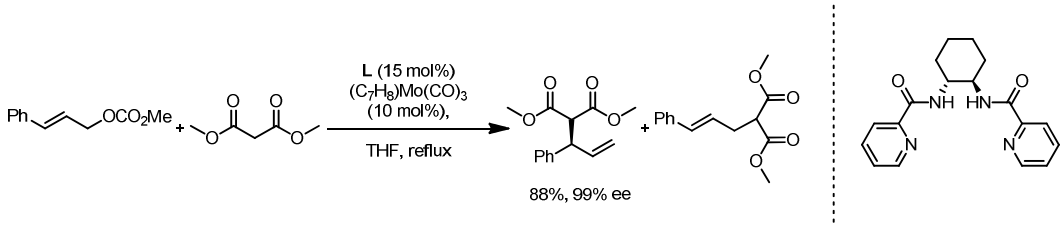


Scheme 3.3. Regioselectivity in AAA by Pd, Mo, W, and Ir.

Interestingly, iridium and tungsten react with the same regioselectivity and especially iridium shows a broader scope in terms of nucleophiles. Noteworthy, the lower cost of molybdenum makes it a better choice over iridium in the asymmetric C–C bond formation. In other words, MoAAA is the most promising methodology to complement PdAAA in order to obtain branched products for enantioselective C-C bond formation via the use of same allylic position. In this direction, the first successful enantioselective

[29] Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1982**, *104*, 5543.
[30] Trost, B. M. *Org. Process Res. Dev.* **2012**, *16*, 185.

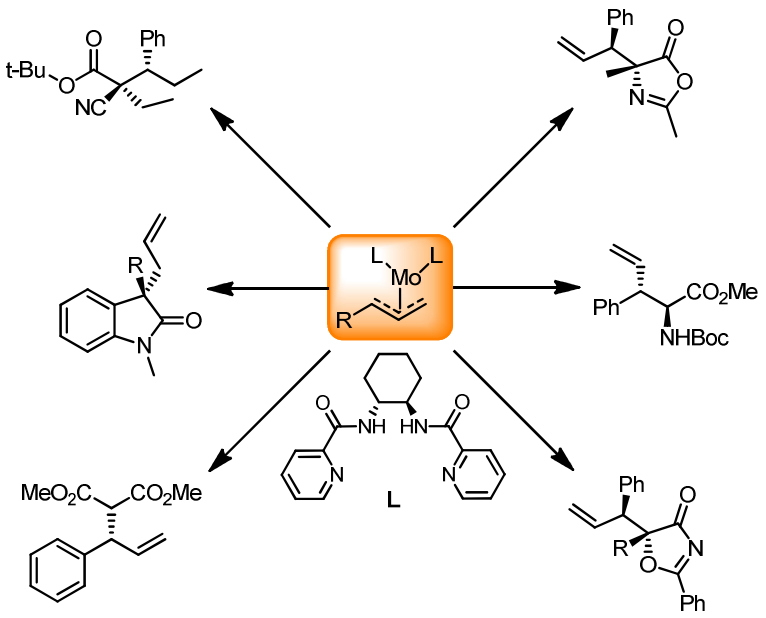
MoAAA was developed by using bis(pyridyl) type ligands by Trost and Hachiya (**Scheme 3.4**).[31]



Scheme 3.4. First enantioselective MoAAA: Trost and Hachiya, 1998.

In MoAAA, the order of reactivity of electrophiles can be summarized as follows: allylic phosphates > allylic carbonates > allylic carboxylates. However, the scope of nucleophiles is restricted to only stabilized carbon nucleophiles like malonate esters and some stabilized enolates; in comparison, Pd and IrAAA have a much broader scope. The regioselectivity in MoAAA, directly related with regular steric and electronic effects, stems from the catalyst and electrophile. Generally, aryl allylic substrates operate better than alkyl electrophiles.[32] In any case, the scope of the MoAAA is relatively broad in C–C bond formation (**Scheme 3.5**).[33]

[31] Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104.
[32] Moberg, C. *Top. Organomet. Chem.* **2012**, *38*, 209.
[33] (a) Trost, B. M.; Zhang, Y. *Chem.– Eur. J.* **2011**, *17*, 2916. (b) Trost, B. M.; Miller, J. R.; Hoffman, C. M. *J. Am. Chem. Soc.* **2011**, *133*, 8165. (c) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548. (d) Trost, B. M.; Dogra, K. *Org. Lett.* **2007**, *9*, 861. (e) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2006**, *128*, 4590. (f) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (g) Trost, B. M.; Andersen, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320.



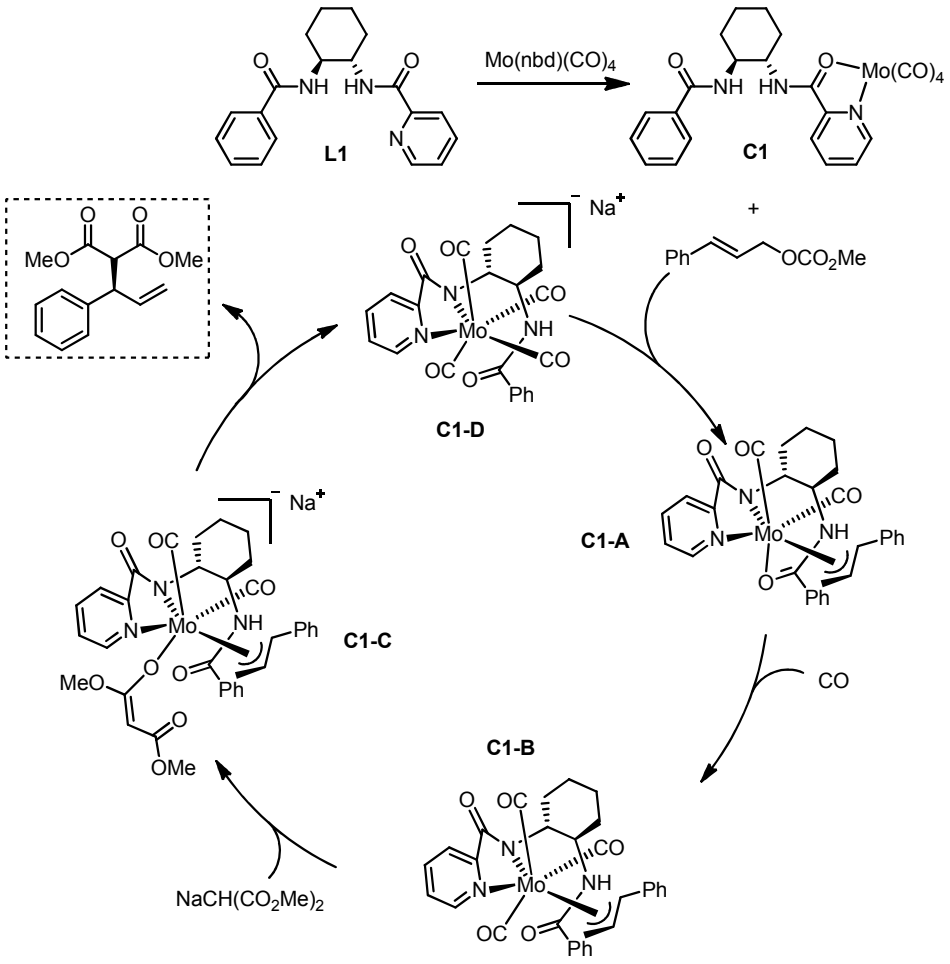
Scheme 3.5. Selected scope of MoAAA reaction.

A better understanding of reactivity was made possible with mechanistic studies that enabled a much broader scope in the methodology.

3.2.1. MECHANISM

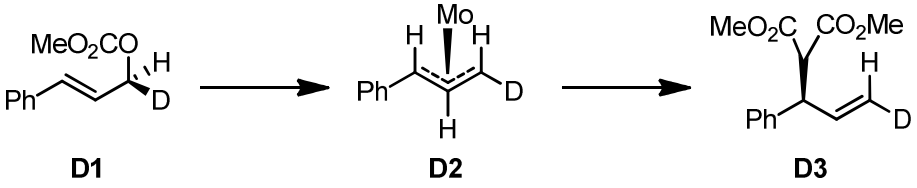
Based on X-ray and NMR studies with the aid of DFT calculations, a mechanism was proposed for MoAAA (**Scheme 3.6**). First of all, **L1** and Mo(norbornadiene)$(CO)_4$ forms a neutral unsymmetrical complex, **C1**. The reaction of allylic substrate forms an 18-electron η^3-allyl Mo(II) complex **C1-A** with a close octahedral geometry supported by X-ray crystallography. The coordination of the amide oxygen is displaced by CO, and this is followed by the coordination of the nucleophile to the metal. Reductive elimination affords the desired product and completes the catalytic cycle. The most vital role in the cycle belongs to CO: in the absence of it, no conversion is observed.[34]

[34] (a) Krska, S. W.; Hughes, D. L.; Reamer, R. A.; Mathre, D. J.; Sun, Y.; Trost, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12656. (b) Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S.; Reamer, R. A.; Palucki, M.; Yasuda, N.; Reider, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929.



Scheme 3.6. Mechanism of MoAAA reaction.

The stereoselectivity of MoAAA has been investigated in large detail (**Scheme 3.7**). Overall retention of configuration is observed via a double retention mechanism by deuterium labelling studies. This is in contrast to the double inversion mechanism observed in PdAAA. The retention–retention pathway has been investigated by deuterium labeled ^{1}H NMR studies, favoring π-allyl complex **D2** for linear carbonates. This points out to the addition of molybdenum from the same side as the leaving group, the carbonate. Upon addition of sodium dimethyl malonate, the complex is converted into product with retention of stereochemistry and without transposition of deuterium.



Scheme 3.7. Stereoselectivity of MoAAA confirmed by deuterium-labelling studies.

3.2.2. LIGANDS

The enantiodiscriminating event happens in the coordination sphere of molybdenum, therefore the chiral space for asymmetric induction is more compact than PdAAA.[35] Hence, the general chiral ligands are based on less bulky pyridine rings than the regular Trost ligand used in PdAAA (**Figure 3.4**). As can be seen from the mechanistic studies the bidentate coordination from nitrogen atoms of pyridine groups is not required. This is supported by the fact that ligand **L1**, containing only one pyridine unit, was more selective than the regular ligand **L**. In addition, the C_2 symmetry has been found to be unnecessary by the use of various C_1 symmetric diamine backbones (**L2**-**L4**).[36] Despite all these facts, since bipyridyl ligand **L** is easier to synthesize even on large scale and for both enantiomers, it is the first choice of ligand for MoAAA. With these ligands, generally very high selectivity is observed (>20:1 branched to linear ratio, 99% ee). Bisoxazoline ligands (**L5**, **L6**) developed by Glorius and Pfaltz are another heterocyclic moieties which work well in MoAAA with excellent results.[37]

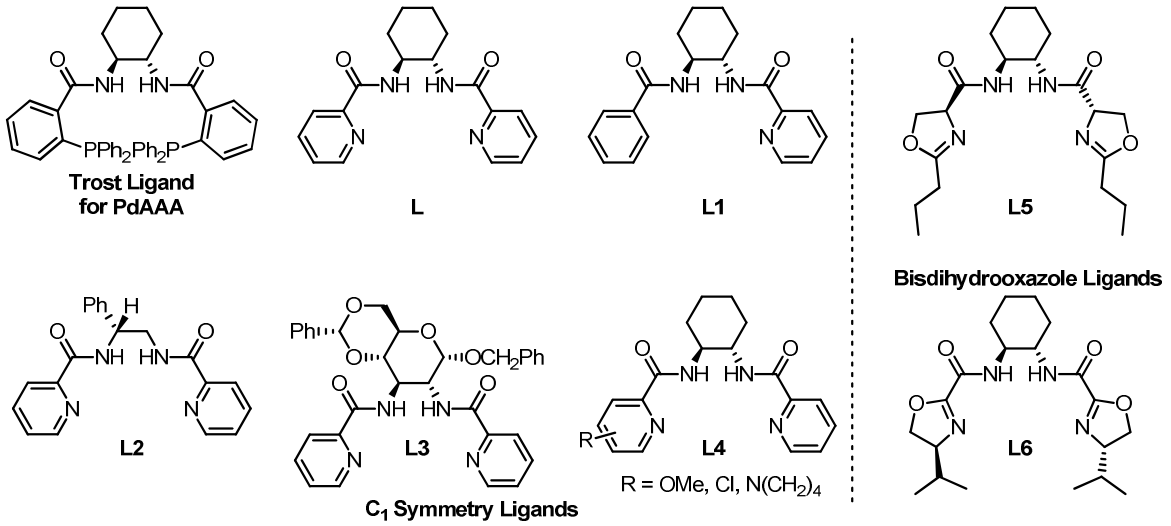


Figure 3.4. Ligands developed for MoAAA.

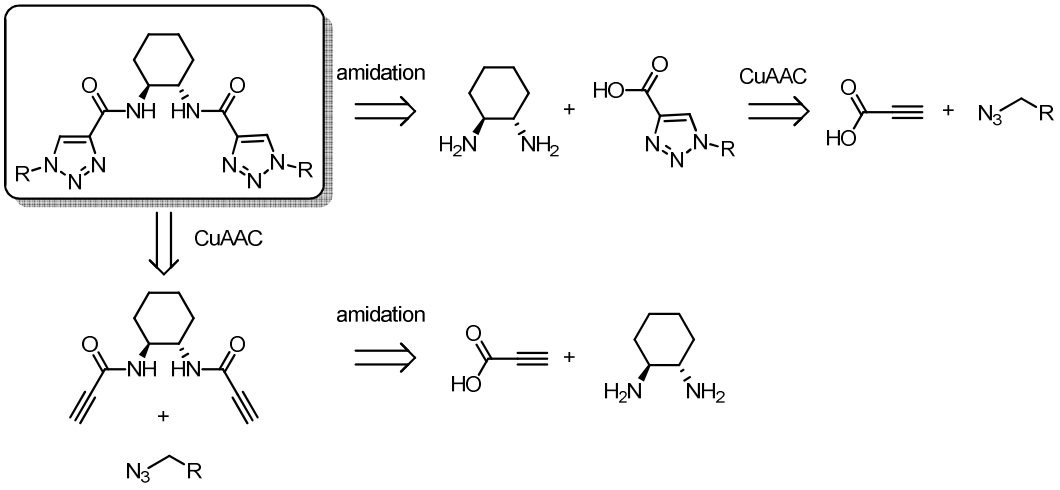
Remarkably, Moberg and co-workers developed polymer-supported ligands and showed that under microwave conditions with hexacarbonyl molybdenum the reaction is complete in less than 10 min, adding versatility to the reaction. The observed acceleration

[35] Lloyd-Jones, G. C.; Krska, S. W.; Hughes, D. L.; Gouriou, L.; Bonnet, V. D.; Jack, K.; Sun, Y.; Reamer, R. A. *J. Am. Chem. Soc.* **2003**, *126*, 702.
[36] Malkov, A. V.; Gouriou, L.; Lloyd-Jones, G. C.; Starý, I.; Langer, V.; Spoor, P.; Vinader, V.; Kočovský, P. *Chem.– Eur. J.* **2006**, *12*, 6910.
[37] Glorius, F.; Pfaltz, A. *Org. Lett.* **1999**, *1*, 141.

is most probably due to superheating phenomena under microwave irradiation at high pressure.[38]

3.3. AIM

In order to take the use of 1,2,3-triazoles in asymmetric metal-catalysis one step further, we envisioned the preparation of chiral "*click*" ligands merging the "*privileged chiral ligands*" and "*click chemistry*" concepts in our design. The aim of this chapter is devoted to the development of modular chiral ligands from commercial materials like chiral diamines, alkynes and azides. Two different strategies using simple amidation and CuAAC reaction resulted in highly selective ligands for MoAAA (**Scheme 3.8**).



Scheme 3.8. Design of the ligands.

[38] Belda, O.; Lundgren, S.; Moberg, C. *Org. Lett.* **2003**, *5*, 2275.

PAPER D

A Highly Enantio- and Regio-Selective Amido-Triazole "Click" Ligand for Molybdenum-Catalyzed Asymmetric Allylic Alkylation Reactions

Manuscript in preparation for Advance Synthesis & Catalysis

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

A Highly Enantio- and Regio-Selective Amido-Triazole "Click" Ligand for Molybdenum-Catalyzed Asymmetric Allylic Alkylation Reactions

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Abstract. Preparation of cyclohexyldiamidotriazole from propiolic acid (**1**) benzyl azide (**2**), and cyclohexyldiamine (**4**) is described with its evaluation in molybdenum catalysed asymmetric allylic alkylation (MoAAA) reactions using aryl carbonates with dimethyl malonate. High enantio- and regioselectivities obtained with the novel chiral triazole ligand **5** either in batch or microwave assited conditions; and its modular nature of synthesis with copper catalysed azide alkyne cycloaddition (CuAAC) and simple amide coupling reactions enable a different approach to ligands stemmed from click chemistry with potential novel diversity in asymmetric catalysis.

Keywords: asymmetric catalysis; click chemistry; molybdenum; copper; triazoles.

In the beginning of the 21st century; click chemistry[1], the very first conceptual idea in chemical synthesis, lead to a new era with its *"cream of the crop"* 1,2,3-triazoles by CuAAC.[2] Almost all synthetic community found a particular interest to incorporate triazole derived from CuAAC into their research, from biological systems to materials chemistry and much more beyond. In general, it became a tool-box reaction for post-modification of functional groups with its orthogonal nature.[3]

In chemical biology, CuAAC lead the way, allowing easy and fine tuning of biopolymers and which resulted in new directions such as conjugations with small molecules.[3o, 4] Recent developments involved *in vivo* type bioorthogonal CuAAC that itself prone to find applications in many areas in addition to imaging of cellular process.[4c, 5] In medicinal chemistry, CuAAC is now a classical method of introducing molecular diversity. This orthogonal chemistry combined with controlled/living polymerization techniques, generated a whole new window in polymer science,[6] immediate impacts in macromolecular chemistry mostly have been in *e.g.* end group modifications, novel dendrimers, small molecule immobilizations onto all *"nano"* surfaces.[3k, 3m, 3n, 7] In the literature, there has been also a huge effort to catalyze the CuAAC reaction in order to accelerate the reaction and reduce the amount of copper used.

Particularly in catalysis, CuAAC derived ligands have been a relatively new area where metal catalyzed reactions with such ligands have a very intruding potential to use its fine tuning for structural diversity.[8] Interestingly, triazoles found to be acting as donor ligands in CuAAC itself; and copper complexes showed very increased level of activity. Also in the literature there is a great number different catalytical systems for CuAAC.[5a, 5c, 9]

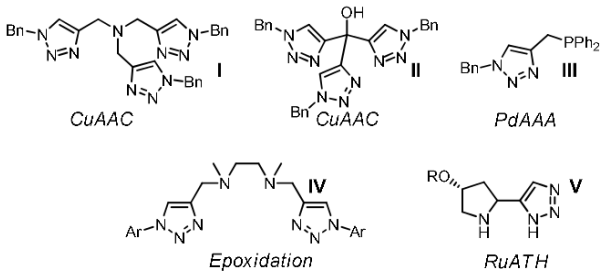


Figure 1. Triazole based CuAAC ligands used in metal-catalyzed reactions.

In this direction, following the seminal work,[8a, 9g, 10] we also developed TTM.CuCl[8g, 11] that has been deliberately used as catalyst for 1,2,3-triazoles as linkers in polymer supported catalysis and its ability to work with copper-chelating substrates enabled us and others to take the advantage.[12] But still in literature, triazoles have been vastly used for selective binding as metal chelators either with N-2 or N-3 atoms.[13] There are several racemic ligands using triazole structure in their backbone for reactions other than catalysing CuAAC, such as monophosphines (ClickPhos)[8c], (Clickphine)[8d] and

tetradentate bis-triazole ligands[8h]. There have been only few examples with enantioselective examples; namely, ferrocenyl diphosphines (ClickFerrophos) by Fukuzawa and co-workers [8f, 8k] in Ru-catalyzed asymmetric transfer hydrogenation (ATH), Pd-catalyzed allylic alkylation reactions (PdAAA), and Rh-catalyzed hydrogenation, standing as the best example; P-chirogenic phosphines (ChiraClick) by Kann and co-workers [8e] in PdAAA with very low enantioselectivity, and amino acid derived ligands by Adolfsson and Tinnis [8i] in RhATH with very low catalyst loading and good enantioselectivities for ATH conditions. Recently, proline-derived aminotriazoles developed in our research group showed the direct metal-triazole interaction clearly, with potential diverse ligand family and good catalytic activity in RuATH.[8j] But in general, practical examples of enantioselective reactions with triazole ligands mostly remain unexplored to our knowledge.

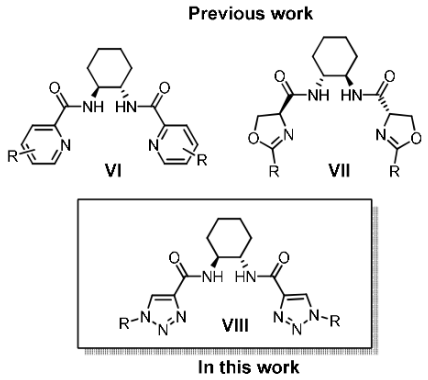
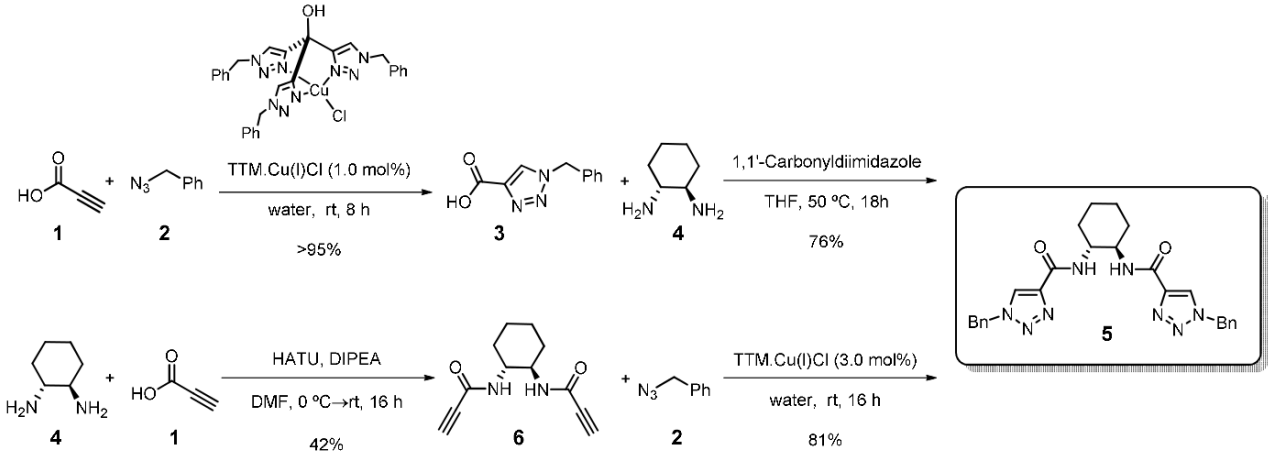


Figure 1. General backbone of MoAAA ligands.

One of the most powerful enantioselective carbon-carbon and carbon-heteroatom bond forming methodologies, asymmetric allylic alkylation reaction (AAA)[14], has been extensively studied with different metals. Complementary to the well-known Pd-catalyzed process[15] in terms of regioselectivity, Mo counter-part has been investigated intensively to find a relative ligand family for asymmetric induction by Trost and others.[15d, 16] The branched product formation has wider nucleophile spectrum with Ir catalyzed reaction where it is not only limited to only C-C but also C-heteroatom bond forming reactions. However, molybdenum is more attractive due to being a cheaper metal that combined with its experimental ease of handling under microwave conditions. Upon the discovery by Trost and Hachiya[17] that pyridyl-amide ligands induces very high regio- and enantio-selectivity and parallel to the mechanistic studies, new and different allylic addition products have been obtained by the ease of this methodology.[15d, 16, 18]

The importance of σ donor nitrogen ligands in MoAAA was crucial and we envisioned that triazoles might also be highly active and selective. In a specific example Lammertsma and co-workers showed that triazoles have selective binding onto Mo.[19] In line of all these information, we were encouraged that CuAAC derived ligands (two steps from commercial materials) from diaminocyclohexane would provide rapid access to a new ligand family for MoAAA. Herein, we present preparation and catalytic activity of "*click*" amidotriazole ligand for MoAAA with highly enantio- and regio-selectivities. Evaluation of catalytic activity in MoAAA of different electrophiles with malonates revealed excellent yields, enantio- and regioselectivities. Microwave assited conditions were also investigated.

