# *Program & Abstracts*

*Conference venue*:

University of Łódź, Faculty of Chemistry, Tamka-Str. 12,

The Large Hall, A-1

Organizing committee:

| | |
|---|---|
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Organizing Committee thanks to WITKO company
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VIII[th] International Mini-Symposium

*''The Huisgen Cycloaddition Reaction as a Universal Tool in Chemistry, Biology, and Medicine'*

# Program

*Special Guest Lecture*

***11:30-12:15*** **Wolfgang Weigand**
University of Jena, Germany

***12:15-13:15*** *Lunch*

***13:25*** ***Official Opening***

## *Session 1:* ***Chairman: Prof. Zbigniew Kamiński***

*Keynote Lecture*

**13:30 – 14:15** **Hans Ulrich Reissig**
***KL*** Free University of Berlin, Germany

*Invited Lectures*

**14:15 – 14:45** **Karol Kacprzak**
***IL-1*** Adam Mickiewicz University in Poznań, Poland

**14:45 – 15:15** **Wafaa Abdou**
***IL-2*** National Research Center in Cairo, Egypt

**15:15 – 15:45** **Zbigniew Leśnikowski**
***IL-3*** Institute of Medicinal Biology, PAS Łódź, Poland

*15:45 – 16:15* *Coffee break*

## *Session 2* ***Chairman: Prof. Piotr Kiełbasiński***

*Invited Lectures*

**16:15 – 16:45** **Peter R. Schreiner**
***IL-4*** Justus Liebig University in Giessen, Germany

**16:45 – 17:15** **Keith ó Proinsiasa**
***IL-5*** Institute of Organic Chemistry, PAS Warsaw, Poland

**17:15 – 17:45** **Florence Dumarcay-Charbonnier**
***IL-6*** University of Lorraine, Nancy, France

*Short Lectures*

**17:45 – 18:00** **Marcin Jasiński**
***SL-1*** University of Łódź, Poland

**18:00 – 18:15** **Bogna Rudolf**
***SL-2*** University of Łódź, Poland

*18:15 – ……* *Garden Grill Party*

TriMen Chemicals

## ***Special Guest Lecture***

# From Primordial to Bio-inspired Hydrogen Production

**Wolfgang Weigand**

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In 1845, Berzelius has reported the geochemically and primordially important reaction[1] of iron sulfide with hydrogensulfide to form pyrite, which was forgotten for many decades.

$$FeS + H_2S \rightarrow FeS_2 + H_2;\ \Delta G° = -26.9\ kJ\ mol^{-1}\ (25\ °C, 1\ bar)$$

It was revisited by several groups[2] and used for hydrogenation reactions of e.g. carbon dioxide or nitrogen. In that context, the Berzelius can be seen as a primordial model for the hydrogenase enzyme. In other words, the structure of catalytically active Fe,S centres of Fe,S proteins are not inventions of the biological world, rather they are mimicking these iron sulfur minerals that are older and which themselves have catalytic activity in the absence of protein.

Here we will present a short story of "chemical evolution" starting from FeS to Fe,S enzymes e.g. [FeFe]-hydrogenases.[3] Moreover, the synthesis of novel [FeFe] hydrogenase model complexes using thioketones as heterodienes as well as of complexes containing heavier group 14, 15 and 16 elements will be presented.[4] In the light of recent results, the influences of the substituents and heteroatoms on the molecular structure as well as the reactivity will be discussed. Finally, the electrochemical as well as photocatalytic properties of these complexes have been also studied.[5]

[1] J. J. Berzelius, Traité de Chimie. 2; Didot: Paris, 1845.
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[3] T. Alpermann, K. Rüdel, R. Rüger, F. Steiniger, S. Nietzsche, S. Förster, A. Fahr, W. Weigand, *Orig. Life Evol. Biosph*. **2011***, 41*, 103.
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***KL***

# The Huisgen Reaction - 1,3-Dipolar Cycloaddition - Click Reaction

**Hans-Ulrich Reissig**

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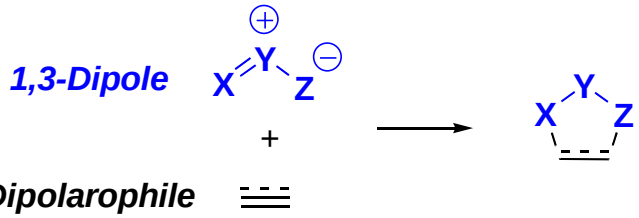
In 1960 Rolf Huisgen introduced the concept of 1,3-dipolar cycloadditions to the chemical community.[1] The Munich group systematically defined the 1,3-dipolar species of the second period elements (C, N, O) and as a consequence new entities were predicted and experimentally investigated. Due to these studies the 1,3-dipolar cycloaddition to multiple bond systems became a general principle comparable to the Diels-Alder reaction and it is now one of the most flexible (and selective) methods for the synthesis of many types of heterocycles.




A new unexpected boost to the field resulting in an explosion of new applications was initiated by Barry Sharpless who invented the term “click chemistry” and suggested that 1,3-dipolar cycloadditions of organic azides with alkynes should be a prototype of this kind of reaction.[2] The subsequently developed copper-catalyzed [3+2] cycloaddition[3] of these precursors was examined in countless examples in biological and supramolecular systems also having impact on material science. Based on the Sharpless idea Carolyn Bertozzi introduced strain-promoted azide alkyne cycloadditions[4] that are possible without the use of metal catalysts and hence of particular importance to studies in living organism.

The lecture will be closed by presenting selected studies of the Berlin group using 1,3-dipolar cycloadditions.

[1] First lectures: *Fonds der Chemischen Industrie*, München (April 7, 1960) and *Royal Society of Chemistry*, London (December 8, 1960, Centenary Lecture). First reviews: R. Huisgen, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565-598 and 633-645.

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## IL-1

# When Cinchona Alkaloids Meet Cu(I) Catalysed 1,3-Dipolar Huisgen Cycloaddition (CuAAC)

**Karol Kacprzak**

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Cinchona alkaloids and their numerous derivatives occupy a privileged position as catalysts for asymmetric synthesis [1] selectors for enantioselective separation and sensing [2] as well as in medicinal chemistry, where quinine and quinidine are known for very long time as antimalarial and antiarrythmic drugs, respectively [3].

Cinchona alkaloid structure is ideally suited for diverse modification and with the introduction in 2001 a concept of click chemistry, CuAAC reaction was quickly recognized as novel, practical and valuable tool toward their novel application.

In my lecture brief CuAAC-driven chemistry of Cinchona alkaloids will be presented with the special emphasis on applications of Cinchona alkaloid-1,2,3-triazoles. These include among other, highly efficient and operationally simple CuAAC immobilization of Cinchona alkaloids onto solid support [4], preparation of novel chiral stationary phases for chromatography [5-7] as well as immobilized organocatalysts [8]. On the field of medicinal chemistry CuAAC conjugation of Cinchona alkynes and azides with various bioactive molecules, such as nucleosides [9-11], polyether antibiotics [12] and steroids resulted in discovery of few very potent cytotoxic leads.

**Acknowledgements:**
Financial support from European Regional Development Fund within the Innovative Economy Operational Programme project UDA-POIG.01.03.02-30-067/12 is kindly acknowledged.

**References:**

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[6] K. Kacprzak, N. Maier, W. Lindner *J. Sep. Sci*., **2010**, *33*, 2590
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[8] R. Porta, M. Benaglia, F. Coccia, F. Cozzi, A. Puglisi *Adv. Synth. Catal* , **2015**, *357*, 377
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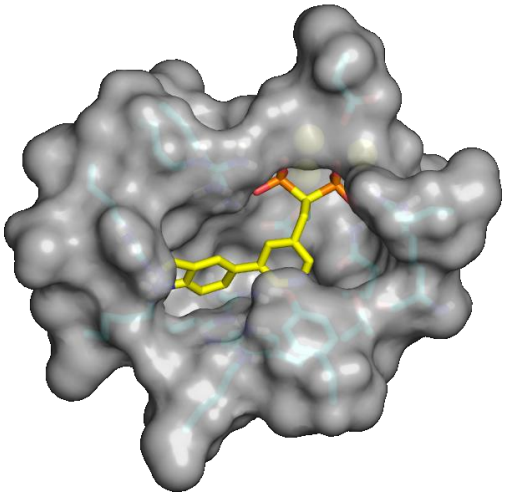
***IL-2***