The ligand synthesis was aimed to be direct and easily prepared since the pyridyl- derivatives can be synthesized in one step from commercial materials. For triazole synthesis, CuAAC reaction is the key step; our building blocks consist of simple azides and terminal alkynes; in such a way that either a CuAAC of CHDA derived di-propagyl amide **6** with a benzyl azide (**2**) or an amide coupling of **3** with CHDA (**4**).



Scheme 1. Synthesis of the ligand.

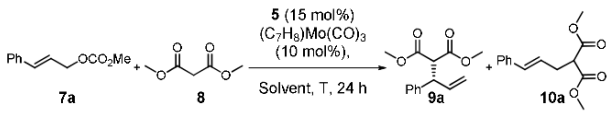
All of those reactions were relatively easy sequences with relevant reported procedures but overall, somehow minor optimizations of reaction conditions were necessary to proceed (see Scheme 1).

In the first strategy, CuAAC of propiolic acid (**1**) with benzyl azide (**2**) was performed using our TTM.CuCl catalyst at room temperature *on water*[20] and just with simple filtration the product was used directly in the next step, amide coupling, with CHDA (**4**) using 1,1′-carbonyldiimidazole (CDI). This sequential synthesis approach afforded **5** in very good yield (72% over 2 steps) and purity.

Afterwards, we put effort to develop more general strategy to synthesize a versatile backbone from which a diverse set of ligand family might be synthesized in a "*click*" approach. At this stage when CDI was used as coupling agent a polymerized crude was obtained whenever the acid **1** and CDI mixed at different concentrations and temperatures (0 and 23 ºC), similar to literature observarion. Screening experimentally a little bit of amide coupling methodology, using either HBTU or HATU, amidation afforded **6** and after workup the crude was subjected into CuAAC conditions using TTM.CuCl as catalyst with benzyl azide (**2**) to afford **5** in 34% overall yield. In this way, having even the crude of **6**, a family of these ligands can be prepared very in a modular manner. With **5** in hand, next we started to screen reaction conditions for MoAAA using cinnamyl methyl carbonate (**7a**), dimethyl malonate (**8**), and sodium hydride leading to dimethyl 2-(1-phenylallyl)malonate (**9a**) as the major product.

In the preliminary tests, the most reproducible results with labile ligated Mo salt were obtained with $C_7H_8Mo(CO)_3$ (cycloheptatriene molybdenum tricarbonyl) with respect to $Mo(CO)_3(NCCH_2CH_3)_3$ (Tricarbonyltris(propionitrile)molybdenum). In the very first results in tetrahydrofuran (THF) made apparent the superiority of the ligand in terms of enantio- and regio-selectivity (95%, 95:5). However, the conversion (20%) was the limiting factor in order to get a fully working system (see Table 1). Taking this result as our reference, we decided to screen reaction conditions to further develop our system. The successful system was shielded by the limited solubility of the ligand. In THF with in logical reaction and catalyst molarities, the ligand precipitates, and in order to gain access to a more homogenous system a through screening of solvents were done.

Table 1. Effect of Solvent[a].

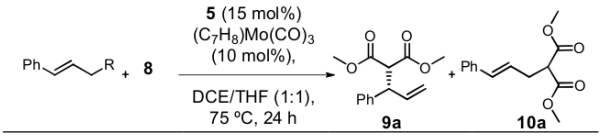


Solvent	T [ºC]	Yield [%][b]	**9a**:**10a**[c]	ee [%][d]
THF	60	20	95:5	95
DCE	75	14	94:6	nd[e]
DCE–THF (1:2)	75	73	93:7	98
DCE–THF (1:1)	75	80	97:3	98

[a] Reaction Conditions: (See Experimental Section).
[b] Isolated yield.
[c] Branched to linear ratio by ^{1}H-NMR of crude.
[d] Determined by Chiral HPLC columns.
[e] nd: not determined.

Finally, 1,2-dichloroethane (DCE) was found to be essential in order get the ligand soluble however, the solubility of *in situ* generated dimethyl sodiomalonate was very limited in only DCE that resulted a lower yield (14%). After this point, mixture of DCE–THF (1:1) was afforded best conditions in hand. In general experimental set up, a two-pot generation of catalyst and nucleophile was followed; DCE was used to form the active metal-ligand complex and THF was used to form dimethyl sodiomalonate. Following, the effect of leaving group was in question and the trend was the same that was observed in pyridyl- ligands.

Table 2. Effect of Leaving Group [a].

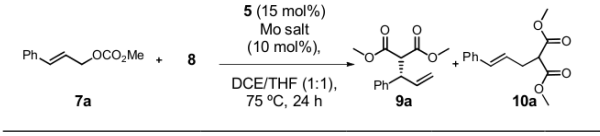


R[b]	Yield [%][c]	**9a**:**10a**[d]	ee [%][e]
-OCO_2Me	80	97:3	98
-Ac	49	95:5	98

[a] Reaction Conditions: (See Experimental Section).
[b] –OCO_2Me: methyl carbonate; -Ac: acetate.
[c] Isolated yield…
[d] Branched to linear ratio by ^{1}H-NMR of crude.
[e] Determined by Chiral HPLC columns.

The acetate (-Ac) group afforded only a moderate conversion to the products but selectivities were still in excellent range (see Table 2). Having controlled most of the parameters, bench top stable molybdenum salt was screened another time to see its effect.

Table 3. Effect of Molybdenum Salt [a].



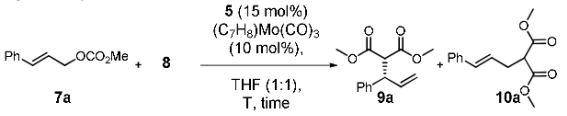
Mo salt[b]	Activation Time [min]	Yield [%][c]	**9a**:**10a**[d]	ee [%]
$(C_7H_8)Mo(CO)_3$	15	80	97:3	98
$Mo(CO)_6$	45	67	94:6	98

[a]Reaction Conditions: (See Experimental Section).

[b] $(C_7H_8)Mo(CO)_3$:Cycloheptatriene molybdenum tricarbonyl; $Mo(CO)_6$: molybdenum hexacarbonyl.
[c] Isolated yield.
[d] Branched to linear ratio by ^{1}H-NMR of crude.
[e] Determined by Chiral HPLC columns.

The activation time for molybdenum hexacarbonyl ($Mo(CO)_6$) that was observed by color change in complexation mixture in DCE took much longer time than the labile ligated counter-part (see Table 3). The observation was proven to be parallel with the lower yield of the reaction. Since the availability and previous effort by Belda and Moberg for the use of $Mo(CO)_6$ was present, we were motivated to optimize microwave conditions with this Mo salt. Following the precedent reference; the screening started at 160 ºC within 10 min.

Table 4. Condition Screening for Microwave Assisted MoAAA. [a]



T [ºC]	Time [min]	Yield [%][b]	**9a**:**10a** [c]	ee [%][d]
160	10	21	nd [e]	nd
120	30	10	nd	nd
120	120	20	nd	nd
100	90	38	nd	nd
80	120	70	95:5	98
80	180	99	97:3	98

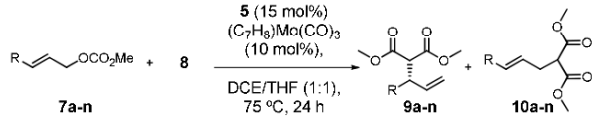
[a] Reaction Conditions: (See Experimental Section).
[b] Isolated yield.
[c] Branched to linear ratio by ^{1}H-NMR of crude.
[d] Determined by Chiral HPLC columns.
[e] nd: not determined.

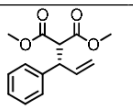
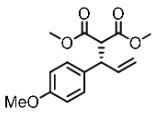
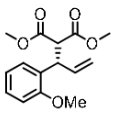
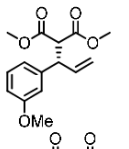
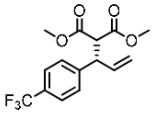
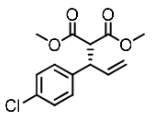
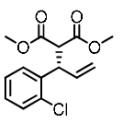
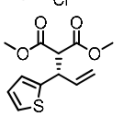
At around such elevated temperatures, with respect to our batch conditions and the literature, our ligand was ineffective. As the temperature got decreased and the time was increased; interestingly we found that in very low temperature (80 ºC) to what was previously reported, our ligand was active where the pyridyl-ligands were reported ineffective (see Table 4). Overall, triazole ligand enables a low temperature profile for microwave assisted MoAAA reaction with very good selectivities. In microwave conditions the ligand works only in THF without any problems.

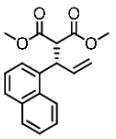
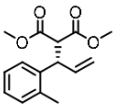
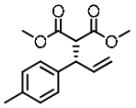
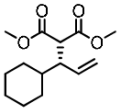
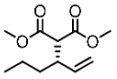
After having set all important preliminary parameters, the scope of the reaction was the final objective of this project. For the synthesis of electrophiles typical three step process was followed, starting from a cinnamyl aldehyde derivative, first with a Wittig-Horner reaction, and having the *E*-selective ester, it was reduced to corresponding alcohol with standard DIBAL-H conditions. With allylic alcohol in hand, it was transformed into the allylic carbonate in overall comparable yields with ease.

Gratifyingly, all these allyl alcohol derived, aryl carbonates with different substitution patterns were evaluated and in general excellent catalytic activity in terms of yield and enantio- and regio- selectivity were obtained. No further attempts were done to optimize reactions based on substrate depended results. Phenyl ring with different substitutions such as electron-deficient (entry 5), electron-rich (entry 2) and sterically challenging (entry 3, 7, 10) substrates work very well. Electron-rich thiophene (entry 8) and bulkier naphthalene (entry 9) work fine as well. In general, no deterioration of ee was observed within the broad scope. However, when alkyl- counter-parts of the substrates was utilized no reactivity was observed.

Table 5. Scope [a].



Entry	Product		Yield [%][b]	**9**:**10**[c]	ee [%][d]
1		**9a**	80	97:3	98
2		**9b**	98	98:2	97
3		**9c**	94	97:3	99
4		**9d**	52	93:7	99
5		**9e**	76	90:10	99
6		**9f**	89	94:6	99
7		**9g** [e]	94 (92)	95:5 (91:9)	95 (97)
8		**9i**	99	93:7	98

9		**9j**	88	96:4	97
10		**9k**	95	97:3	98
11		**9l**	84	95:5	95
12		**9m**	<5	nd [f]	nd
13		**9n**	<5	nd	nd

[a] Reaction Conditions: (See Experimental Section).
[b] Isolated yield.
[c] Branched to linear ratio by ^{1}H-NMR of crude.
[d] Determined by Chiral HPLC columns.
[e] 1.0 mmol scale, in parenthesis.
[f] nd: not determined.

Gratifyingly, all these allyl alcohol derived, aryl carbonates with different substitution patterns were evaluated and in general excellent catalytic activity in terms of yield and enantio- and regio- selectivity were obtained. No further attempts were done to optimize reactions based on substrate depended results. Phenyl ring with different substitutions such as electron-deficient, electron-rich and sterically challenging substrates work very well. Electron-rich thiophene and bulkier naphthalene work fine as well. In general, no deterioration of ee was observed within the broad scope. However, when alkyl- counter-parts of the substrates was utilized no reactivity was observed.

In conclusion, the ligand developed from very general and simple CuAAC methodology, is one of the first practical catalytic system in an advanced modern asymmetric reaction where a triazole ligand used. The excellent selectivities either in batch or microwave conditions make this ligand a possible candidate for further development in different reactions. The synthesis of the ligand enables an easy approach to generate a direct set of ligand family with very diverse nature that might help to extend the scope of MoAAA further.

Experimental Section

Experimental Procedure for MoAAA in Batch Conditions

Into a 15-mL round bottom vial (Ø=1 cm), was weighed Cycloheptatriene molybdenum tricarbonyl (5.9 mg, 0.022 mmol, 10 mol%) and the amide-triazole ligand **5** (16 mg, 0.033 mmol, 15 mol%), into another vial, sodium hydride (10.4 mg, 0.434 mmol, 2.0 equiv) was added from glove box. The vials were evacuated and re-filled with Argon for 3 times. To the catalyst vial was added 1,2-dichloroethane (1 mL) and stirred at 75 ºC for 15 min. At the same time, to the nucleophile vial was added tetrahydrofuran (1 mL), dimethyl malonate (0.063 g, 0.48 mmol, 2.2 equiv) and stirred at rt for 15 min until a clear solution formed. The catalyst was transferred to nucleophile vial via cannula and the appropriate allylic carbonate (electrophile) (0.217 mmol, 1 equiv) via syringe. The reaction mixture was stirred at 75 ºC. After 24 h, the reaction mixture was poured into water (5 mL) and was extracted with diethyl ether (3×10 mL) and the organic layers were dried over magnesium sulfate, were filtrated and were concentrated under reduced pressure and **9**/**10** ratio was determined by the ^{1}H NMR of the crude. Later, the crude was purified by flash column chromatography [silica gel Ø=1 cm, h=15 cm, and eluted with hexanes–ethyl acetate (98:2)] to afford products.

Experimental Procedure for Microwave assisted-MoAAA

Two different stock solutions were prepared: *Solution-1*, with the malonate, was prepared by adding dimethyl malonate (**8**) (880 µL, 7.70 mmol) to a suspension of sodium hydride (16.2 mg, 0.680 mmol) in tetrahydrofuran (10 mL). *Solution-2*, was prepared by dissolving **7a** (1,36 g, 7.10 mmol) in tetrahydrofuran (10 mL). Molybdenum hexacarbonyl (6.9 mg, 0.026 mmol) and **5** (17 mg, 0.034 mmol) were added to a microwaves vial and sealed; were evacuated and re-filled with Argon for 3 times. *Solution-1* (1.5 mL, 1.16 mmol of the nucleophile), *Solution-2* (1 mL, 0.71 mmol of the electrophile) and *N*,*O*-Bis(trimethylsilyl)acetamide (BSA) (220 µL) were added and the sample was heated in the microwave cavity in CEM Discover instrument with specific set of options: maximum power = 300 W; ramp time: up to 30 min (until set temperature achieved); hold time: 3 h; temperature = 80 ºC and power max mode kept on; maximum pressure = 300 PSI with stirring on. After 3 h, the reaction mixture was diluted with diethyl ether (10 mL) and the orange solution was filtrated and analyzed by ^{1}H-NMR for the branched to linear ratio. Later, the crude was purified by flash column chromatography [silica gel Ø=1 cm, h=15 cm, and eluted with hexanes–ethyl acetate (98:2)] to afford products.

Acknowledgements

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Supporting Information

A Highly Enantio- and Regio-Selective Amido-Triazole "Click" Ligand for Molybdenum-Catalyzed Asymmetric Allylic Alkylation Reactions

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1. GENERAL INFORMATION

Unless otherwise stated all the reactions were done under inert conditions (exclusion of air and moisture); under positive pressure of Argon into flame dried round bottom flasks equipped with stirring bar. All temperatures given for reaction conditions are externally measured. The screening and reaction optimization of Molybdenum-catalyzed allylic alkylations (MoAAA) were done under extreme precautions to exclude air and moisture; in flame dried 15-mL (diameter= 1 cm) disposable borosilicate vials equipped with stirring bar and heated with external temperature control using aluminum blocks. Reactions were monitored by ^{1}H-NMR (see Instrumentation), TLC.

2. MATERIALS

Commercial materials were used as received with following exceptions: All the solvents were used from Solvent Purification System and 1,2-Dichloroethane purchased from Aldrich (product #: 284505, CAS #: 107-06-2) in anhydrous form and further dried over 4 Å activated molecular sieves at least 24h prior to use. All solvents used in MoAAA were subjected to freeze thaw pump cycle three times prior to use. Molybdenum salts were purchased from Strem, Cycloheptatriene molybdenum tricarbonyl (product #: 42-0350, CAS #: 12125-77-8, red crystals) stored in glove box and used as received, molybdenum hexacarbonyl (product #: 42-1350, CAS #: 13939-06-5, white crystals) used as received. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns.

All electrophiles, carbonates, were synthesized according to prior report.[1]

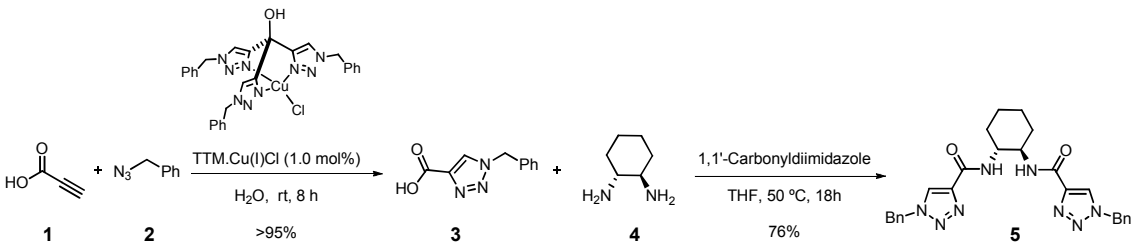
3. INSTRUMENTATION

^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300, 400, or 500 MHz and at 100 or 125 MHz, respectively; on a spectrometer in $CDCl_3$ at room temperature (unless otherwise stated). Chemical shifts (δ) were reported with respect to tetramethylsilane as internal standard, or to the corresponding solvent residual peak, in ppm. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses made in C.A.I. Microanálisis Elemental, Universidad Complutense de Madrid (Spain). High Resolution Mass Spectra (HRMS) were performed by the High Resolution Mass Spectromety Service

at the Institute of Chemical Research of Catalonia on Waters GCT gas chromatograph coupled time-of-flight mass spectrometer (GC/MS-TOF) with electron ionization (EI). The optical rotation was recorded on Jasco P-1030 Polarimeter and reported as $[\alpha]^{D}_{26}$ (*c* in g/100 mL, solvent). Thin layer chromatography (TLC), Merck pre-coated TLC plates (silica gel 60 GF_{254} , 0.25 mm) were used, using UV light as the visualizing agent and an acidic mixture of ceric ammonium molybdate (CAM) or basic aqueous potassium permanganate ($KMnO_4$), and heat as developing agents. Reactions under microwave irradiation were performed in CEM Discover instrument with specific set of options: maximum power = 300 W; ramp time: 5 min; hold time: depending on reaction in h; temperature = 80 ºC and power max mode kept on; maximum allowed pressure = 300 PSI with stirring on. Organic solutions were concentrated under reduced pressure on a rotary evaporator. Enantiomeric purity were determined by HPLC using commercial chiral columns as stationary phase (methods specified for each compound under its name, see below).

4. SYNTHESIS OF THE LIGANDS

4.1. FIRST-GENERATION SYNTHESIS



***N,N'*-((*1R,2R*)-cyclohexane-1,2-diyl)bis(1-benzyl-1H-1,2,3-triazole-4-carboxamide) (5)**

Into a 10-mL vial was added tris(1-benzyl-1H-1,2,3-triazol-4-yl)methanol.CuCl[2] (0.017 g, 0.029 mmol, 1.0 mol%), propiolic acid (**1**) (0.200 g, 2.86 mmol, 1 equiv) and benzyl azide (**2**) (0.418, 3.14 mmol, 1.10 equiv) in water (5 mL) and was stirred at rt for 8 h. The reaction mixture turned from transparent liquid into a blue–white solid and the reaction mixture was filtrated and was washed with cold acetone (3×5 mL) and the crude white solid **3**[3] was used directly on next step without any further purification.

1-benzyl-1H-1,2,3-triazole-4-carboxylic acid (**3**) (0.556 g, 2.74 mmol, 2.50 equiv) and 1,1'-carbonyldiimidazole (0.437g, 2.63 mmol, 2.40 equiv) were added as solid in

tetrahydrofuran (10 mL) and was stirred at 50 ºC. After 1.5 h, the heterogeneous mixture was diluted with tetrahydrofuran (3×15 mL) and cannula transferred into another flask with a pre-stirred mixture (at 50 ºC for 30 min) of (1R,2R)-cyclohexane-1,2-diamine (**4**) (0.125 g, 1.095 mmol, 1.00 equiv) in tetrahydrofuran (45 mL) at 50 ºC. After 16 h, the volatiles were removed under reduced pressure, followed by extraction with dichloromethane (3×50 mL) over aqueous potassium carbonate $_{(sat)}$ (15 mL). Combined organic layers were dried over sodium sulfate, were filtrated and were concentrated under reduced pressure and the crude was purified by flash column chromatograpghy [silica gel Ø=3 cm, h=15 cm, and eluted with DCM–MeOH (95:5 to 90:10)] to afford 76% desired product **5** (0.403 g, 0.832 mmol).

Physical form: white solid

TLC (15% methanol in dichloromethane, UV_{254}, CAM), R_f: 0.72

mp: 294 – 295 ºC.

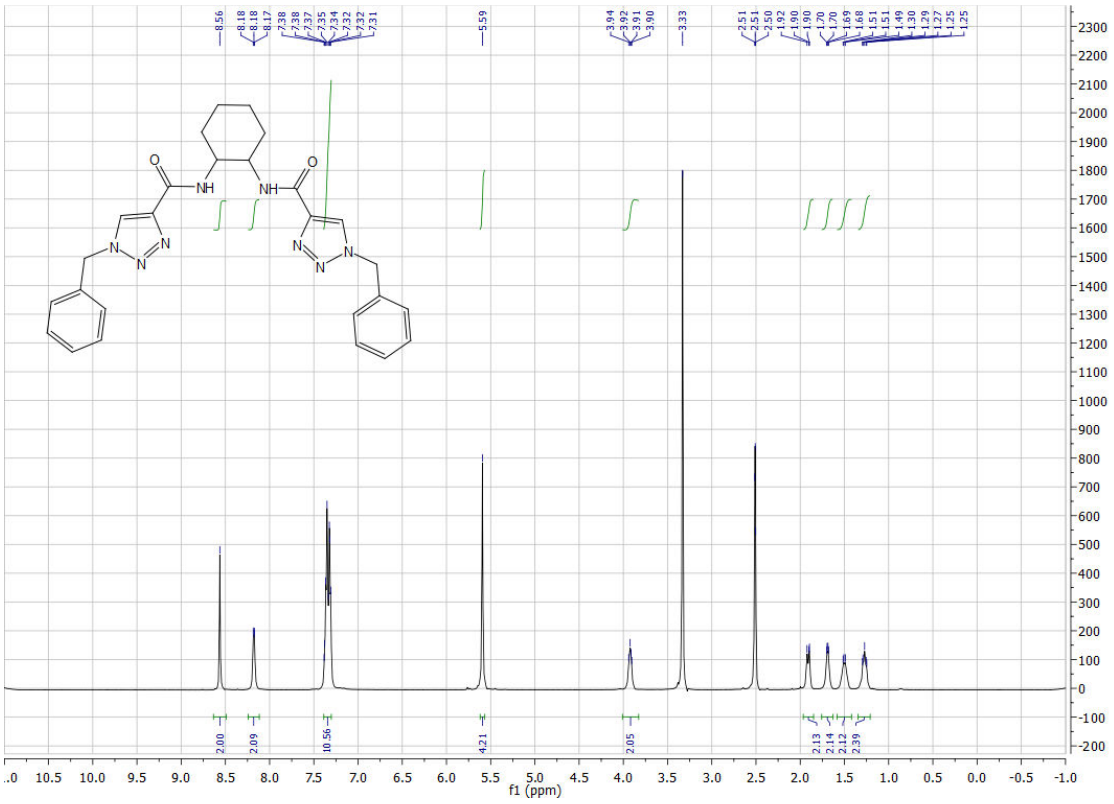
^{1}H-NMR (500 MHz, DMSO-d_6): δ 8.56 (s, 2H), 8.18 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.30 (m, 10H), 5.59 (s, 4H), 4.01 – 3.83 (m, 2H), 1.97 – 1.85 (m, 2H), 1.76 – 1.63 (m, 2H), 1.58 – 1.42 (m, 2H), 1.35 – 1.21 (m, 2H) ppm.

^{13}C-NMR (126 MHz, DMSO): δ 159.4, 142.8, 135.6, 128.8, 128.2, 128.0, 126.4, 53.0, 51.8, 31.6, 24.4 ppm.

FTIR: 3335 (s), 3118 (s), 2927 (s), 2855 (s), 1640 (s), 1567 (s), 1502 (s), 1458 (s), 1264 (s), 1049 (s), 715 (s) cm^{-1}.

HRMS (ESI) (*m/z*): calc'd for $C_{26}H_{29}N_8O_2$, $[M+H]^+$: 485.2416, found: 485.2408.