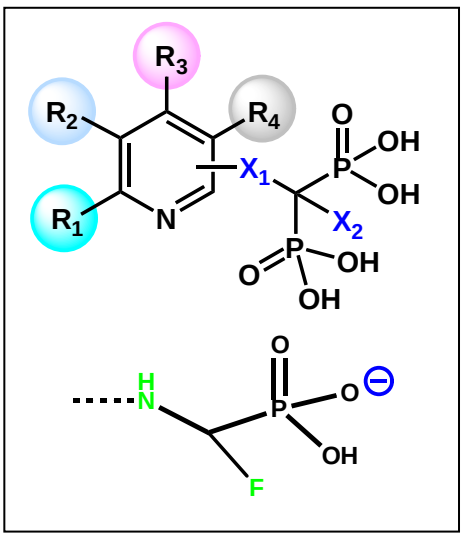
# Novel Bisphosphonate Inhibitors of Prenyl Synthase Enzymes as Potential Therapeutics

**Wafaa Abdou**

*National Research Center, Cairo, Egypt*

Methylenebisphosphonates (MBPs) are the most widely used and effective anti-resorptive agents for the treatment of diseases in which there is an increase in osteoclastic resorption. The pronounced selective activity of MBPs for bone tissues rather than others is the basis for their value in clinical practice Recently, pharma laboratory studies increasingly suggest that N-BPs (e.g., ibandronate and zoledronate) can induce important antitumor effects, and in particular in prostate and breast cancer cells *in vitro* and *in vivo* by promoting apoptosis, and inhibiting cell adhesion and invasive potential. Nevertheless, it has been noted that the *in vitro* concentrations of N-BPs required inducing breast cancer cell apoptosis are higher than those required for osteoclast apoptosis. This recent discoveries of antitumor potency of N-BPs was attributed to the differences of their molecular mechanism of action. Thus, BPs can be grouped in two main different classes: first-generation non- N-BPs, second generation N-BPs. First-generation BPs, such as clodronate and etidronate, are metabolized intracellularly to analogues of ATP-by inhibiting ATP-dependent enzymes. In contrast, second-generation N-BPs such as risedronate, ibandronate, and zoledronate, interfere with other metabolic reactions, notably those in the mevalonate biosynthetic pathway, by inhibiting human farnesyldiphosphatesynthase (hFPP). The inhibition of hFPP synthase prevents the prenylation of small GTPases (e.g., Ras, Rho, Rab), which are important signaling proteins. Our researh program considered an elaboration of a diveristy of nitrogen and/or sulfur containing BPs. Several of these BPs reflected remarkable antitumor activity against breast (especially MDA-MB-231/ATCC and BT-549), and myeloma (LOXIMVI, MALME-3M, and MI4) carcinoma cell lines.






Mechanism of action of nitrogen-containing bisphosphonates.

## *IL-3*

# Cu(I)-Catalyzed Huisgen Azide-Alkyne 1,3-Dipolar Cycloaddition Reaction in Boron Cluster-Nucleoside Conjugates Chemistry

**Zbigniew J. Leśnikowski**

*Laboratory of Molecular Virology and Biological Chemistry, Institute of Medical Biology, Polish Academy of Sciences, Lodowa 106, 92-232 Łódź, Poland*

Pioneered by Huisgen in the 1960s, the 1,3-dipolar cycloaddition reaction between acetylenes and azides was brought back into focus by Medal, Sharpless and others when they developed the concept of "click chemistry" and of copper(I) salts catalysis of the cycloaddition process. Soon an array of applications of Huisgen-Medal-Sharpless reaction in all areas of organic, bioorganic and medicinal chemistry appeared. Methods for side-specific protein modification, activity-based protein profiling and copper-free "click chemistry" *in vivo* have been also elaborated. Medicinal chemistry is still dominated by organic chemistry therefore most of the marketed drugs are purely organic molecules. In approach to surpass this limitation we become interested in use of boron clusters and their complexes with metals in design of biologically active molecules. Over the last 40 years, the development of nucleic acids and nucleoside analogues for medicinal uses has had a marked impact on clinical chemotherapy as applied to antiviral and anticancer treatment. Numerous nucleoside analogues were successfully developed for the treatment of human immunodeficiency viruses (HIV), hepatitis B and C viruses (HBV, HCV), herpes simplex virus (HSV), cytomegalovirus (CMV) or varicella zoster virus (VZV). Thus, modification of nucleosides with boron clusters using a "click chemistry" approach was an obvious aim. In this direction we developed several methods and were the first to use Huisgen-Medal-Sharpless reaction in boron cluster chemistry.[1,2]

In the present communication methods developed mainly in author's laboratory will be discussed.[3] They are usually based on construction of two types of building blocks: one is the boron-cluster donor equipped with a terminal azido or ethynyl function, the second is the nucleoside–boron cluster acceptor, similarly furnished with a terminal alkyne or azido group. The combination of all four possibilities, two types of boron-cluster donors and two types of boron-cluster acceptors, provides high versatility for the proposed methodology. Biological testing of the obtained libraries of compounds for cytotoxicity, antiviral and antibacterial activity, inhibition of blood platelets activation and active oxygen species (ROS) production as well as modulation of purinergic receptors activity will be also discussed.[4]

**Acknowledgments:** These works were supported in part by grant N405 051 32/3592, K152/H03/2007/10, POIG.01.01.02-10-107/09 and 2014/13/B/NZ1/03989, from the Polish Ministry of Sciences and Higher Education and National Research Center.