$[\alpha]^D_{26}$ = –37.6 (c = 0.10 in DMSO)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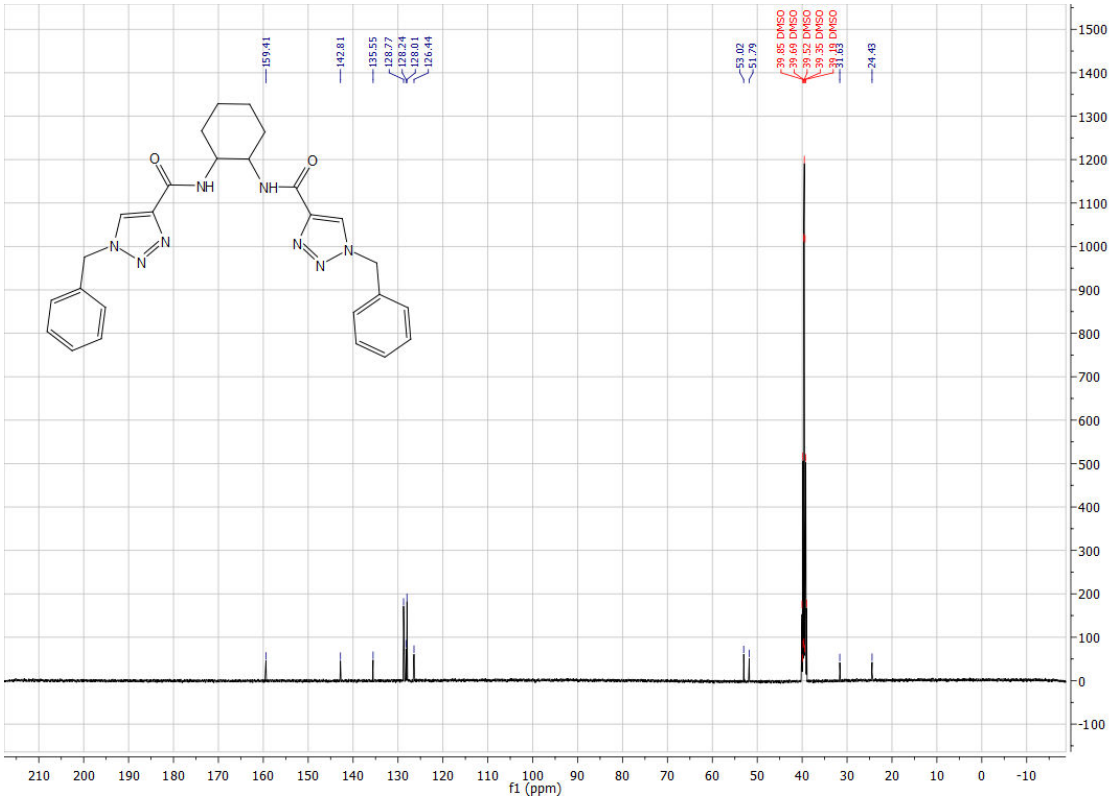
f1 (ppm)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51.79
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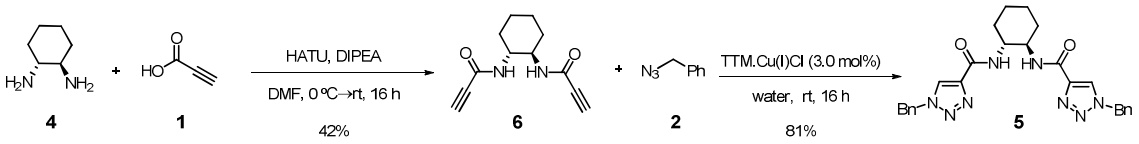
39.69 DMSO
39.52 DMSO
39.35 DMSO
39.18 DMSO
24.48
NH
NH
O
O
N
N
N
N
N
f1 (ppm)

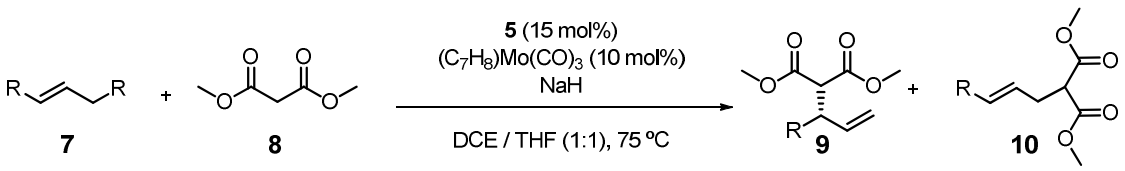
4.2. SECOND GENERATION SYNTHESIS OF 5



(1R,2R)-cyclohexane-1,2-diamine (**4**) (100 mg, 0.876 mmol, 1 equiv) was added as solid and was dissolved with dimethylformamide (3 mL). Propiolic acid (**1**) (0.252 g, 3.59 mmol, 4.10 equiv), 0.5 M HATU (1.328 g, 3.50 mmol, 4.00 equiv) solution in dimethylformamide (7 mL) and N,N-diisopropylethylamine (1.22 mL, 7.01 mmol, 8.00 equiv, d=0.740 g/mL at rt) were added drop-wise at 0 ºC, and reaction mixture were allowed heat at rt. After 18 h, the volatiles were removed under reduced pressure and the crude was poured into 1.0 M hydrochloric acid (10 mL) and extracted with ethyl acetate (3×20 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (10 mL), was dried over sodium sulfate and was filtered. The volatiles were removed under reduced pressure and the orange crude was filtered over a short plug of silica gel with dichloromethane-methanol (95:5) and the volatile were removed under reduced pressure, finally, **6** was used as crude in next step without further purification.

Into a 5-mL vial was added N,N'-((1R,2R)-cyclohexane-1,2-diyl)dipropiolamide (**6**) (0.160 g, 0.733 mmol, 1 equiv), benzyl azide (**2**) (0.390 g, 2.93 mmol, 4.00 equiv) and TTM.CuCl (0.013 g, 0.022 mmol, 3.0 mol%) in water (1 mL) at rt. After 16 h, water was filtrated and the solid was dried by vacuum filtration for 15 min and the dried solid was purified by flash column chromatography [silica gel Ø=1 cm, h=15 cm, and eluted with dichloromethane–methanol (95:5)] to afford **5** in 81% yield.

5. MOLYBDENUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION IN BATCH CONDITIONS



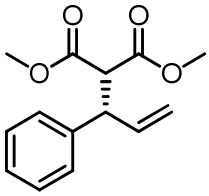
Into a 15-mL round bottom vial (Ø=1 cm), was weighed Cycloheptatriene molybdenum tricarbonyl (5.9 mg, 0.022 mmol, 10 mol%) and the amide-triazole ligand **5**

(16 mg, 0.033 mmol, 15 mol%), into another vial, sodium hydride (10.4 mg, 0.434 mmol, 2.0 equiv) was added from glove box. The vials were evacuated and re-filled with Argon for 3 times. To the catalyst vial was added 1,2-dichloroethane (1 mL) and stirred at 75 ºC for 15 min. At the same time, to the nucleophile vial was added tetrahydrofuran (1 mL), dimethyl malonate (0.063 g, 0.48 mmol, 2.2 equiv) and stirred at rt for 15 min until a clear solution formed. The catalyst was transferred to nucleophile vial via cannula and the appropriate allylic carbonate (electrophile) (0.217 mmol, 1 equiv) via syringe. The reaction mixture was stirred at 75 ºC. After 24 h, the reaction mixture was poured into water (5 mL) and was extracted with diethyl ether (3×10 mL) and the organic layers were dried over magnesium sulfate, were filtrated and were concentrated under reduced pressure and **9**/**10** ratio was determined by the ^{1}H NMR of the crude. Later, the crude was purified by flash column chromatography [silica gel Ø=1 cm, h=15 cm, and eluted with hexanes–ethyl acetate (98:2)] to afford products.MoAAA products.

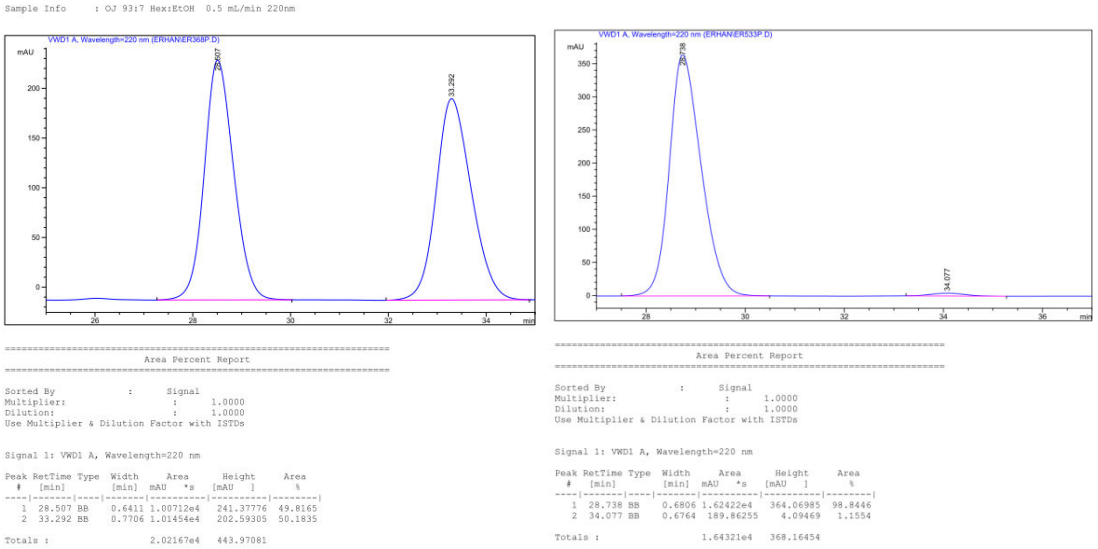
6. EXPERIMENTAL PROCEDURE FOR MICROWAVE ASSISTED-MOAAA

Two different stock solutions were prepared: *Solution-1*, with the malonate, was prepared by adding dimethyl malonate (**8**) (880 µL, 7.70 mmol) to a suspension of sodium hydride (16.2 mg, 0.680 mmol) in tetrahydrofuran (10 mL). *Solution-2*, was prepared by dissolving **7a** (1,36 g, 7.10 mmol) in tetrahydrofuran (10 mL). Molybdenum hexacarbonyl (6.9 mg, 0.026 mmol) and **5** (17 mg, 0.034 mmol) were added to a microwaves vial and sealed; were evacuated and re-filled with Argon for 3 times. *Solution-1* (1.5 mL, 1.16 mmol of the nucleophile), *Solution-2* (1 mL, 0.71 mmol of the electrophile) and *N*,*O*-Bis(trimethylsilyl)acetamide (BSA) (220 µL) were added and the sample was heated in the microwave cavity in CEM Discover instrument with specific set of options: maximum power = 300 W; ramp time: up to 30 min (until set temperature achieved); hold time: 3 h; temperature = 80 ºC and power max mode kept on; maximum pressure = 300 PSI with stirring on. After 3 h, the reaction mixture was diluted with diethyl ether (10 mL) and the orange solution was filtrated and analyzed by ^{1}H-NMR for the branched to linear ratio. Later, the crude was purified by flash column chromatography [silica gel Ø=1 cm, h=15 cm, and eluted with hexanes–ethyl acetate (98:2)] to afford products.

9a



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.22 (m, 5H), 6.05 (m, 1H), 5.17 – 5.09 (m, 2H), 4.16 – 4.12 (m, 1H), 3.91 (d, *J* = 11.0 Hz, 1H), 3.76 (s, 3H), 3.51 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 168.2, 167.8, 139.9, 137.8, 128.6, 127.9, 127.1, 116.6, 57.3, 52.6, 52.4, 49.7 ppm. HPLC: 98% ee (Chiral OJ column, 220 nm, hexanes–ethanol (93:7), flow: 0.5 mL/min, t_R: 28.74 min, t_R: 34.08 min).



Sample Info : OJ 93:7 Hex:EtOH 0.5 mL/min 220nm

VWD1 A, Wavelength=220 nm (ERHAN\ER368P.D)

mAU

min

VWD1 A, Wavelength=220 nm (ERHAN\ER533P.D)

mAU

min

Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	28.507	BB	0.6411	1.00712e4	241.37776	49.8165
2	33.292	BB	0.7706	1.01454e4	202.59305	50.1835

Totals : 2.02167e4 443.97081

Area Percent Report

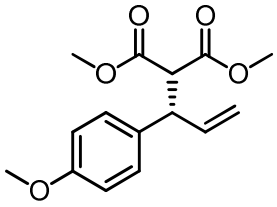
Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

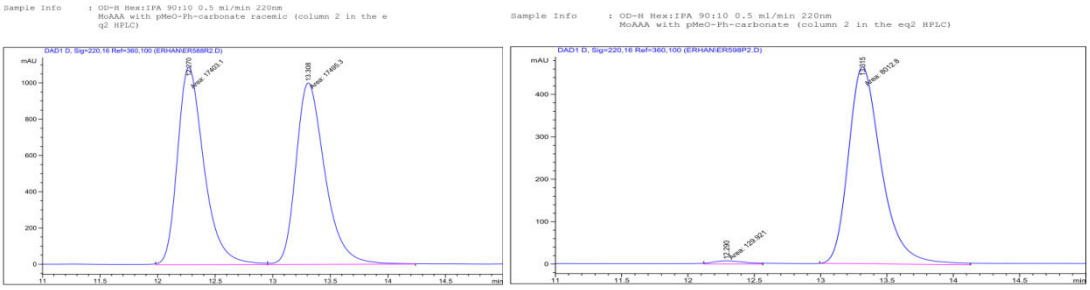
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	28.738	BB	0.6806	1.62422e4	364.06985	98.8446
2	34.077	BB	0.6764	189.86255	4.09469	1.1554

Totals : 1.64321e4 368.16454

9b



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 – 7.11 (m, 2H), 6.86 – 6.80 (m, 2H), 5.97 (ddd, *J* = 17.0, 10.2, 8.0 Hz, 1H), 5.14 – 5.01 (m, 2H), 4.06 (dd, *J* = 11.0, 8.1 Hz, 1H), 3.82 (d, *J* = 11.0 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.51 (s, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ 168.4, 168.1, 158.7, 138.2, 132.0, 129.1, 116.4, 114.2, 57.7, 55.3, 52.7, 52.6, 49.0 ppm. HPLC: 99% ee (Chiral OD-H column, 220 nm, hexanes–isopropanol (90:10), flow: 0.5 mL/min, , t_R: 12.29 min, 13.31 min).



Sample Info : OD-H Hex:IPA 90:10 0.5 ml/min 220nm MoAAA with pMeO-Ph-carbonate racemic (column 2 in the eq2 HPLC)

DAD1 D, Sig=220,16 Ref=360,100 (ERHAN\ER588R2.D)

Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=220,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.270	MF	0.2665	1.74031e4	1088.46240	49.8680
2	13.308	FM	0.2912	1.74953e4	1001.25635	50.1320

Totals : 3.48984e4 2089.71875

Sample Info : OD-H Hex:IPA 90:10 0.5 ml/min 220nm MoAAA with pMeO-Ph-carbonate (column 2 in the eq2 HPLC)

DAD1 D, Sig=220,16 Ref=360,100 (ERHAN\ER598P2.D)

Area Percent Report

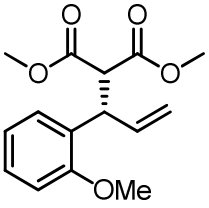
Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 D, Sig=220,16 Ref=360,100

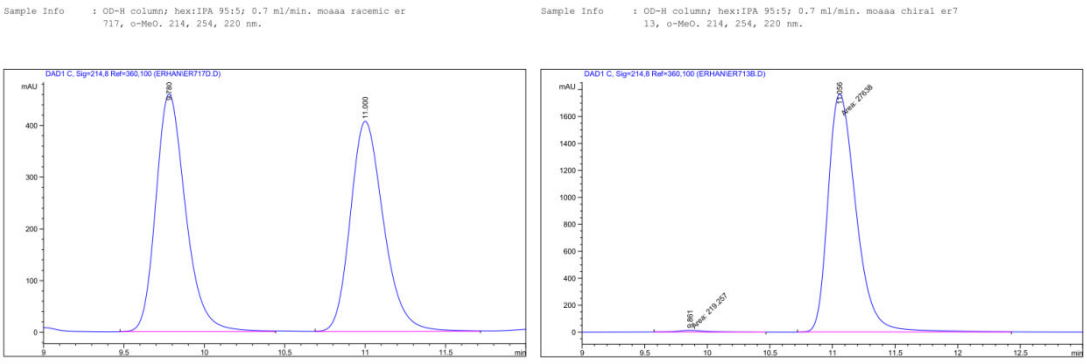
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.290	MM	0.2792	129.92108	7.75528	1.5955
2	13.315	MM	0.2875	8012.79541	464.51578	98.4045

Totals : 8142.71649 472.27106

9c



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.10 (m, 2H), 6.93 – 6.79 (m, 2H), 6.14 (ddd, *J* = 17.1, 10.1, 8.4 Hz, 1H), 5.17 – 4.97 (m, 2H), 4.41 – 4.29 (m, 1H), 4.19 (d, *J* = 10.7 Hz, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 3.49 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ168.8, 168.4, 157.3, 137.0, 129.6, 128.3, 120.8, 116.9, 111.2, 55.5, 52.4, 46.2 ppm. HPLC: 99% ee (Chiral OD-H column, 214 nm, hexanes–isopropanol (95:5), flow: 0.7 mL/min, t_R: 9.86 min, 11.06 min).



Sample Info : OD-H column; hex:IPA 95:5; 0.7 ml/min. moaaa racemic er717, o-MeO. 214, 254, 220 nm.

DAD1 C, Sig=214,8 Ref=360,100 (ERHAN\ER717D.D)

Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=214,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.780	BB	0.1983	5927.18604	459.94983	50.2777
2	11.000	BB	0.2221	5861.70215	406.85416	49.7223

Sample Info : OD-H column; hex:IPA 95:5; 0.7 ml/min. moaaa chiral er713, o-MeO. 214, 254, 220 nm.

DAD1 C, Sig=214,8 Ref=360,100 (ERHAN\ER713B.D)

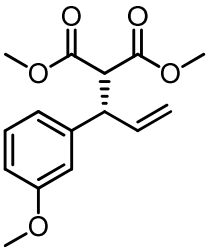
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

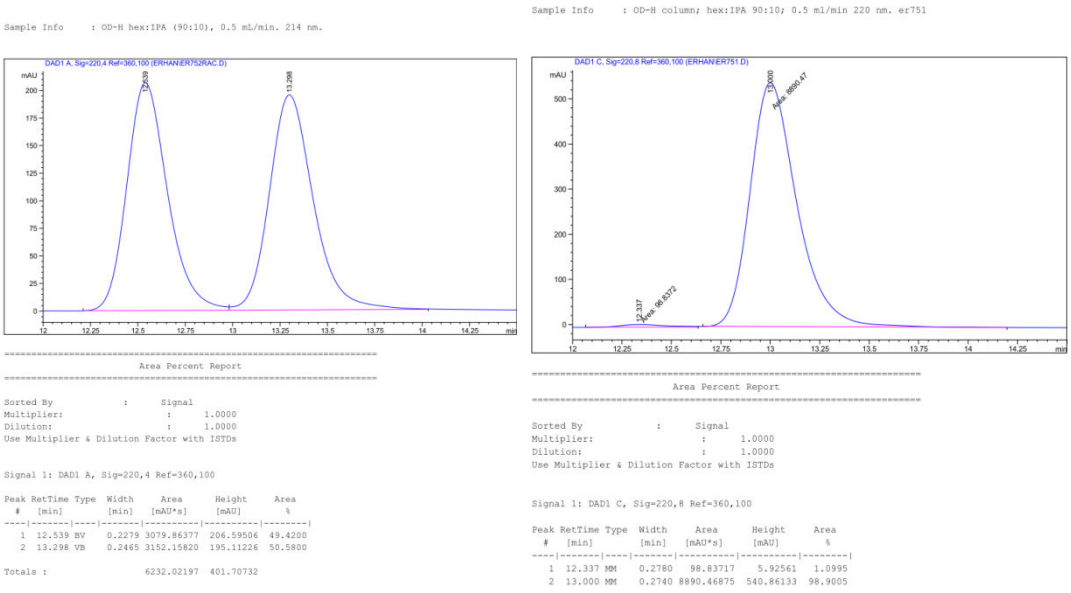
Signal 1: DAD1 C, Sig=214,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.861	MM	0.2748	219.25716	13.29847	0.7871
2	11.056	MM	0.2605	2.76380e4	1768.10645	99.2129

9d



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (td, *J* = 7.5, 1.2 Hz, 1H), 6.85 – 6.72 (m, 3H), 5.97 (ddd, *J* = 17.0, 10.2, 8.2 Hz, 1H), 5.17 – 5.03 (m, 2H), 4.08 (dd, *J* = 11.0, 8.2 Hz, 1H), 3.86 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 168.3, 167.9, 159.8, 141.7, 137.8, 129.7, 120.2, 116.8, 113.9, 112.6, 57.4, 55.3, 52.7, 52.6, 49.9 ppm. HPLC: (Chiral OD-H column, 214 nm, hexanes–isopropanol (90:10), flow: 0.5 mL/min, t_R: 12.54 min, 13.30 min).



Sample Info : OD-H hex:IPA (90:10), 0.5 mL/min. 214 nm.

DAD1 A, Sig=220,4 Ref=360,100 (ERHAN\ER75\2RAC.D)

mAU

12.539 BV

13.298 VB

Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.539	BV	0.2279	3079.86377	206.59506	49.4200
2	13.298	VB	0.2465	3152.15820	195.11226	50.5800

Totals : 6232.02197 401.70732

Sample Info : OD-H column; hex:IPA 90:10; 0.5 ml/min 220 nm. er751

DAD1 C, Sig=220,8 Ref=360,100 (ERHAN\ER751.D)

mAU

12.337 MM Area: 98.8372

13.000 MM Area: 8890.47

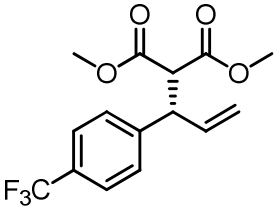
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

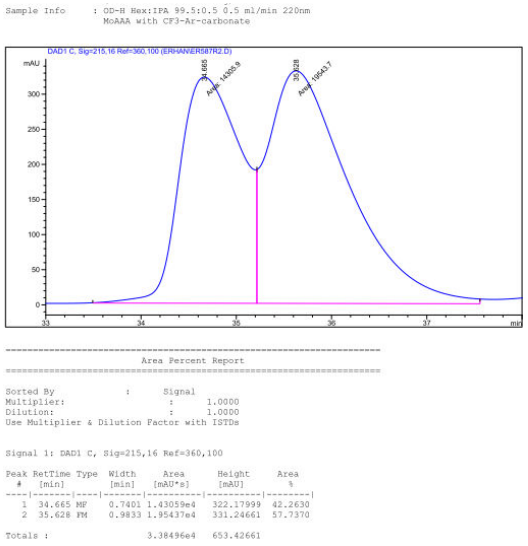
Signal 1: DAD1 C, Sig=220,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.337	MM	0.2780	98.83717	5.92561	1.0995
2	13.000	MM	0.2740	8890.46875	540.86133	98.9005

9e



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.3, 2H), 5.97 (ddd, *J* = 16.9, 10.3, 8.2 Hz, 1H), 5.15 (m, 1H), 5.12 (s, 1H), 4.19 (dd, *J* = 10.9, 8.2 Hz, 1H), 3.88 (d, *J* = 10.9, 1H), 3.75 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 168.0, 167.7, 144.3, 137.0, 128.5, 125.8 – 125.7 (q, *J* = 3.7 Hz, -CF_3), 125.3, 117.7, 57.1, 52.9, 52.7, 49.5 ppm. HPLC: >99% ee (Chiral OD-H column, 220 nm, hexanes–isopropanol (99.5:0.5), flow: 0.5 mL/min, t_R: 32.08 min).



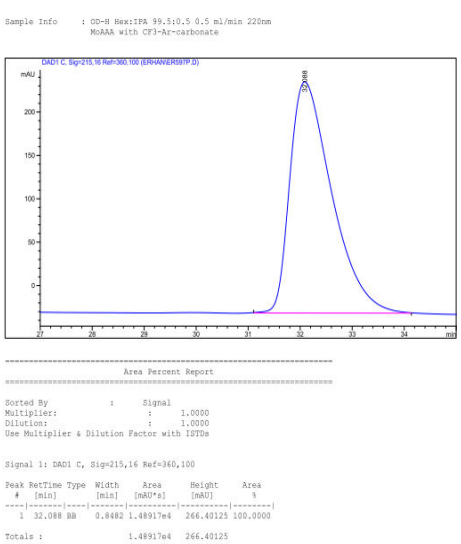
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=215,16 Ref=360,100

Peak	RetTime	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.665	MF	0.7401	1.43059e4	322.17999	42.2630
2	35.628	FM	0.9833	1.95437e4	331.24661	57.7370

Totals : 3.38496e4 653.42661



Area Percent Report

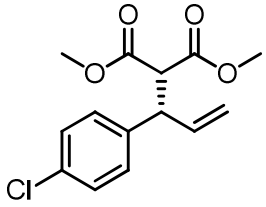
Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=215,16 Ref=360,100

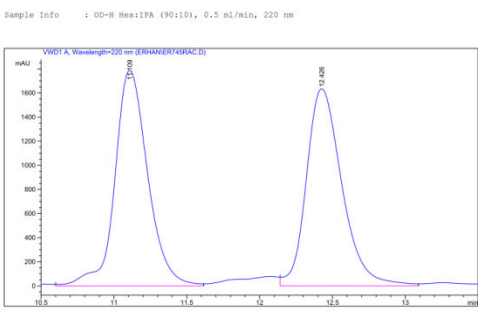
Peak	RetTime	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.088	BB	0.8482	1.48917e4	266.40125	100.0000

Totals : 1.48917e4 266.40125

9f



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.03 – 5.87 (m, 1H), 5.17 – 5.05 (m, 2H), 4.09 (dd, *J* = 10.9, 8.1 Hz, 1H), 3.82 (d, *J* = 11.0 Hz, 1H), 3.74 (s, 3H), 3.52 (s, 3H) ppm. ^{13}C-NMR (126 MHz, $CDCl_3$): δ 168.1, 167.8, 138.5, 137.4, 133.1, 129.5, 128.9, 117.2, 57.3, 52.8, 52.6, 49.1 ppm. HPLC: 99% ee (Chiral OD column, 220 nm, hexanes–isopropanol (99:1), flow: 0.7 mL/min, t_R: 11.07 min, 11.94 min).



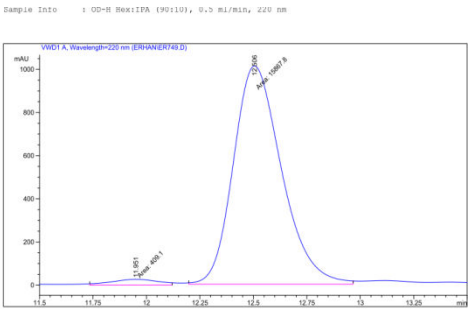
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak	RetTime	Type	Width [min]	Area [mAU *s]	Height [mAU]	Area %
1	11.109	VV	0.2413	2.80495e4	1787.33997	50.3093
2	12.426	VV	0.2619	2.77046e4	1633.48987	49.6907

Totals : 5.57541e4 3420.82983



Area Percent Report

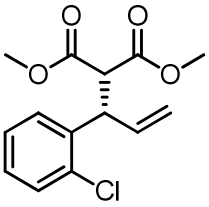
Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak	RetTime	Type	Width [min]	Area [mAU *s]	Height [mAU]	Area %
1	11.951	MM	0.2553	409.10016	26.71011	2.5134
2	12.506	MM	0.2613	1.58678e4	1011.91815	97.4866

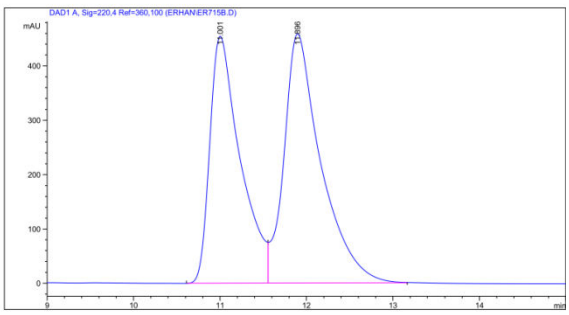
Totals : 1.62769e4 1038.62827

9g



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, 1H), 7.24 – 7.10 (m, 3H), 5.99 (ddd, *J* = 17.0, 10.2, 8.1 Hz, 1H), 5.21 – 5.06 (m, 2H), 4.68 (dd, *J* = 10.7, 8.1 Hz, 1H), 4.03 (d, *J* = 10.7 Hz, 1H), 3.74 (s, 3H), 3.55 (s, 3H) ppm. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.2, 167.8, 137.7, 136.2, 134.2, 130.3, 128.8, 128.3, 127.2, 117.9, 56.1, 52.8, 45.7 ppm. HPLC: 95% ee (Chiral OD-H column, 220 nm, hexanes–isopropanol (90:10), flow: 0.5 mL/min, t_R: 11.95 min, 12.51 min).

Sample Info : OD column; hex:IPA 99:1; 0.7 ml/min. moaaa racemic er71
5. 214, 254, 220 nm.



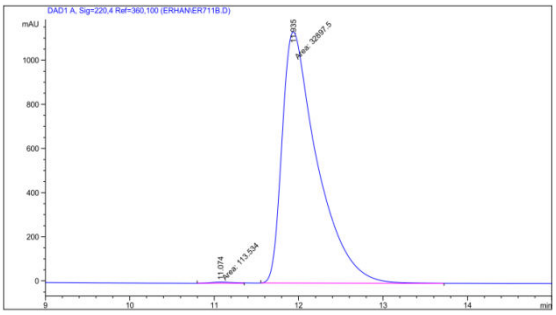
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.755	BV	0.2494	94.36989	5.11063	0.3304
2	5.421	VV	0.2272	1615.65442	105.18708	5.6573

Sample Info : OD column; hex:IPA 99:1; 0.7 ml/min. moaaa chiral er711
-p-Cl. 214, 254, 220 nm.



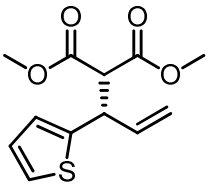
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

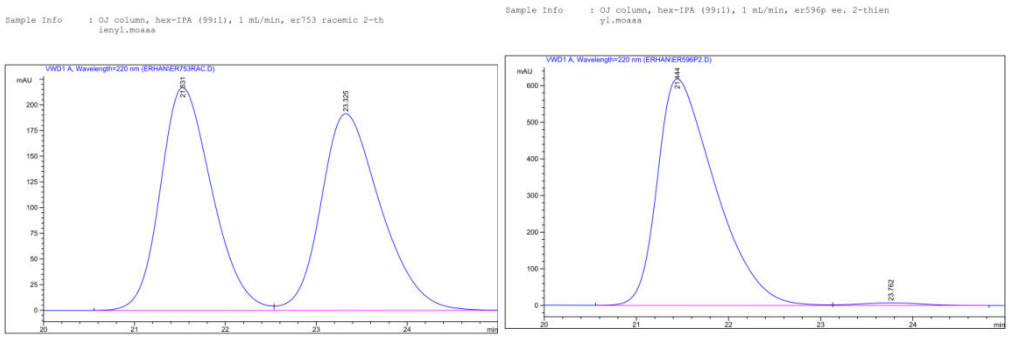
Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.074	MM	0.3281	113.53448	5.76643	0.3439
2	11.935	MM	0.4815	3.28975e4	1138.67603	99.6561

9i



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.97 – 6.83 (m, 2H), 6.03 (ddd, *J* = 17.0, 10.1, 8.4 Hz, 1H), 5.27 – 5.06 (m, 2H), 4.42 (ddd, *J* = 10.3, 8.4, 0.9 Hz, 1H), 3.84 (d, *J* = 10.2 Hz, 1H), 3.73 (s, 3H), 3.61 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 167.8, 167.8, 143.2, 137.3, 126.9, 125.0, 124.5, 117.3, 58.4, 52.7, 44.9 ppm. HPLC: 98% ee (Chiral OJ column, 220 nm, hexanes–isopropanol (99:1), flow: 1 mL/min, t_R: 21.44 min, t_R: 23.76 min).



Sample Info : OJ column, hex-IPA (99:1), 1 mL/min, er753 racemic 2-thienyl.moaaa

VWD1 A, Wavelength=220 nm (ERHAN\ER753RAC.D)

Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	21.531	BV	0.6089	8562.52734	216.98030	49.4971
2	23.325	VB	0.6923	8736.51367	191.55263	50.5029
Totals :				1.72990e4	408.53293	

Sample Info : OJ column, hex-IPA (99:1), 1 mL/min, er596p ee. 2-thienyl.moaaa

VWD1 A, Wavelength=220 nm (ERHAN\ER596P2.D)

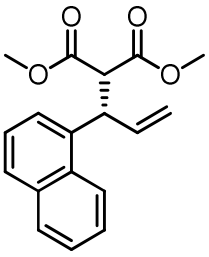
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

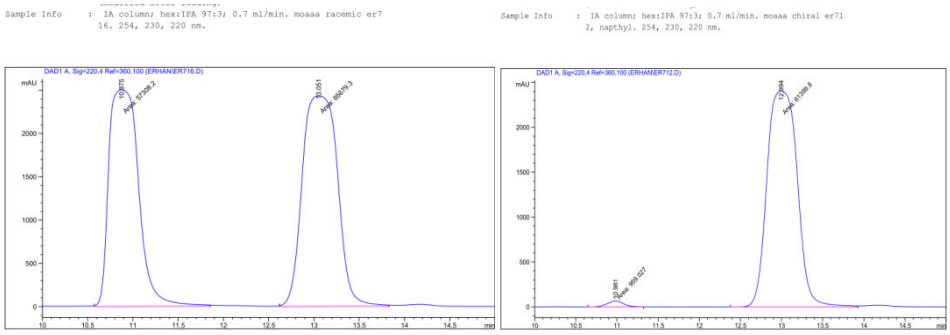
Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	21.444	VB	0.6577	2.69284e4	618.76031	98.8139
2	23.762	BB	0.6861	323.23245	7.09144	1.1861
Totals :				2.72517e4	625.85176	

9j



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, *J* = 8.6 Hz, 1H), 7.84 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.74 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.61 – 7.35 (m, 4H), 6.08 (ddd, *J* = 17.1, 10.2, 8.0 Hz, 1H), 5.27 – 4.93 (m, 3H), 4.16 (d, *J* = 10.8 Hz, 1H), 3.78 (s, 3H), 3.38 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 168.6, 168.0, 137.8, 136.3, 134.2, 131.5, 129.0, 127.9, 126.4, 125.8, 125.4, 124.5, 123.4, 117.2, 57.1, 52.8, 52.6, 44.3 ppm. HPLC: 97% ee (Chiral IA column, 220 nm, hexanes–isopropanol (97:3), flow: 0.7 mL/min, t_R: 10.98 min, 12.99 min).



Sample Info : IA column; hex:IPA 97:3; 0.7 ml/min. moaaa racemic er716. 254, 230, 220 nm.

DAD1 A, Sig=220,4 Ref=360,100 (ERHAN\ER716.D)

Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.875	MM	0.3812	5.73082e4	2505.51978	46.5968
2	13.051	MM	0.4493	6.56793e4	2436.45044	53.4032

Sample Info : IA column; hex:IPA 97:3; 0.7 ml/min. moaaa chiral er712, napthyl. 254, 230, 220 nm.

DAD1 A, Sig=220,4 Ref=360,100 (ERHAN\ER712.D)

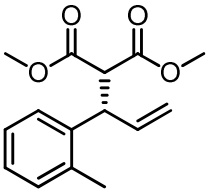
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

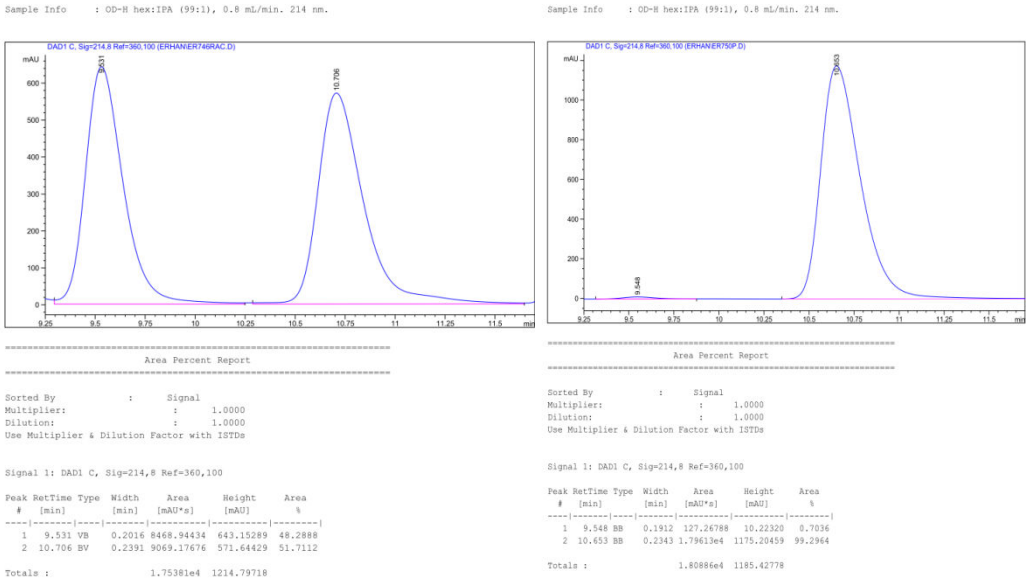
Signal 1: DAD1 A, Sig=220,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.981	MM	0.2389	959.02661	66.89211	1.5379
2	12.994	MM	0.4252	6.13998e4	2406.59106	98.4621

9k



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.04 (m, 4H), 5.85 (ddd, *J* = 17.0, 10.2, 8.0 Hz, 1H), 5.12 – 4.97 (m, 2H), 4.41 (d, *J* = 1.0 Hz, 1H), 3.96 (d, *J* = 11.4 Hz, 1H), 3.76 (s, 3H), 3.48 (s, 3H), 2.41 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ 168.6, 168.0, 138.2, 137.7, 136.6, 130.9, 126.9, 126.3, 126.3, 116.6, 57.0, 52.7, 52.5, 45.1, 19.8 ppm. HPLC: 98% ee (Chiral OD-H column, 214 nm, hexanes–isopropanol (99:1), flow: 0.8 mL/min, t_R: 9.55 min, 10.65 min).



Sample Info : OD-H hex:IPA (99:1), 0.8 mL/min. 214 nm.

DAD1 C, Sig=214,8 Ref=360,100 (ERHANER74GRAC.D)

mAU

9.531 10.706

min

Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=214,8 Ref=360,100

Peak	RetTime	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.531	VB	0.2016	8468.94434	643.15289	48.2888
2	10.706	BV	0.2391	9069.17676	571.64429	51.7112
Totals :				1.75381e4	1214.79718	

Sample Info : OD-H hex:IPA (99:1), 0.8 mL/min. 214 nm.

DAD1 C, Sig=214,8 Ref=360,100 (ERHANER75OP.D)

mAU

9.548 10.653

min

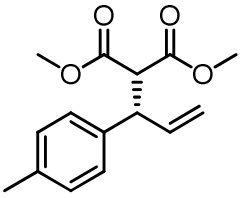
Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=214,8 Ref=360,100

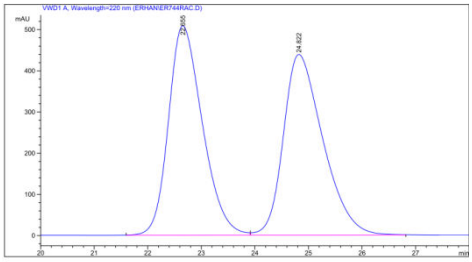
Peak	RetTime	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.548	BB	0.1912	127.26788	10.22320	0.7036
2	10.653	BB	0.2343	1.79613e4	1175.20459	99.2964
Totals :				1.80886e4	1185.42778	

9l



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 4H), 5.97 (ddd, *J* = 17.0, 10.2, 8.2 Hz, 1H), 5.15 – 5.02 (m, 2H), 4.07 (ddt, *J* = 11.0, 8.2, 1.0 Hz, 1H), 3.85 (d, *J* = 11.0 Hz, 1H), 3.73 (s, 3H), 3.50 (s, 3H), 2.30 (s, 3H) ppm. ^{13}C-NMR (101 MHz, $CDCl_3$): δ168.4, 168.0, 138.1, 137.0, 136.8, 129.5, 127.8, 116.5, 57.5, 52.7, 52.5, 49.5, 21.2 ppm. HPLC: 95% ee (Chiral OJ column, 220 nm, hexanes–isopropanol (93:7), flow: 0.7 mL/min, t_R: 22.61 min, 24.79 min).

Sample Info : OJ Hex:IPA (93:7), 0.7 ml/min, 220 nm



Area Percent Report

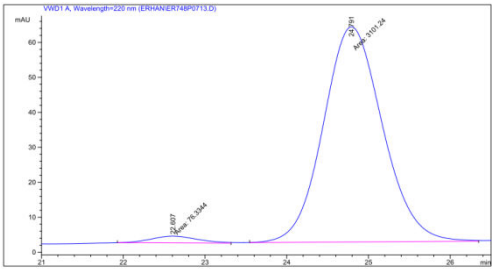
Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	22.655	BV	0.6763	2.23617e4	508.31665	49.8315
2	24.822	VB	0.7796	2.25129e4	438.44958	50.1685

Totals : 4.48745e4 946.76624

Sample Info : OJ Hex:IPA (93:7), 0.7 ml/min, 220 nm



Area Percent Report

Sorted By : Signal
Multiplier: : 1.0000
Dilution: : 1.0000
Use Multiplier & Dilution Factor with ISTDs

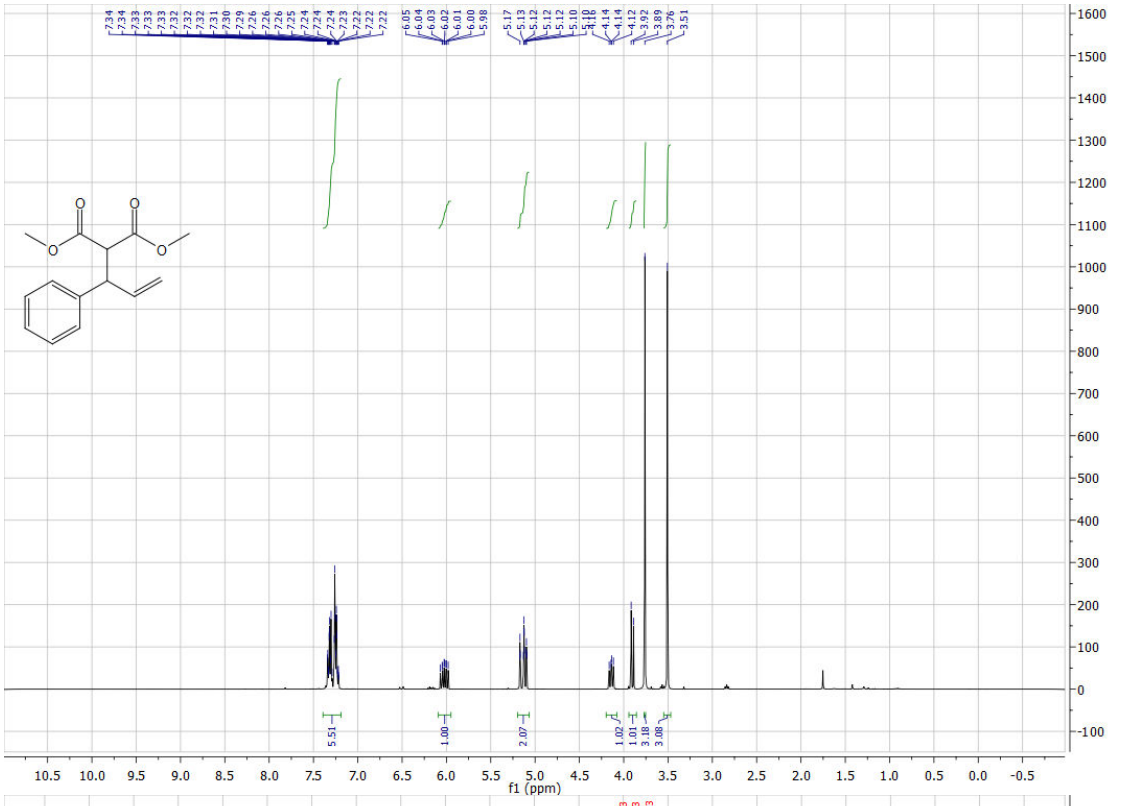
Signal 1: VWD1 A, Wavelength=220 nm

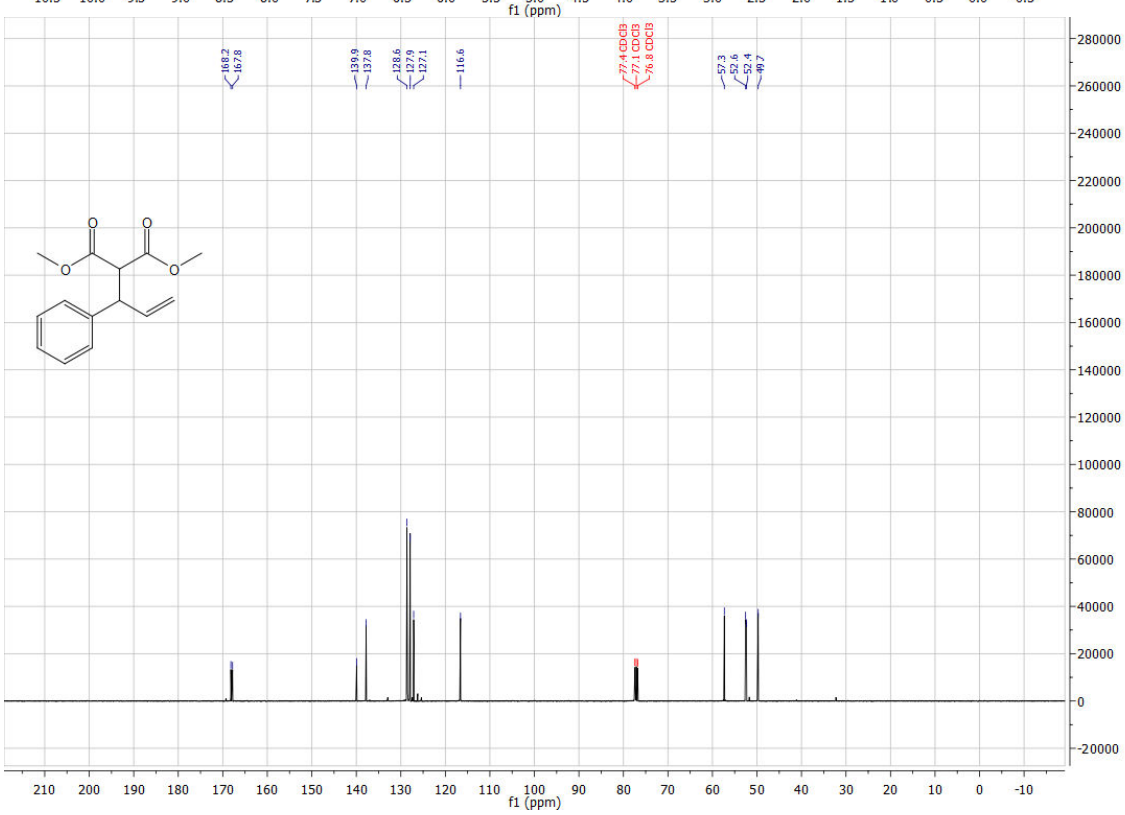
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	22.607	MM	0.6579	76.33443	1.93382	2.4023
2	24.791	MM	0.8403	3101.23657	61.51165	97.5977