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## ***IL-4***

# Enantioselective Multicatalysis[1]

**Peter R. Schreiner**

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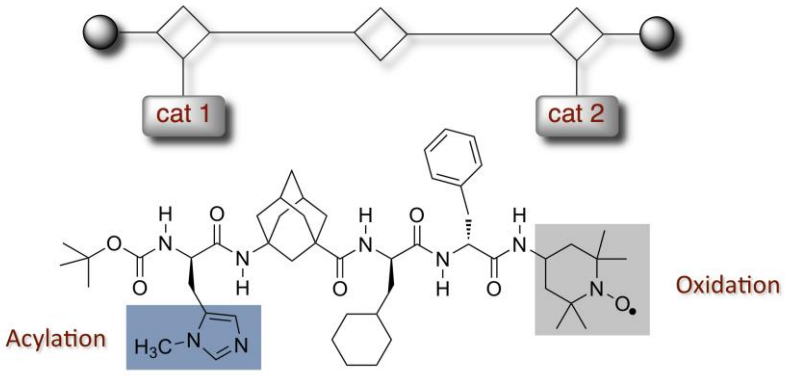
Stereoselective, homogeneously catalyzed cascade reactions are a key toward resource-efficient and sustainable transformations at the forefront of synthetic chemistry. These types of reactions are labeled as domino, tandem, cascade or zipper transformations. Arguably, there is no concept that utilizes a multicatalyst system (*cf*. Figure) where a variety of organocatalytic moieties is strung together on an arbitrary backbone.[1] This concept is reminiscent of an assembly line where each interconnected station performs a particular function and only their proper sequence gives the desired product. It is also akin to many biological processes such as protein biosynthesis.

Here we present our efforts towards organocatalytic enantioselective concurrent "assembly line" reactions by utilizing *multicatalysts* with orthogonal (i.e., independent) catalytic moieties. A far-fetched but not unreasonable goal would be the use of a library of such catalytic moieties that can be assembled to serve the purpose of synthesizing a complex organic molecule in one pot by a programmed series of catalyzed reactions utilizing a retrosynthetic algorithm. It is clear that our one-pot multicatalyst approach has some operational advantages (e.g., saving of solvents, time, and simpler workup) that become apparent as the number of catalyzed steps[2] increases. The present talk provides proof-of-principle studies of a new concept in catalysis,[3] including demanding reactions such as cross-coupling of alcohols[4] and the first enantioselective Dakin-West reaction.[5]

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## *IL-5*

# Huisgen Cylcoaddition – an Essential Tool in Vitamin $B_{12}$ Conjugation Reactions

**Keith ó Proinsias and Dorota Gryko***

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Vitamin $B_{12}$ (cobalamin, $B_{12}$) is of major importance to all mammalians.[1,2] As we cannot generate this essential vitamin it must be ingested by consuming products such as meat and milk. Cobalamin has a very unique and specific uptake pathway which chemists and biologists have graciously taken advantage of utilizing it as a delivery vehicle for active compounds to their desired locations.

Currently, only limited procedures are available for the construction of vitamin $B_{12}$ conjugates with biologically active compounds. The most straightforward methodology was developed by Russell-Jones involving the reaction of cobalamin with CDI or CDT and subsequently with other amines or alcohols giving carbamates or carbonates at 5'position.[2]

Though this method is universally applied it possesses few disadvantages including pH sensitivity. Fortunately, our group has prepared desirable derivatives incorporating alkyne and azide groups into the vitamin generating more robust compounds.[4] By utilizing Huisgen cycloaddition reactions conjugation can easily be achieved giving a stable delivery vehicle.