Totals : 3177.57101 63.44547

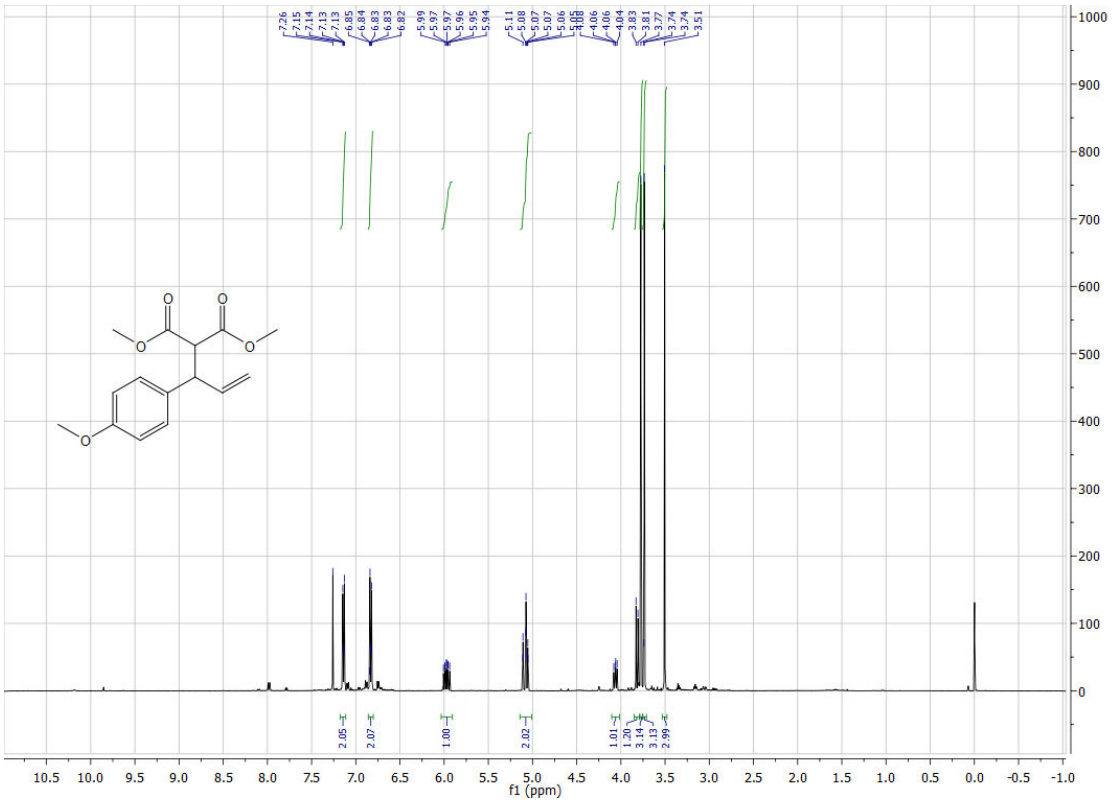
7. NMR SPECTRA AND HPLC CHROMATOGRAM OF MOAAA PRODUCTS

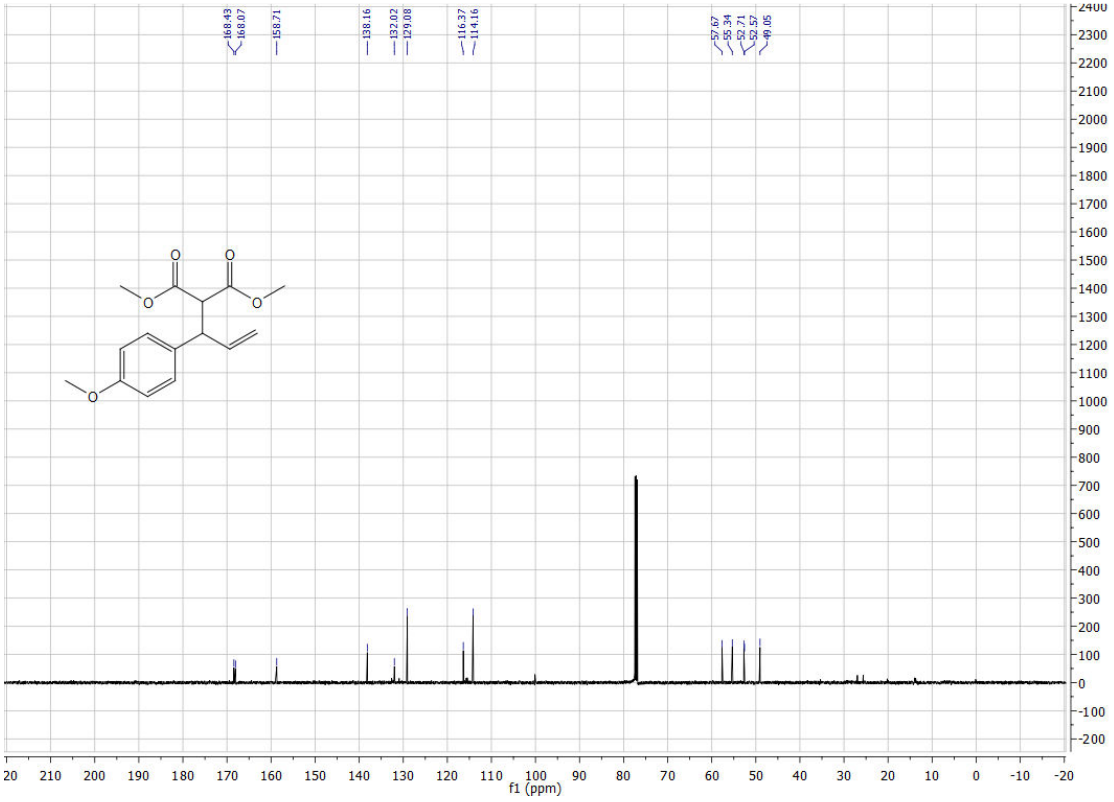
9a



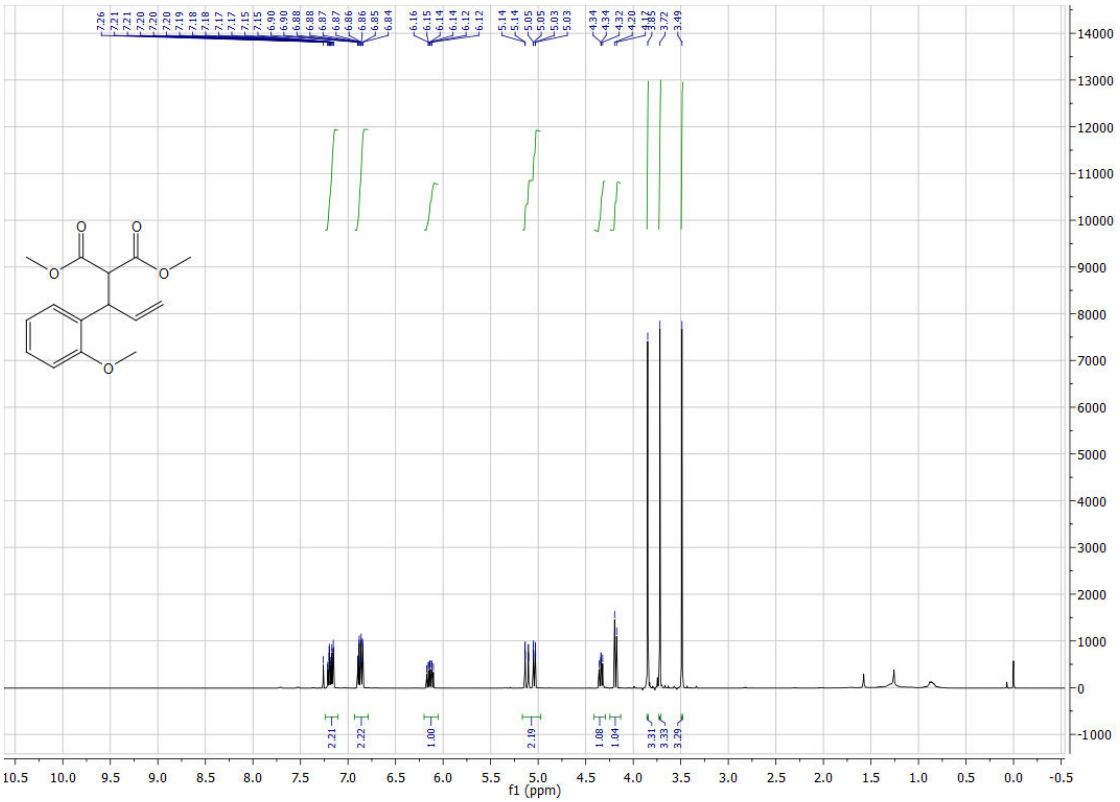


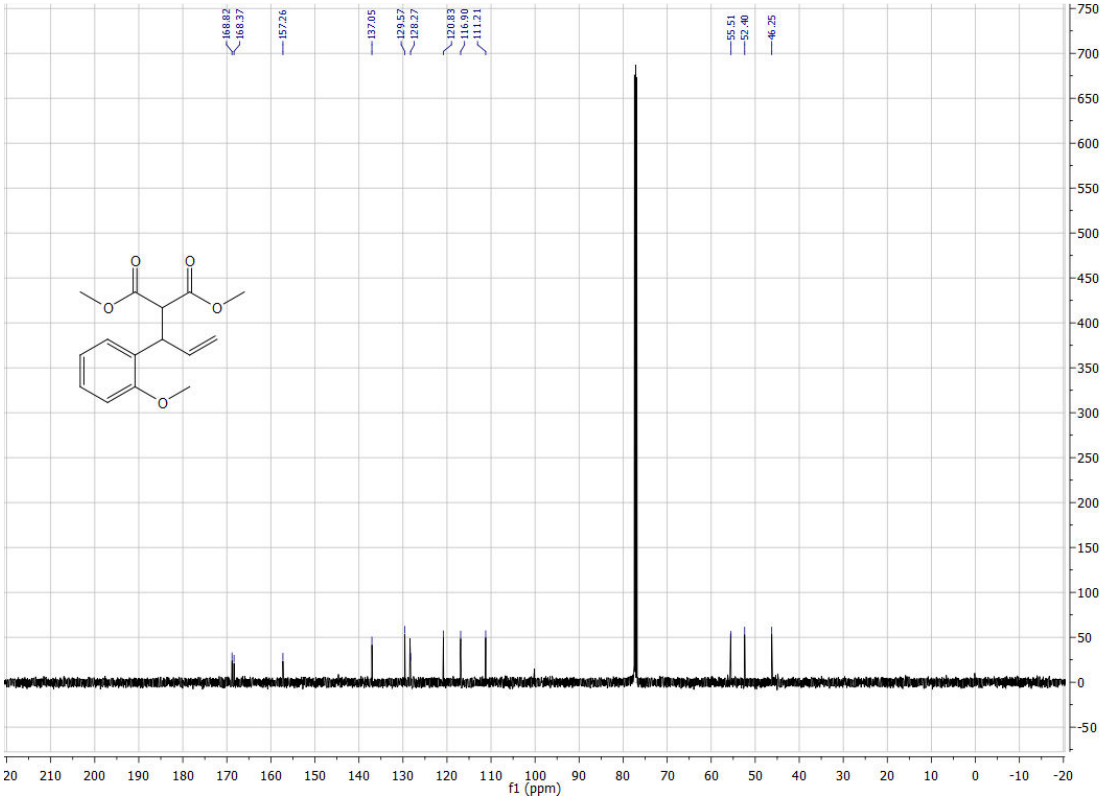
9b


7.26
7.15
7.14
7.13
7.13
6.85
6.84
6.83
6.83
6.82
5.99
5.97
5.97
5.96
5.95
5.94
5.11
5.08
5.07
5.07
5.06
5.05
4.08
4.06
4.06
4.04
4.04
3.83
3.81
3.77
3.74
3.51
2.05
2.07
1.00
2.02
1.01
1.20
3.14
3.13
2.99
f1 (ppm)

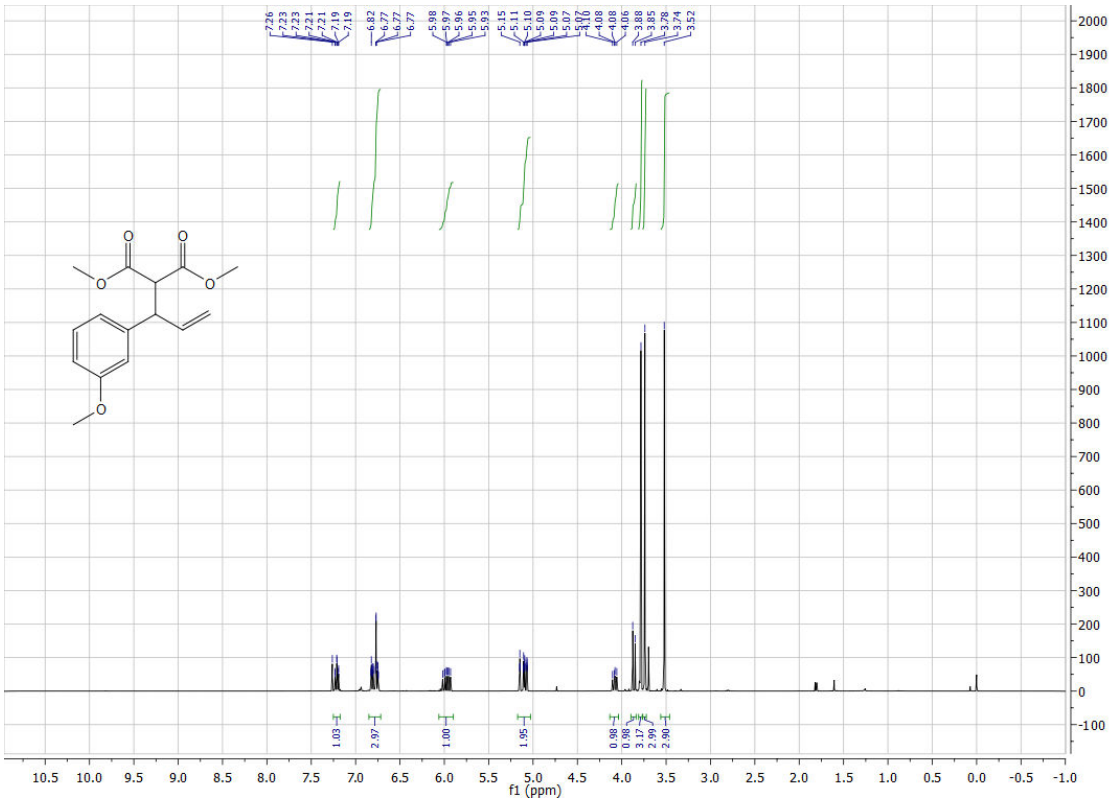

168.43
166.07
158.71
138.16
132.02
129.08
116.37
114.16
57.67
55.34
52.71
52.57
40.05
f1 (ppm)

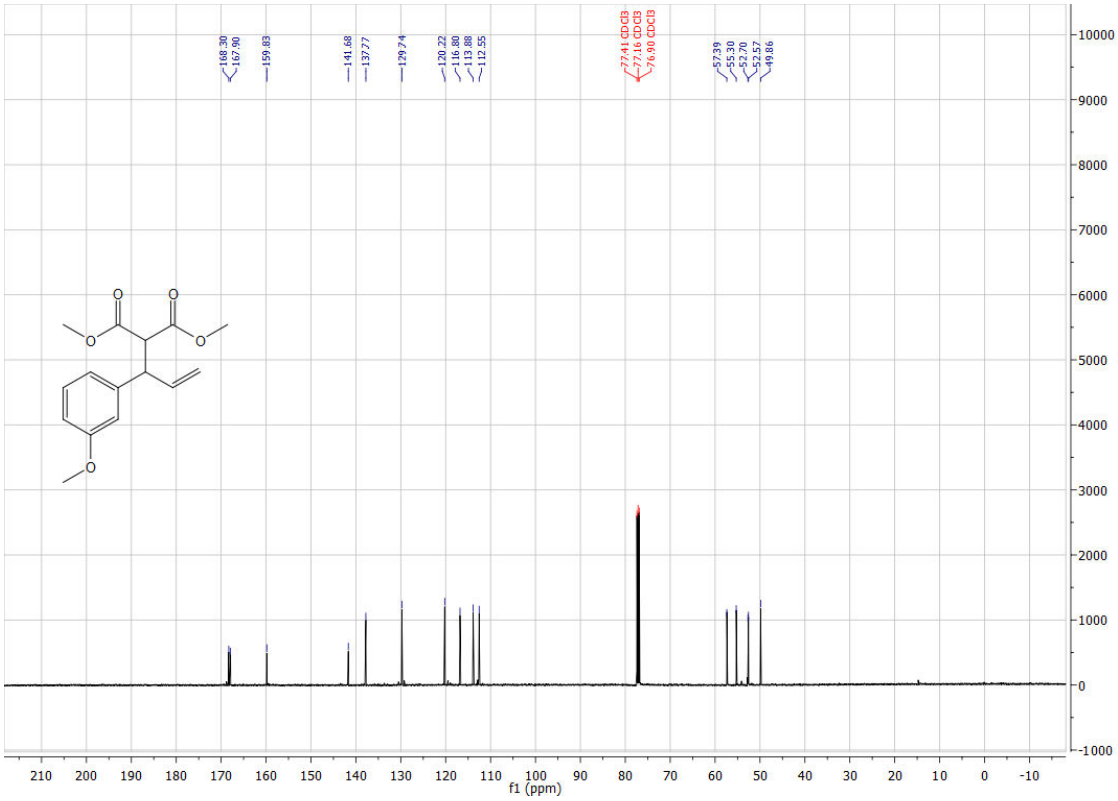
9c



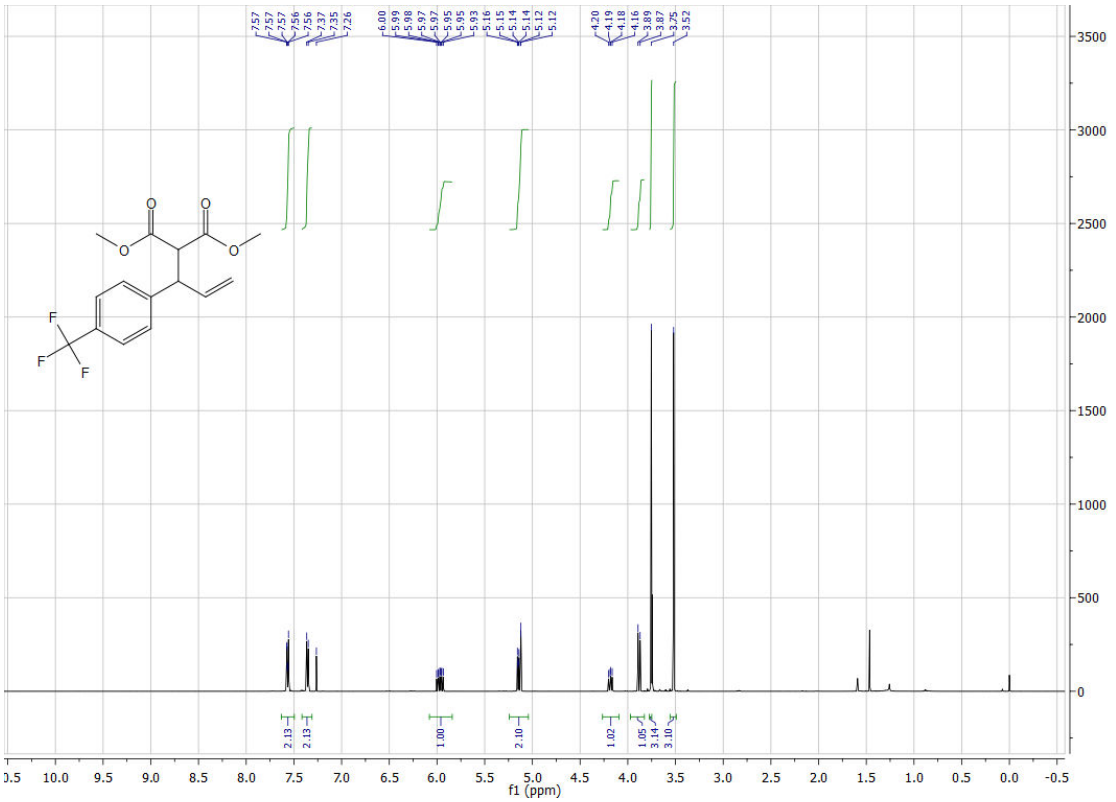


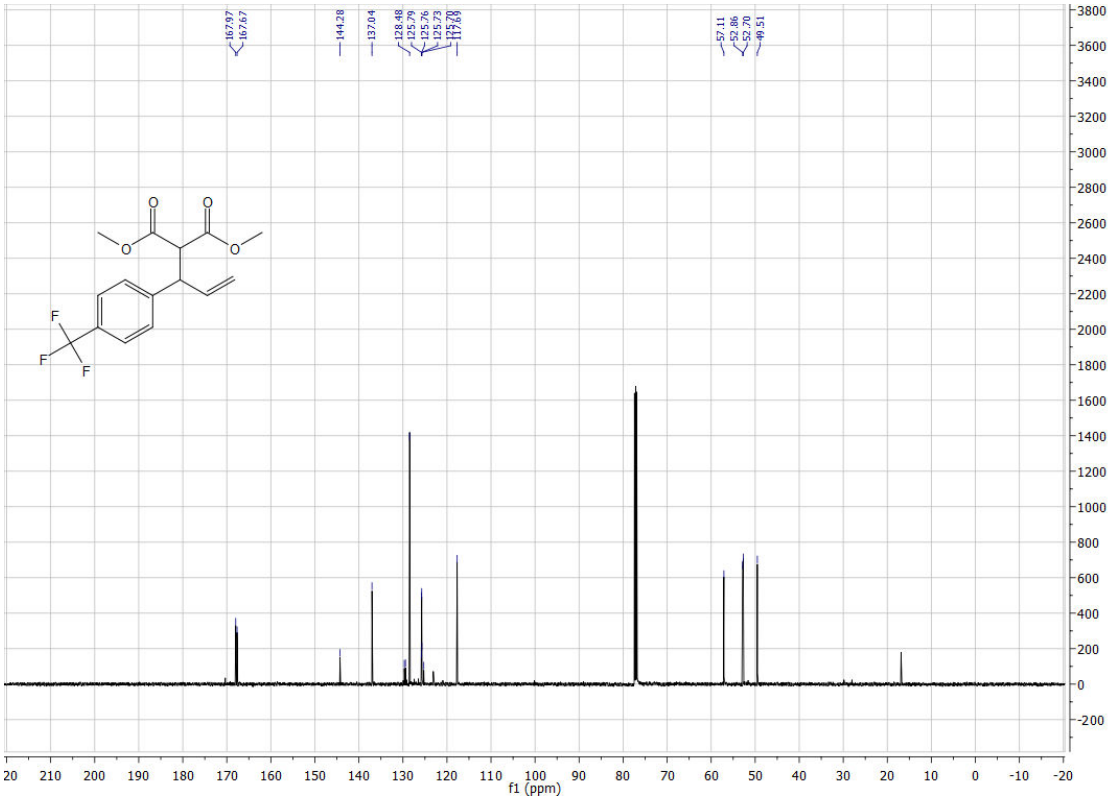
9d


7.26
7.23
7.23
7.21
7.21
7.19
7.19
6.82
6.77
6.77
6.77
6.77
5.98
5.97
5.96
5.95
5.93
5.15
5.11
5.10
5.09
5.09
5.07
5.10
4.08
4.08
4.06
3.88
3.85
3.78
3.74
3.52
1.03
2.97
1.00
1.95
0.98
0.98
3.17
2.99
2.90
f1 (ppm)

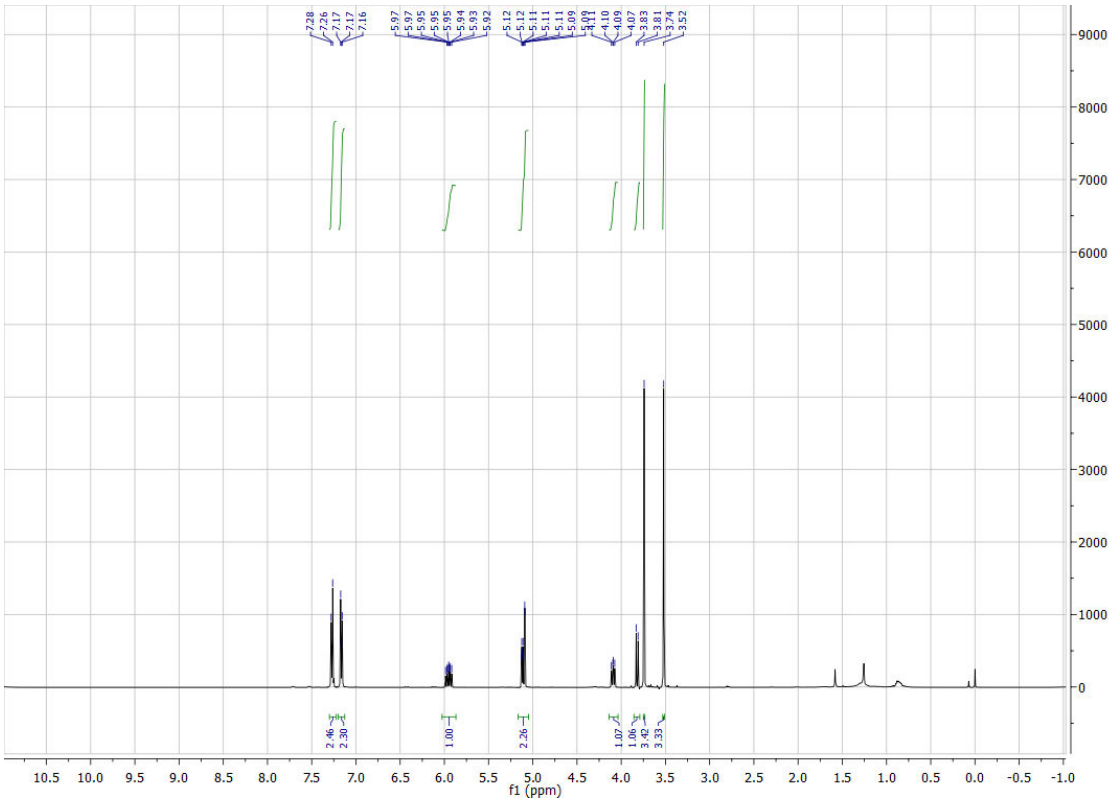

168.30
167.90
159.83
141.68
137.77
129.74
120.22
116.80
113.88
112.55
77.41 CDCl3
77.16 CDCl3
76.90 CDCl3
57.39
55.30
52.70
52.57
49.86
f1 (ppm)

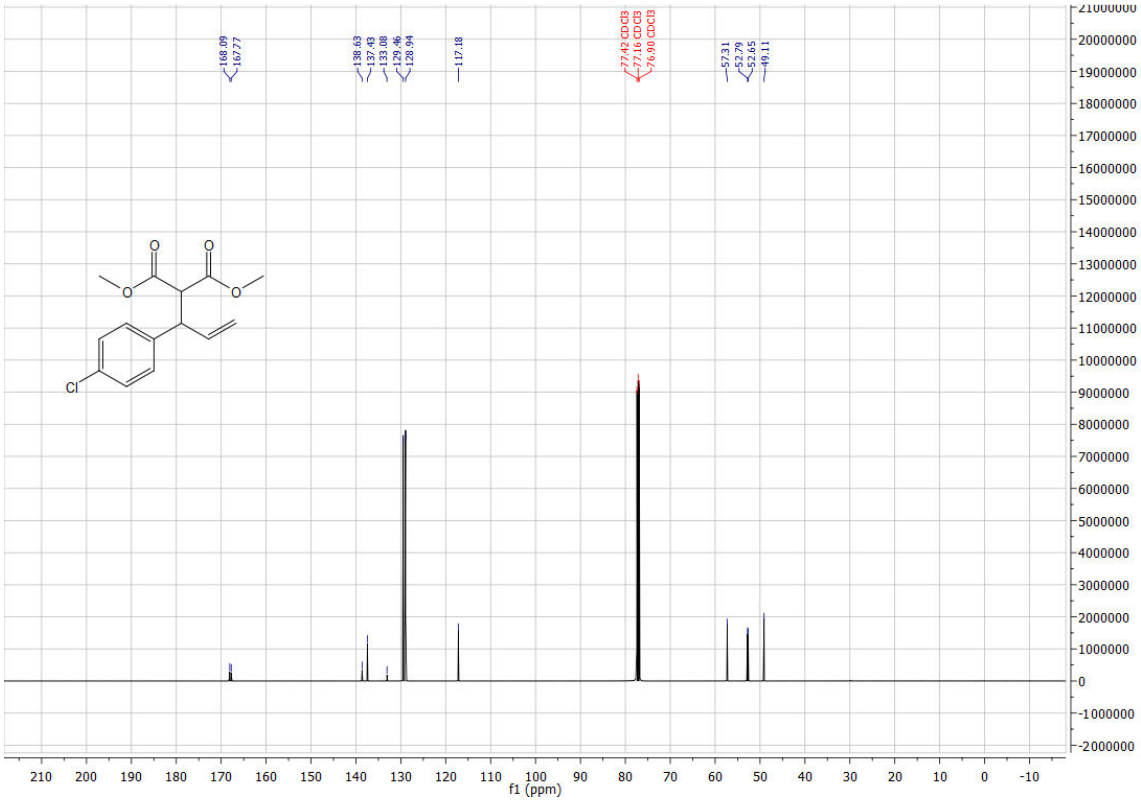
9e



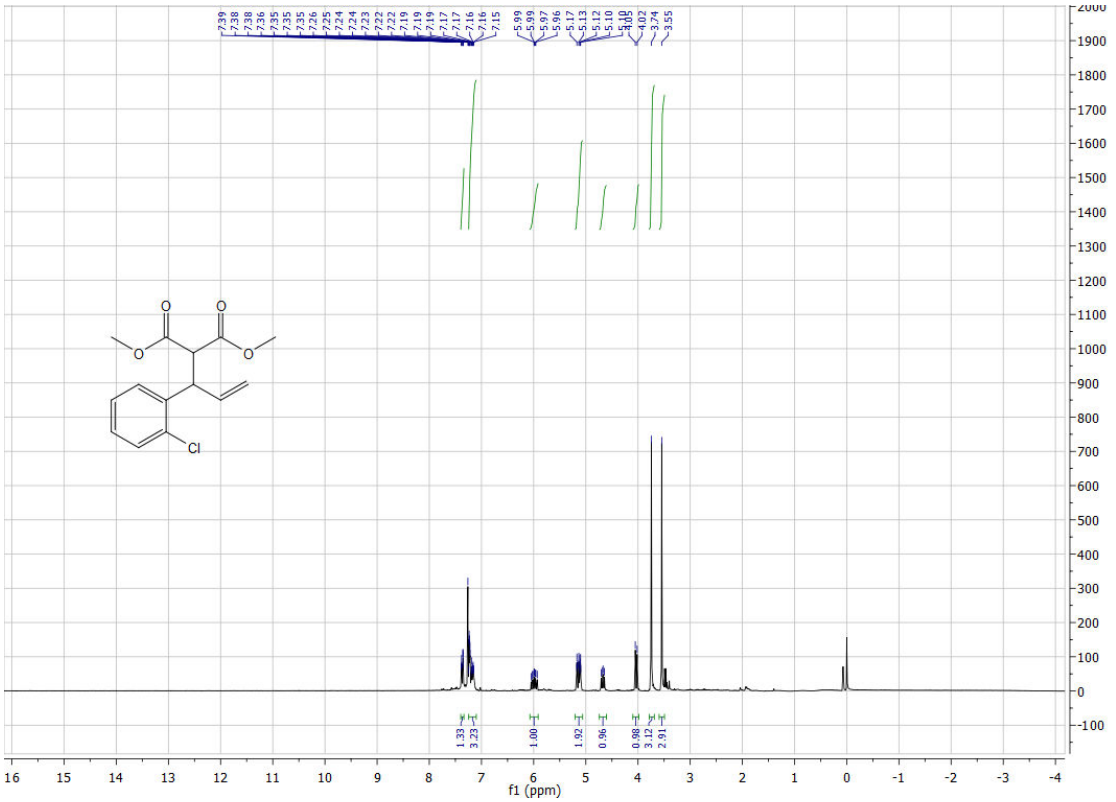


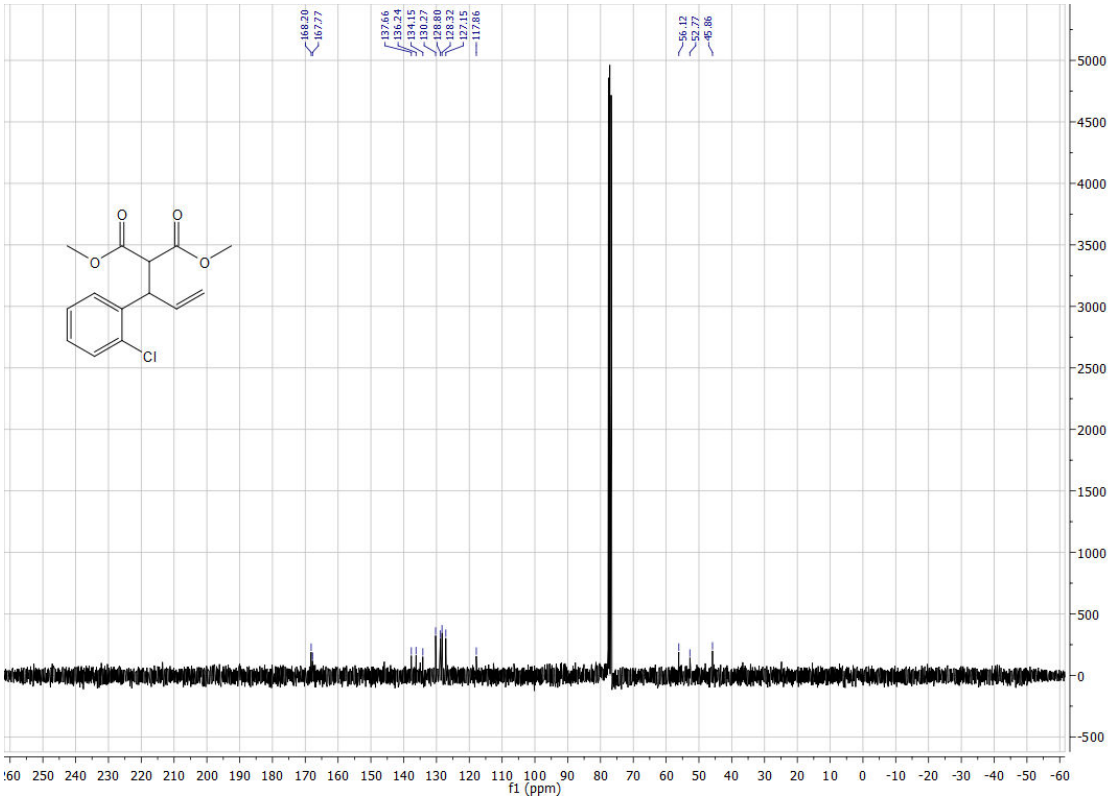
9f



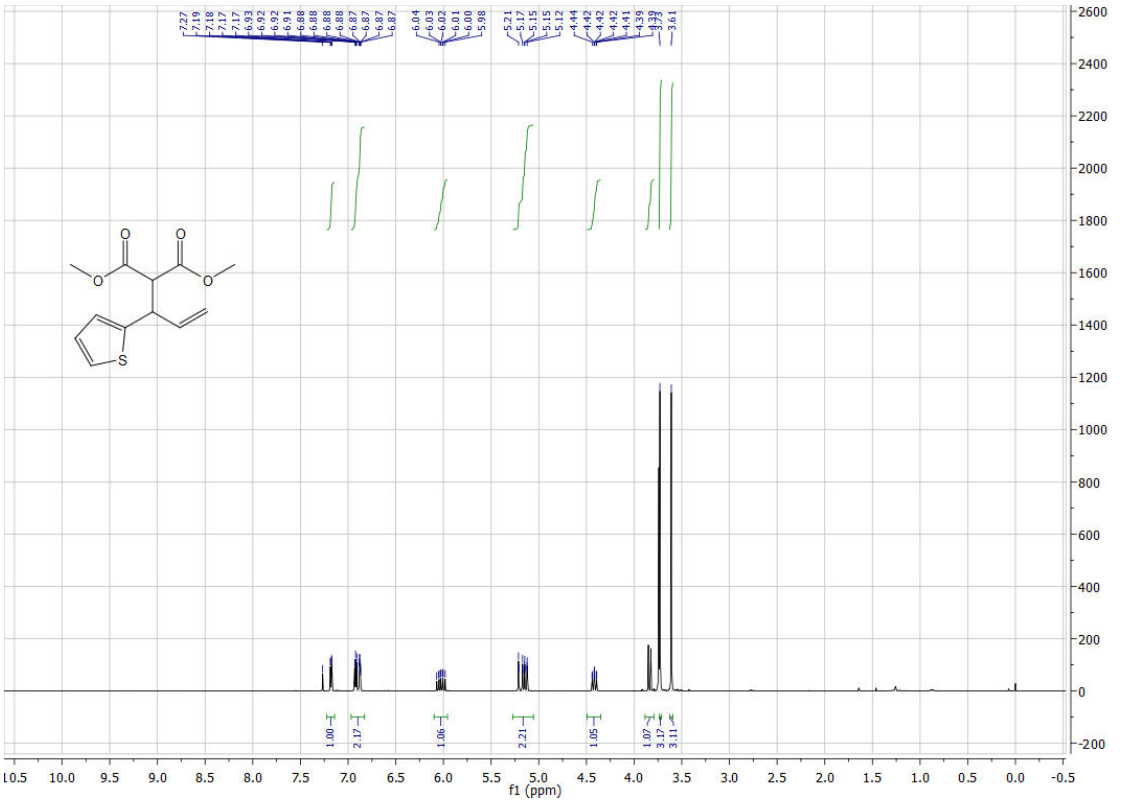


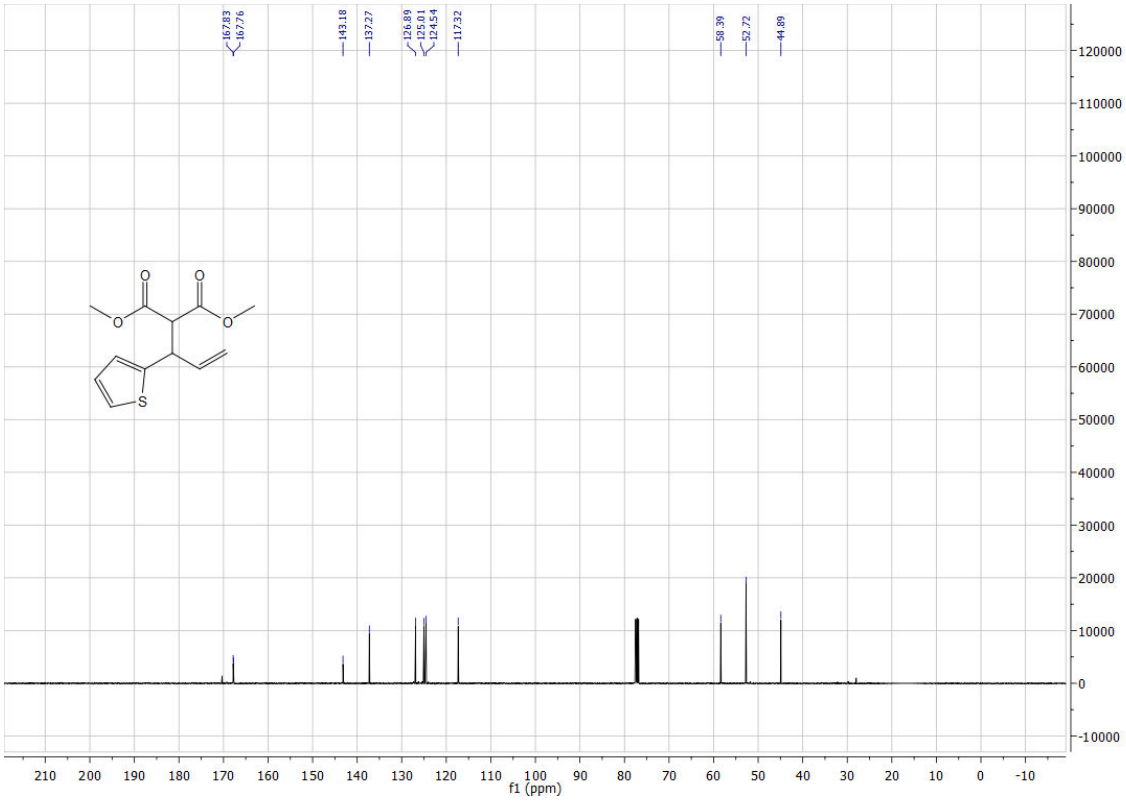
9g



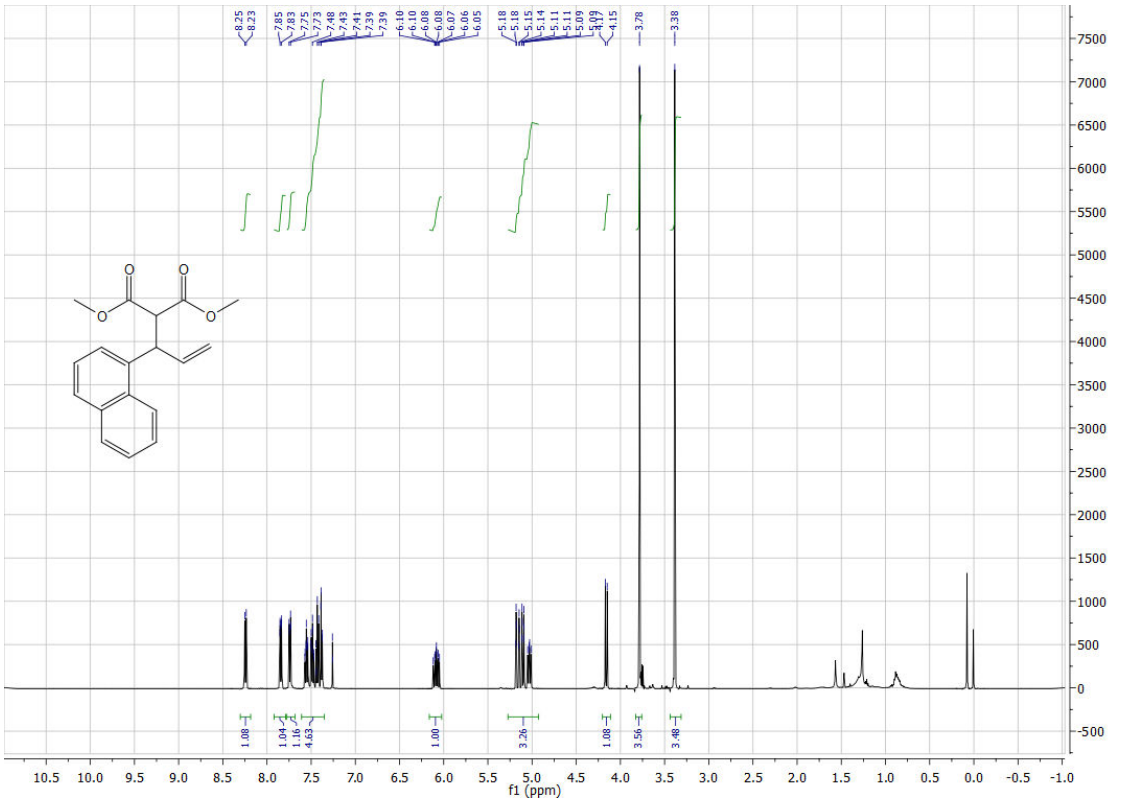


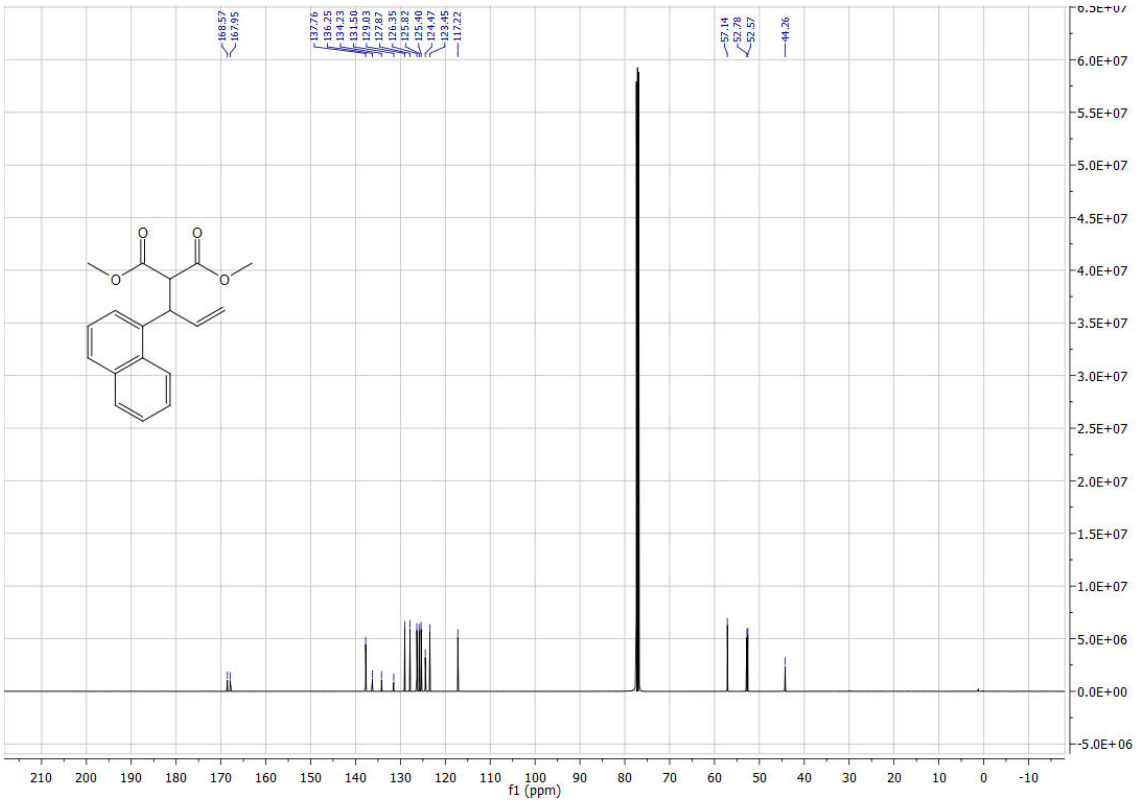
9i



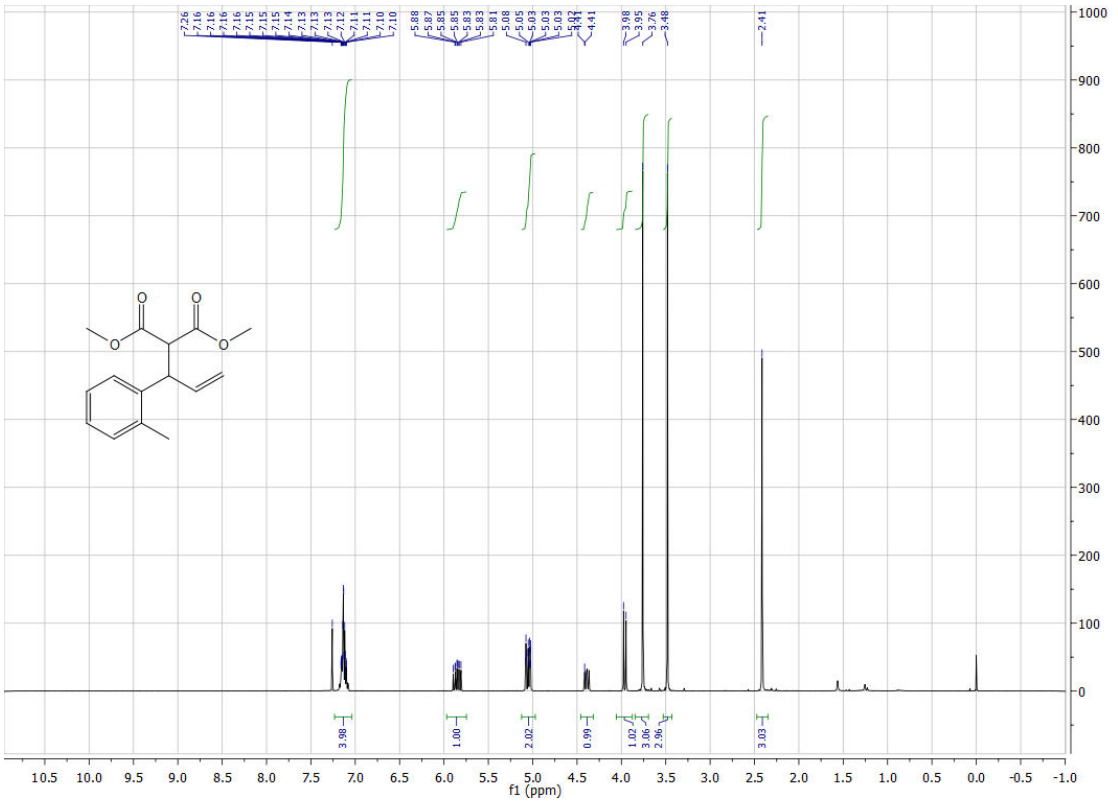


9j


8.25
8.23
7.85
7.83
7.75
7.73
7.48
7.43
7.41
7.39
7.39
6.10
6.10
6.08
6.08
6.07
6.06
6.05
5.18
5.18
5.15
5.14
5.11
5.11
5.09
5.09
4.17
4.15
3.78
3.38
1.08
1.04
1.16
4.63
1.00
3.26
1.08
3.56
3.48
f1 (ppm)


160.57
156.95
137.76
136.25
134.23
131.50
129.03
127.87
126.35
125.82
125.40
124.47
123.45
117.22
57.14
52.78
52.57
44.26
f1 (ppm)