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## ***IL-6***

# New symmetric bis-triazol ligands using Click Chemistry: towards supramolecular 1:1-complexes of Bis-lariat Hosts and Bis-sulfonates Guests

**Joly, Jean-Pierre; Dumarçay-Charbonnier, Florence*; Marsura, Alain**

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The complexation of metal ions (lanthanides, alkali, alkaline earth and transition metals) and small molecules (amines and analogous compounds) by crown ethers is well known.[1, 2] Joly *et al.* have recently described the efficient synthesis of different ligands ether containing two [1,2,3]-triazole ligands as sidearms, via the Cu(I)-catalyzed Huisgen dipolar cycloaddition from a $C_2$-symmetric diaza-crown.[3,4] They used various alkyl-substituent on the azide (*e.g.* benzyl, phenyl, *etc.*). These hosts yielded stable mononuclear $Cu^{II}$, $Zn^{II}$ or $Ni^{II}$ complexes with different geometries and coordination in solid state.

Varying the nature of organic azides used in this $Cu^{I}$-catalyzed Huisgen reaction gave access to a variety of synthetic receptors endowed with supramolecular and catalytic behaviors.

On the other hand, modified cyclodextrins are well known for their ability to form inclusion complexes with a lot of substrates in water. Our expertise on their synthesis and on their supramolecular properties led us to describe simple, rapid and controlled synthesis of new highly organized supramolecular species, *i.e.* bis-cyclodextrinyl-diazacrown-[2] cryptorotaxanes.[5]

In this way, a new symmetric lariat was synthesized from the same [18-4-2] aza-crown ether and mono-azido-cyclodextrin via “click chemistry”. We present here new organized supramolecular assemblies involving the new water-soluble pseudo-cryptand as host and bis-sulfanilate and bis-tosylate metal salts as guests.[6]

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## ***SL-1***

# Huisgen-Sharpless-Meldal approach to sulfur-rich crown ethers

**Monika Stefaniak, Marcin Jasiński, Piotr Seliger, Natalia Gutowska, Jarosław Romański**

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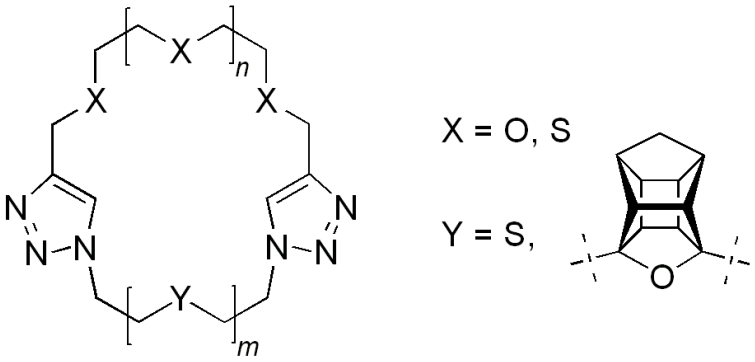
Numerous applications of Huisgen-Sharpless-Meldal[1] (HSM) cycloaddition covering such areas as natural products, drug discovery, bioconjugates, supramolecular scaffolds, polymers, and other special materials has been demonstrated up to date. Although the title reaction has been shown as a highly efficient tool for intramolecular macrocyclization processes, the syntheses of crown ethers via intermolecular fashion remain still little explored. Our preliminary results[2] on the synthesis and complexing properties of new sulfur-rich macrocycles including derivatives bearing Cookson's birdcage unit will be presented.

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## SL-2

# Conjugation of metallocarbonyl complexes based on click-chemistry

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Over the past years we have explored the chemistry of the metallocarbonyl $\eta^5$-$C_5H_5$)M(CO)$_n$($\eta^1$-*N*-maleimidato) complexes of Fe (n=2), Mo, W (n=3) which were applied as labels of peptides and proteins with potential applications in immunoanalysis [1-2]. "Click chemistry" processes are selective and powerful reactions that are increasingly used to synthesize bioconjugates possessing numerous functional subunits with fluorescent or electrochemical properties [3]. It appeared of interest to synthesize alkyne (terminal or cycloalkyne) [4] or norbornene metallocarbonyl derivatives [5] that would be able to react with organic azides or tetrazines in a bioorthogonal way. Such processes could be entries to new selective labeling methods of biomolecules, using the CuAAC (Copper(I)-catalyzed azide–alkyne cycloaddition), SPAAC (Strain-promoted azide-alkyne cycloaddition) and iEDDA (inverse electron demand Diels-Alder) reactions. Herein we report the synthesis of metallocarbonyl complexes bearing alkyne or norbornene ligands and a preliminary study of their reactions with organic azide or tetrazine derivatives.

Fig.1 Structures of metallocarbonyl complexes which are able to react with organic azides or tetrazines

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