9k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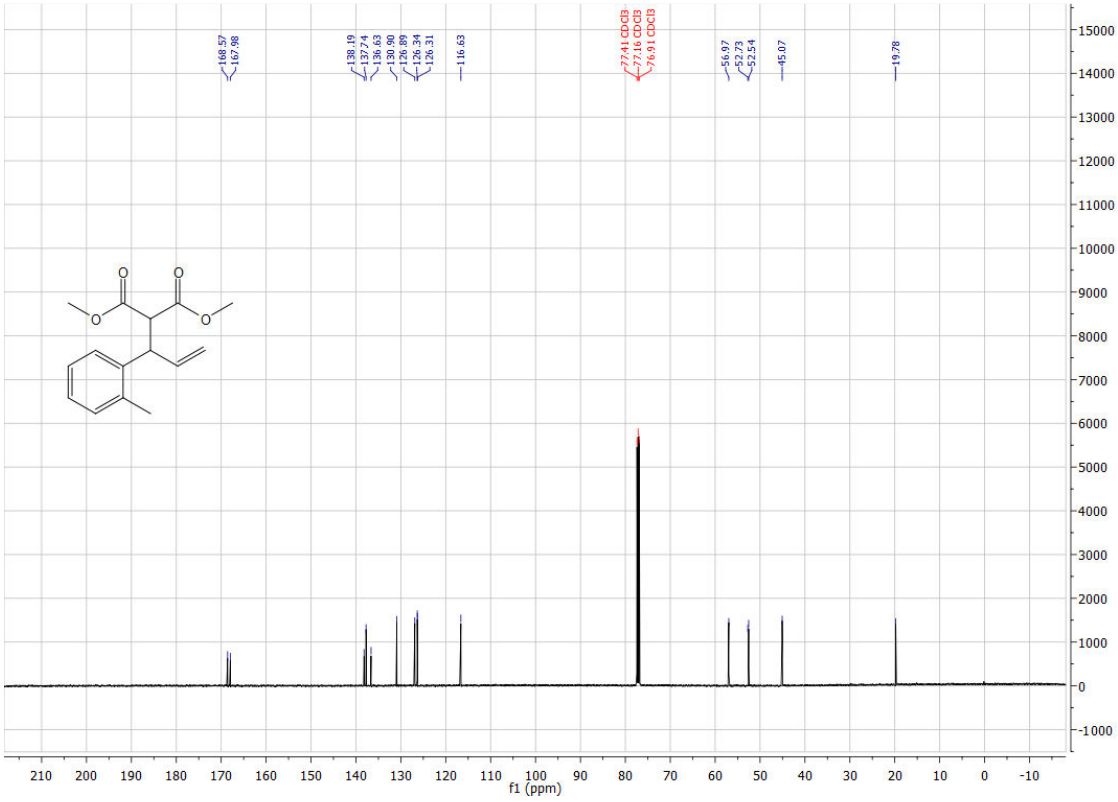
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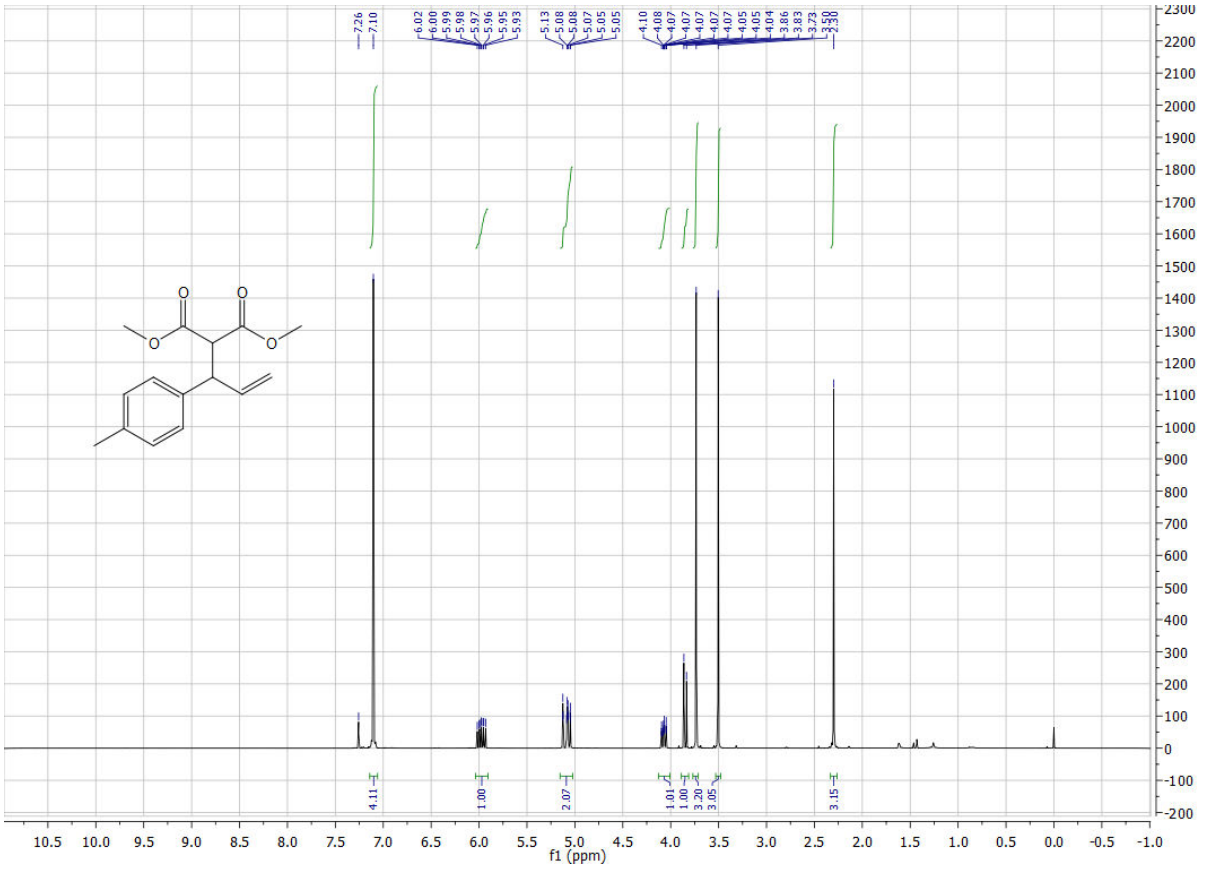
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4.05
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3.86
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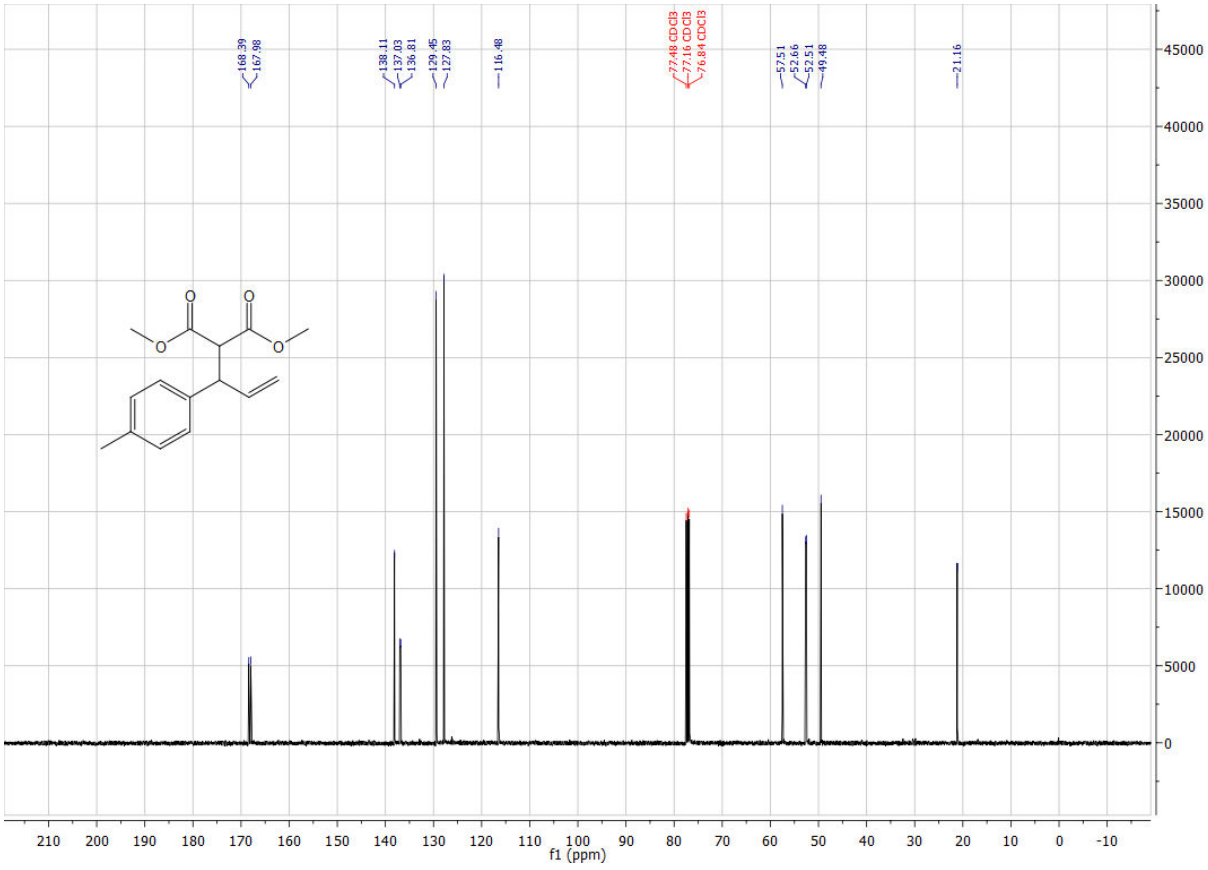
f1 (ppm)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76.84 CDCl3
57.51
52.66
52.51
49.48
21.16
f1 (ppm)

References

[1] B. M. Trost, J. R. Miller, C. M. Hoffman, *J. Am. Chem. Soc.* **2011**, *133*, 8165-8167.

[2] S. Özçubukçu, E. Ozkal, C. Jimeno, M. A. Pericàs, *Org. Lett.* **2009**, *11*, 4680-4683.

[3] L. S. Campbell-Verduyn, L. Mirfeizi, R. A. Dierckx, P. H. Elsinga, B. L. Feringa, *Chem. Commun.* **2009**, *0*, 2139-2141.

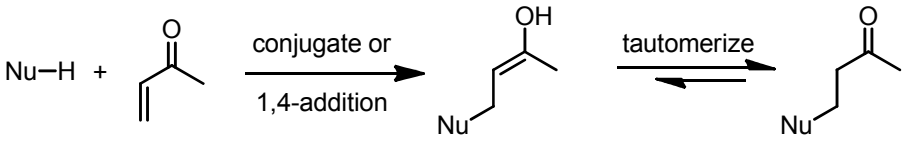
Chapter IV

CONTENTS

4. "*CLICK*" IMINE-TRIAZOLE LIGANDS FOR ENANTIOSELECTIVE COPPER-CATALYZED CONJUGATE ADDITION TO CYCLIC ENONES

4.1. COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMETALLIC REAGENTS

The enantioselective conjugate addition of organometallic reagents is one of the most useful approaches for the synthesis of optically active, complex molecules. Regarding the nucleophile, there are two possible modes of action in these additions: a) addition of soft carbon nucleophiles via Michael addition and b) hard carbon nucleophiles, which require a transition metal directed approach in order to prevent addition to the carbonyl group (1,2-addition) of the Michael acceptor.[1] Nowadays, one of the most common methods is organocopper chemistry using chiral ligands (**Scheme 4.1**).[2]



Scheme 4.1. Schematic representation of conjugate addition.

Based on the pioneering work with chiral auxiliaries involving stoichiometric amounts of a copper species, a copper-catalyzed methodology took the field into a more practical version. In the earlier period, the nucleophiles were mainly based on Grignard reagents. Upon the introduction of dialkylzinc reagents[3] and with the development of chiral phosphorus ligands, one of the primary methodologies in catalytic asymmetric addition to Michael acceptors was introduced (**Scheme 4.2**).[4]

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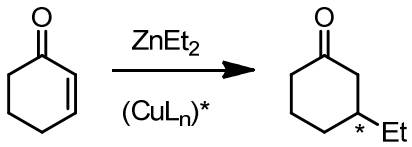
[1] (a) Michael, A. *Journal für Praktische Chemie* **1887**, *35*, 349 (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, *2001*, 0171 (c) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299.

[2] (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346. (b) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, *2002*, 3221. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (d) Jerphagnon, T.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Chem. Soc. Rev.* **2009**, *38*, 1039.

[3] Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427.

[4] (a) Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175. (b) Alexakis, A.; Mutti, S.; Normant, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 6332.



Scheme 4.2. Catalytic asymmetric copper-catalyzed conjugate addition of diethylzinc to cyclohexenone.

In general, a copper-catalyzed process is typically a ligand-accelerated reaction, thus amenable to fine-tuning through ligand optimization. The reaction is not highly solvent dependent although non-coordinating solvents (toluene, dichloromethane, diethyl ether) can speed it up. In these solvents, conjugate addition is complete in 2 h at around –30 °C.

The copper species is the key factor for high catalytic activity and enantioselectivity. For general phosphorus ligands copper(II) triflate is found to be the best copper source. Both copper(I) and copper(II) species have been used successfully in this transformation. Since oxidized metal salts are easier to handle, copper(II) triflate is the copper source of choice in most of the cases and *in situ* reduction by zinc species generates the catalytically active copper(I) species.

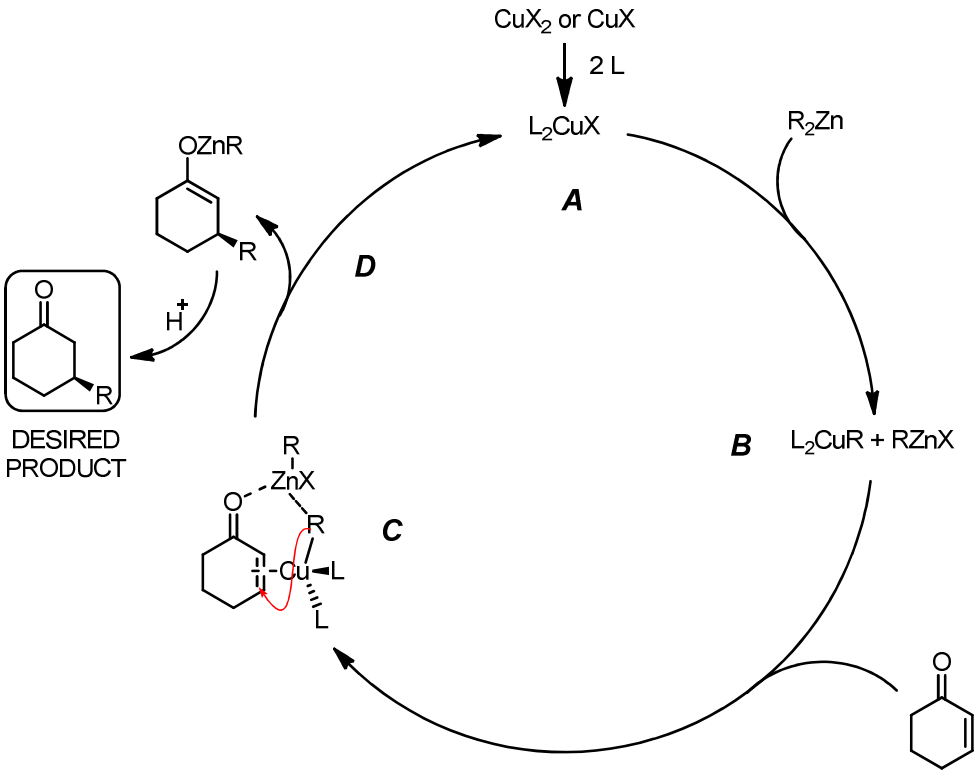
Cyclic enones are locked in a way that no conformational problem stems from the substrate unlike the acyclic ones. In other words, the degrees of conformational freedom are significantly reduced in comparison to their linear counterparts. For this reason, they are generally selected as the test substrate for this reaction.

The broad functional group compatibility of dialkylzinc reagents made them much more suitable for developments in the asymmetric conjugate addition. Either hydroboration/transmetalation or alkyl iodide/diethylzinc exchange sequences allow access to derivatives of different zinc reagents, since the choice of commercial organozinc species is quite limited. Therefore, the cost, pyrophoric properties and water sensitivity of zinc reagents are the only limiting factors in the use of these organometallic reagents.

4.1.1. MECHANISM

The alkyl transfer from zinc to copper is the essential step to form new organocopper species in order to alkylate α,β-unsaturated substrates. Basically, following

the studies in organocopper and zincate chemistry, a general catalytic cycle can be proposed (**Scheme 4.3**). Presumably, *in situ* reduction of copper(II) species leads to the formation of copper(I)/ligand complex as L_2CuX (**A**). Alkyl transfer from Zn to Cu affords L_2CuR and RZnX (**B**). The coordination of RZnX to the carbonyl group of enone with the formation of π-complex with L_2CuR generates intermediate **C**. Another alkyl transfer takes place in order to have a zinc enolate **D**, which gets protonated to give the desired product. Overall, this is parallel to similar mechanisms having both Lewis acid accelerated organocopper chemistry and the known π-complexation of such species.[5]



Scheme 4.3. General catalytic cycle for copper-catalyzed 1,4-additions of organozinc reagents.

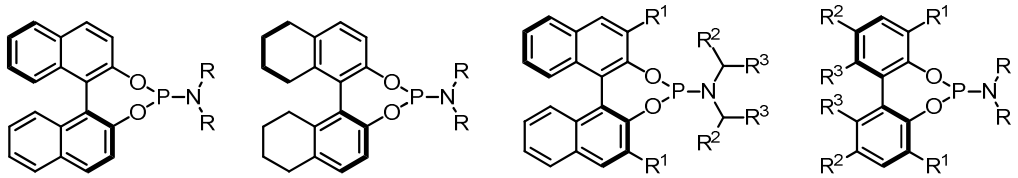
4.1.2. LIGANDS

In the earlier works, it was found that the asymmetric induction was very substrate dependent; so efforts were devoted to the development of ligands with broader scope. The initial and most investigated ligand types were based on trivalent phosphorus ligands, mostly phosphites and phosphoroamidites. The less common family

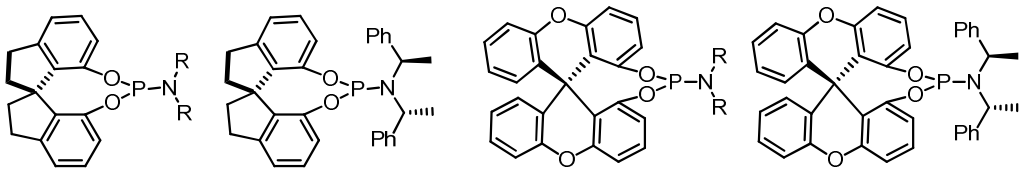
[5] Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH, Weinheim, **2002**, 224.

ligands can be classified into sulfonamides, diaminocarbenes, oxazolines and other heterodonor *S,O* and *N,S* ligands.

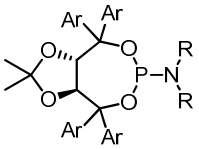
The first successful enantioselective version of copper-catalyzed 1,4-addition was reported by Alexakis and co-workers in 1993 by the combination of catalytic amounts of CuI with a chiral trivalent phosphorus ligand.[6] In 1996, Feringa and co-workers developed BINOL derived phosphoroamidites, monodentate chiral ligands, which gave excellent selectivities in this conjugate addition.[7] After that point, these ligands found successful application in various asymmetric transformations to become a class of one of the privileged ligands in asymmetric catalysis (**Figure 4.1**).



BINOL-based phosphoramidite ligands



Spiro-phosphoramidite ligands



Taddol-based phosphoramidite ligands

Figure 4.1. Phosphoramidite ligands.

Although phosphoramidites are ligands of choice in most of the cases, more than 400 ligands and catalytic systems have been reported for this reaction and, in most of the cases, acceptable levels of activity and selectivity have been observed.

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[6] Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427.
[7] Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620.

Phosphorus ligands other than the versatile phosphoramidites usually contain one of the general backbones of the privileged ligand structures like ferrocene, BINOL, proline and cyclohexyldiamine in combination with either diphosphines, aminophosphine-oxazolines, amino acid derived phosphines and phosphorus-thioamides. They all gave acceptable results under test conditions (*i.e.* cyclohexenone, >90% ee) nevertheless, they either suffered from low catalytic activity or erosion in enantioselectivity with more challenging substrates (**Figure 4.2**).

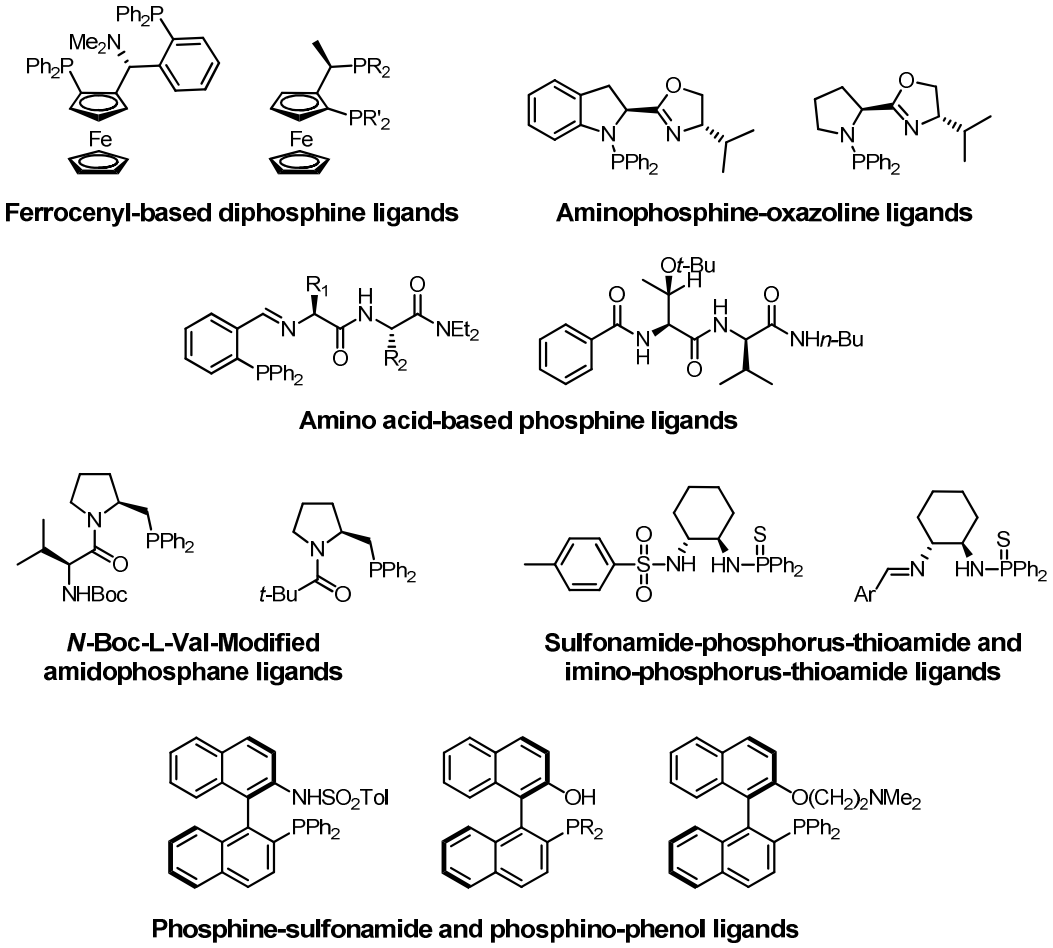


Figure 4.2. Other general phosphorus ligands.

The rest of the ligands can be classified as non-phosphorus ligands, which have been less studied in this transformation. Hoveyda and Hird looked into the potential of these phosphorus-free ligands in the asymmetric conjugate addition by peptide-based ligands. In the initial work, phosphine based peptide ligands gave only racemic products so they investigated more on the non-phosphorus versions. With optimization of the backbone, they were able to obtain dialkylzinc addition to tetrasubstituted enones with

very good catalytic activity and enantioselectivity.[8] Later, diamino carbene ligands were investigated; however, only moderate ee's were achieved albeit high catalytic activity was recorded with these ligands. In this direction, other *N*-heterocyclic carbenes (NHC) were used with a second binding site present on the backbone. In general, good enantioselectivities were accomplished only with dialkylzinc reagents (**Figure 4.3**).[9]

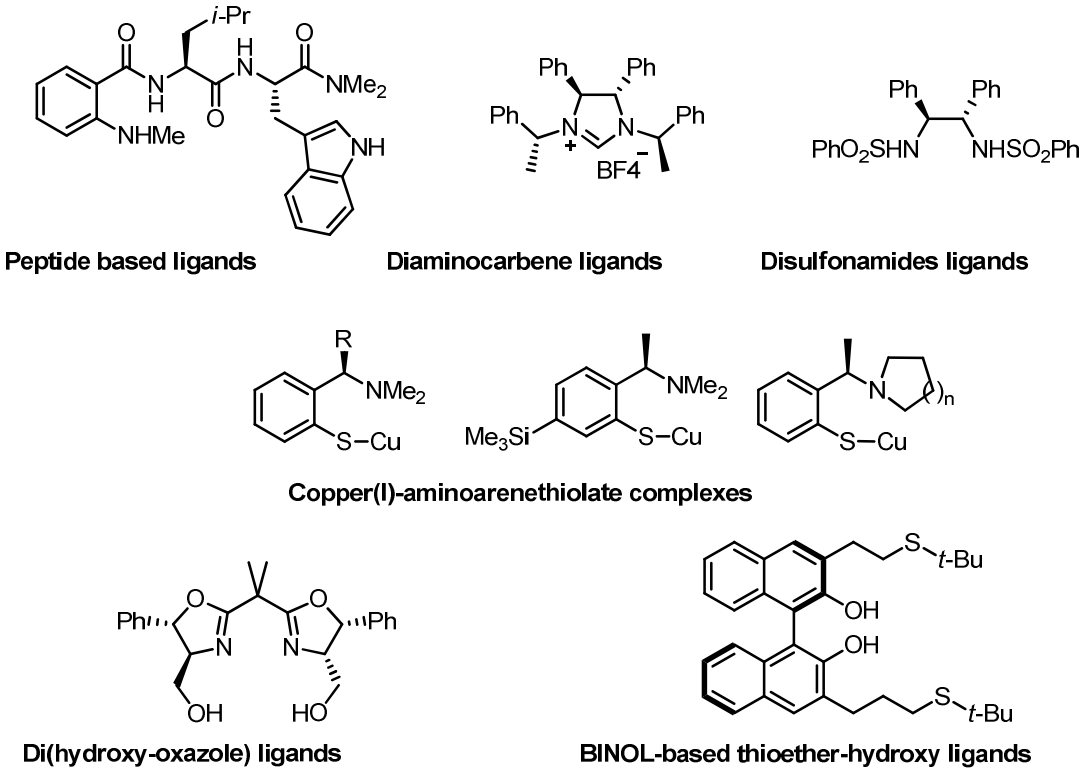


Figure 4.3. Non-phosphorus ligands.

4.2. AIM

Based on the seminal work in the development of 1,2,3-triazoles as ligands in metal-catalyzed reactions[10] and encouraged by our previous results,[11] we wanted to take triazole ligands one step further for metal-catalyzed asymmetric reactions. Due to the experience in our research group with diethylzinc chemistry and copper chemistry, we

[8] Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 14988.
[9] Martin, D.; Kehrli, S.; d'Augustin, M.; Clavier, H.; Mauduit, M.; Alexakis, A. *J. Am. Chem. Soc.* **2006**, *128*, 8416.
[10] Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.
[11] (a) Özçubukçu, S.; Ozkal, E.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2009**, *11*, 4680 (b) Ozkal, E.; Özçubukçu, S.; Jimeno, C.; Pericàs, M. A. *Catal. Sci. Technol.* **2012**, *2*, 195.

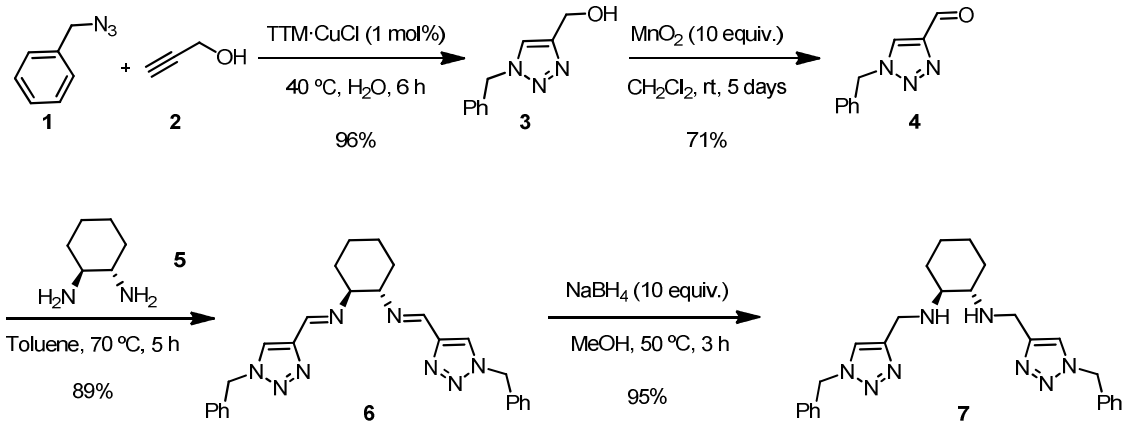
sought to apply that knowledge into chiral click ligands derived from CuAAC reaction for the asymmetric copper-catalyzed conjugate addition of diethylzinc reagents.

4.3. RESULTS AND DISCUSSION

4.3.1. CHIRAL DIIMINO AND DIAMINO TRIAZOLE LIGANDS

Preparation

In order to prepare the target diiminotriazoles, we proceeded to perform the CuAAC reaction of benzyl azide (**1**) and propargyl alcohol (**2**) in the presence of a catalytic amount of TTM·CuCl in water. The triazolyl alcohol **3** was obtained after filtration in gram scale and in pure form. Then, the alcohol **3** was oxidized to aldehyde **4** using manganese dioxide (MnO_2) to yield the triazolyl aldehyde with very good yields. Finally, the reaction of **4** with enantiopure cyclohexyl diamine **5** in toluene at 70 °C to afford the target chiral diimino triazole ligand **6**. Overall, the ligand **6** was synthesized without the need of any column purification in gram scale. Later **6** was reduced to **7** quantitatively using sodium borohydride at 50 °C in 3 h. Having both ligands in hand (**6** and **7**), the stage was set to test them in asymmetric catalysis (**Scheme 4.4**).



Scheme 4.4. Preparation of chiral "click" imino and amino ligands.

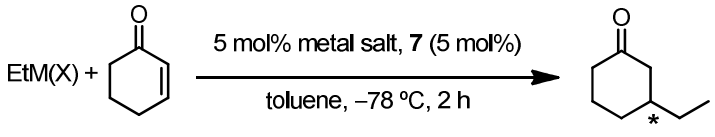
Test in catalysis

In order to test their ability to act as ligands in enantioselective reactions, these ligands were tested as catalysts in copper-catalyzed 1,4-addition of organometallic reagents to cyclic enones. To this end, addition to cyclohexenone was chosen as a

benchmark condition. Different solvents, copper sources, and organometallic reagents were screened.

In the initial study, amine ligand **7** was screened with different copper sources and either with ethylmagnesium bromide or diethylzinc as the nucleophile. Excellent conversions were achieved in most of the conditions screened; however in all cases the reaction gave a racemic product (**Table 4.1**).

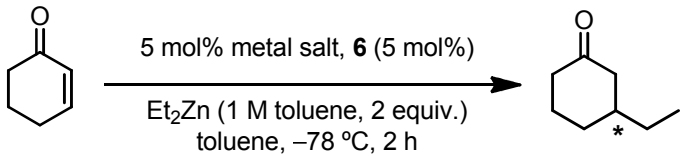
Table 4.1. Initial reaction screening for amine ligand.



Entry	Metal	Reagent	time (h)	Conv (%)	ee (%)
1	CuCN	EtMgBr	3	99	0
2	CuI	EtMgBr	3	99	0
3	$Cu(OTf)_2$	EtMgBr	3	99	0
4	CuOTf	EtMgBr	3	99	7
5	$Cu(OTf)_2$	Et_2Zn	2	14	0
6	$Cu(BF_4)_2 \cdot 6H_2O$	Et_2Zn	2	15	0
7	$Cu(acac)_2$	Et_2Zn	2	42	3
8	$CuCl_2$	Et_2Zn	2	24	0

Then, we turned our attention to the imine ligand **6**; moderate conversion and enantioselectivity were observed using diethylzinc. In order to optimize the enantioselectivity and activity various parameters were screened. Toluene was initially selected as the solvent, since its non-coordinating nature is beneficial in this transformation. Among different metal salts, copper salts, especially $Cu(acac)_2$ afforded the best conversion and higher enantioselectivity (**Table 4.2**, entry 1).

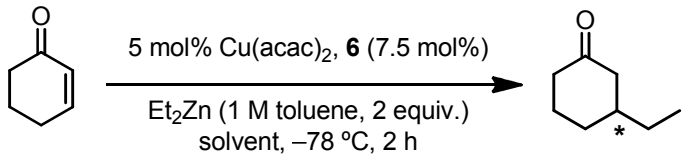
Table 4.2. Initial screening of imine ligand in conjugate addition.



Entry	Metal	Conv. (%)	ee (%)
1	$Cu(acac)_2$	63	45
2	$Co(acac)_2$	3	4
3	$Ni(acac)_2$	26	22
4	$Co(II)OAc{\cdot}4H_2O$	8	4
5	Cu(II)3,5-diisopropylsalicylate hydrate	8	7
6	Cu(II)cyclohexanebutyrate	30	10
7	Bis(2,2,6,6-tetramethyl-3,5-heptanedionato)Cu(II)	9	11
8	Cu(II)2-pyrazinecarboxylate	12	3

Later, the ligand/copper ratio was investigated and 1.5 equivalent of ligand with respect to copper salts gave full conversion. After this, we looked into different copper species but again the best results were obtained by using $Cu(acac)_2$. Next, some additional solvents were screened and it was found that use of hexane gave better enantioselectivity (entry 1) albeit at the cost of a slight decrease in conversion (**Table 4.3**).

Table 4.3. Solvent screening.



Entry	Solvent	Conv. (%)	ee (%)
1	hexane	85	56
2	DCM	28	20
3	Et_2O	73	48
4	hexane[a]	59	58

[a] 1 M solution of Diethylzinc in hexane were used.

Finally, the amount of diethylzinc was investigated and we corroborated that our initial starting point, consisting in the use of 2 equivalents turned out to be optimal in order to achieve full conversion.

After this point, even though we continued further utilizing bulkier commercial diamines to increase the steric bulk of the catalyst, we were unable to improve the results. For this reason, we decided to study the use of such ligands in other transformations.

4.4. CONCLUSION

In this chapter, a general strategy to obtain novel chiral dimino- and diamino-triazole based ligands has been developed. Although only moderate enatioslectivities were obtained with such ligands in copper-catalyzed conjugate addition of organometallic reagents to cyclic enones, the ligands were highly active and the present work constitutes, to our knowledge, the first application of this kind of ligands in this particular transformation.

Moreover, gram scale syntheses of ligands were optimized. The imine derivatives are accessible in three steps without any column purification. In addition, amine ligands are readily available from imine ligands by standard reductive amination. Further modifications of this strategy should allow access to a wide variety of structures to be explored in future.

4.5. EXPERIMENTAL SECTION

Unless otherwise stated, reactions were performed in flame-dried round bottom flasks. The flasks were fitted with rubber septa and stirring bars, and reactions were conducted under a positive pressure of argon. Syringes or cannulae were used to transfer air- and moisture-sensitive liquids.

All copper catalyzed azide-alkyne cycloaddition (CuAAC) reactions were performed in glass vials with stirring bars without any precaution to exclude air and moisture. All flash chromatography purifications were carried out using 60 mesh silica gel and dry-packed columns. For thin layer chromatography (TLC) analysis, Merck pre-coated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used with UV light and phosphomolybdic acid (PMA) or basic aqueous potassium permanganate ($KMnO_4$), followed by heating with developing agents. Solutions were concentrated under reduced pressure on a rotary evaporator with a pump capable of less than 10 mbar at 30 ^{o}C.

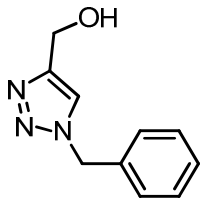
All reagents were used as purchased with the following exceptions: whenever a reaction was performed under exclusion of air and moisture the solvents were purified by using a Solvent Purification System (SPS). Diethylzinc was purchased from Sigma-Aldrich and stored sealed in glove box, 1.0 M solution in toluene was prepared into a Schlenk flask inside the glove box and later it was stored under ambient conditions. For the reaction set up, inert atmosphere and Schlenk techniques were utilized. Cyclohexenone was distilled under inert atmosphere and was kept sealed at –20 °C under argon atmosphere prior to use.

Nuclear Magnetic Resonance (NMR) spectra were recorded at 400 MHz or 500 MHz for ^{1}H and at 100 MHz or 126 MHz for ^{13}C at room temperature (unless otherwise stated). Chemical shifts (δ) are reported in parts per million (ppm) with respect to tetramethylsilane as internal standard, or to the corresponding solvent residual peak ($CDCl_3$: 7.28, $(CD_3)_2SO$: 2.50, CD_3OD: 3.31, D_2O: 4.79). The following abbreviations are used for the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br-s, broad signal. Melting points are all uncorrected. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses were carried out in C.A.I. Microanálisis Elemental, Universidad Complutense de Madrid (Spain). High resolution mass spectrometry analyses were performed in a Waters LCD Premier instrument

operating in ESI (Electro-Spray Ionization) mode by the High Resolution Mass Spectromety Service at the Institute of Chemical Research of Catalonia (ICIQ). *The early experimental work on the use of ligands in copper-catalyzed conjugate additions of diethyl zinc was performed by Dr. Ciril Jimeno in Prof. M. A. Pericàs Group at ICIQ.*

SYNTHESIS OF LIGANDS

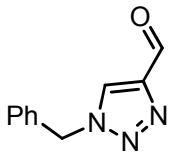
(1-BENZYL-1H-1,2,3-TRIAZOL-4-YL)METHANOL (3)[12]



Benzyl azide (2.81 g, 21.1 mmol, 1 equiv.) was added via syringe to a mixture of propargyl alcohol (1.24 g, 22.2 mmol, 1.05 equiv.) and TTM·CuCl (0.127 g, 0.211 mmol, 10 mol%) in water (20 mL) at rt and was stirred at 40 °C. After 6 h, reaction mixture was cooled to rt and was washed with ethyl acetate (3 × 50 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to afford the desired product as white solid (96% yield, 3.84 g, 20.3 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (s, 1H), 7.30 – 7.18 (m, 5H), 5.42 (s, 2H), 4.63 (s, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.5, 134.7, 129.1, 128.9, 128.3, 122.2, 55.9, 53.7.

1-BENZYL-1H-1,2,3-TRIAZOLE-4-CARBALDEHYDE (4)[13]



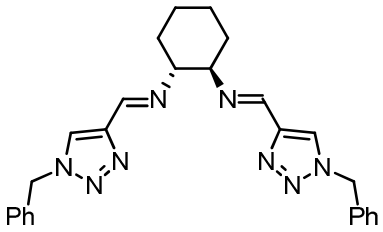
(1-Benzyl-1H-1,2,3-triazol-4-yl)methanol (2.00 g, 10.6 mmol, 1 equiv.) was added as a solid to a mixture of manganese dioxide (9.19 g, 106 mmol, 10.0 equiv.) in dichloromethane (85 mL) at rt and was stirred at rt. After 5 days, the reaction mixture

[12] Girard, C.; Önen, E.; Aufort, M.; Beauvière, S.; Samson, E.; Herscovici, J. *Org. Lett.* **2006**, *8*, 1689.
[13] Chan, T. R.; Fokin, V. V. *QSAR Comb. Sci.* **2007**, *26*, 1274.

was filtered over Celite® and it was washed with dichloromethane (5 × 50 mL). The solution phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the desired aldehyde as a white foam (70% yield, 1.38 g, 7.40 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.14 (s, 1H), 8.07 (s, 1H), 7.43 – 7.32 (m, 5H), 5.62 (s, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 185.2, 147.8, 133.6, 129.5, 129.2, 128.5, 125.1, 54.7.

SYNTHESIS OF THE IMINE LIGAND 6

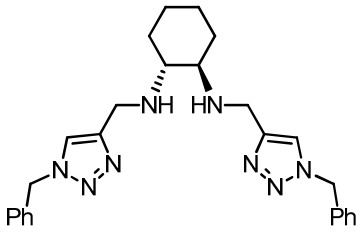


A few activated 4Å molecular sieves and 1-benzyl-1H-1,2,3-triazole-4-carbaldehyde (1.80 g, 9.60 mmol, 2.0 equiv.) were added as solid into a flask with mixture of (*R,R*)-1,2-diaminocyclohexane (0.548 g, 4.80 mmol, 1 equiv.) in toluene (8 mL) and stirred at 70 °C . After 24 h, the heterogeneous white reaction mixture was cooled to rt, was filtered and was washed with ice-cold methanol (3 × 5 mL). The filter cake was collected and was dried under reduced pressure to afford the imine ligand as a white solid (89% yield, 1.93 g, 4.27 mmol).

mp: 192-193 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.31 (s, 2H), 7.82 (s, 2H), 7.45 – 7.24 (m, 10H), 5.56 (d, *J* = 14.7 Hz, 2H), 5.41 (d, *J* = 14.7 Hz, 2H), 3.36 – 3.22 (m, 2H), 1.86 – 1.80 (m, 2H), 1.76 (d, *J* = 3.8 Hz, 2H), 1.73 – 1.61 (m, 2H), 1.48 – 1.39 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 153.2, 146.7, 134.0, 129.3, 129.1, 128.6, 122.3, 74.1, 54.5, 32.8, 24.4.

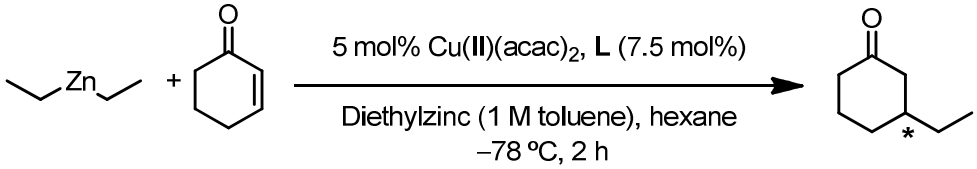
SYNTHESIS OF THE AMINE LIGAND 7



Sodium borohydride ($NaBH_4$, 0.282 g, 7.46 mmol, 10.5 equiv.) was added in small portions to a solution of imine ligand (0.321 g, 0.709 mmol, 1 equiv.) in methanol (5 mL) at 0 °C and stirred at 50 °C. After 3 h, volatiles were removed under reduced pressure and the residue was decomposed by water (10 mL), extracted with diethyl ether (3 × 10 mL), and washed with brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to afford the amine ligand as a white foam (95% yield, 0.308 g, 0.674 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.47 (s, 2H), 7.42 – 7.20 (m, 10H), 5.48 (s, 4H), 3.95 (d, *J* = 13.8 Hz, 2H), 3.74 (d, *J* = 13.8 Hz, 2H), 2.28 – 2.16 (m, 2H), 2.16 – 2.02 (m, 4H), 1.77 – 1.62 (m, 2H), 1.20 (td, *J* = 9.6, 9.1, 3.4 Hz, 2H), 1.07 – 0.95 (m, 2H). **^{13}C NMR** ($CDCl_3$, 100 MHz): δ = 148.0, 134.9, 129.0, 128.6, 128.1, 121.7, 60.9, 54.0, 42.0, 31.4, 24.9.

TYPICAL REACTION CONDITIONS FOR CONJUGATE ADDITION REACTIONS



A mixture of the copper salt (0.025 mmol, 5 mol%) and imine ligand (16 mg, 0.037 mmol, 7.5 mol%) in hexane (1 mL) was stirred at rt. After 1 h, diethylzinc (1.0 M in toluene, 1.0 mL, 1.0 mmol, 2.0 equiv. **caution!** pyrophoric and water sensitive) and cyclohexenone (48 µL, 0.5 mmol, 1 equiv.) were added via syringe at –78 °C and stirred at –78 °C. After 2 h, a sample was taken from the reaction mixture via syringe and it was quenched in a vial with 1 M hydrochloric acid (aq)–diethyl ether mixture (1:1, 1 mL). After 5 min, the ethereal phase was separated and filtered through a short plug of Celite® and analyzed by GC for conversion and enantioselectivity. Chiral GC Analysis: β-dex 225, 120°C isothermal. Starting material: at 10 min, enantiomers of products: at 6.3-6.5 min.

Conclusions & Outlook

CONCLUSIONS AND OUTLOOK

The use of triazole ligands obtained by CuAAC reactions has a great potential in catalysis. The easy access and modularity within the nature of *click chemistry* and the related reactions enables the preparation of a wide variety of diverse sets of ligands for different metal-catalyzed transformations. In the context, the main goal of the thesis was the synthesis of new ligands (with the *click chemistry* idea in mind) for different reactions. This has been accomplished with the synthesis of ligands represented in **Figure 1**.

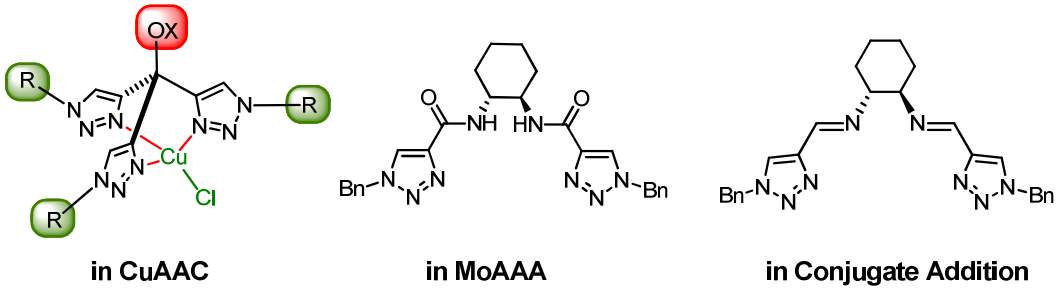


Figure 1. Triazole-based ligands developed in the course of this thesis.

In general, the utilization of easy and modular approaches for the development of *click* ligands in this thesis, renders a significant advancement over existing ligands in terms of activity and selectivity.

In **Chapter 2**, the modular tris(triazolyl)methanols (**TTM**) have been shown to be among one of the most useful ligands for copper-catalyzed azide-alkyne cycloaddition reactions. The three-point binding provided by these ligands efficiently stabilizes Cu(I) against oxidation or complexation with amino, hydroxy, and/or thioether groups present in either reactants or reaction products, probably through favorable self-repair of the catalytic complex. This behavior not only extends the catalyst life and allows much reduced catalyst loadings; it also allows its use with substrates (primary and secondary amines) where most catalysts for CuAAC reactions completely fail.

The first catalyst generation in this family, tolerates a wide range of functional groups on either the alkyne or the azide reactant, being particularly suitable for work in aqueous media. The fully optimized, environmentally benign preparations of TTM derivatives have also been reported. The modification of the first generation catalyst, by

preparation of a small library of tris(aryltriazolyl)methanol derivatives provides catalytic species suitable for work in organic solvents.

At the same time, TTM ligand has been successfully immobilized in one step onto a polystyrene resin and converted into a heterogeneous Cu(I) complex. The PS-supported catalyst behaves as a very active promoter of the CuAAC reaction, as it has been demonstrated with a broad variety of substrates (including free amines and thioethers). Interestingly, it exhibits excellent recycling characteristics.

In **Chapter 3**, the preparation of a chiral amido-triazole ligand was described with its evaluation in molybdenum-catalyzed asymmetric allylic alkylation (MoAAA) reactions using aryl carbonates with dimethyl malonate. High enantio- and regio-selectivity have been obtained with the novel chiral triazole ligand either in conventional heating or under microwave assisted conditions; and its modular nature of synthesis with CuAAC reaction and amide coupling enabled a different approach to ligands from click chemistry with potential novel diversity in asymmetric catalysis.

In **Chapter 4**, chiral imine and amine derivatives of triazole ligands were developed and synthesized in gram scale without any need of purification. Their evaluation in enantioselective copper-catalyzed conjugate additions or organometallic reagents afforded high activity albeit enantioselectivities have been moderate.

Overall, triazole-based ligands have a wide future in metal-catalyzed reactions as valuable catalysts. In addition to very valuable previous works in literature, this thesis clearly expands the use of triazole-based ligands for CuAAC reaction, covalent immobilization of such metal complexes in catalysis and gratifyingly for asymmetric catalysis.