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Tribute

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Professor Zbigniew Czarnocki

A tribute

This special issue of Arkivoc is dedicated to Professor Dr. Zbigniew Czarnocki on the occasion of his 66th birthday, to acknowledge his contribution to synthetic organic chemistry and teaching

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Zbigniew Czarnocki was born in Warsaw, Poland, in 1954. In 1972 he was employed as a manual worker digging trenches for an electrical installation, and in 1975 he worked as an assistant in the analytical laboratory of the Warsaw Steelworks. Zbigniew Czarnocki received B.Sc. and M.Sc. degrees in chemistry in 1977 (University of Warsaw), and in 1983 he was awarded his Ph.D. degree from the University of Warsaw working with Professor Jerzy T. Wróbel on synthetic methodology useful in the construction of selected *Lythraceae* alkaloids.

In 1984 he moved to McMaster University (Hamilton, Canada) to undertake a two-year post-doctoral study with Professor David B. MacLean. In 1987 and 1989 he again visited McMaster University as a research associate and visiting scientist. The main area of his research interest was the diastereoselective synthesis of natural nitrogen heterocycles from D- and L-glyceraldehyde.

On returning to the University of Warsaw, Zbigniew Czarnocki obtained his habilitation degree (*summa cum laude*) in 1993 and in 2002 he became a full professor in the Faculty of Chemistry (University of Warsaw). From 1996 till 2002 he served as the vice-Dean of the Faculty and from 1996 has been head of the Laboratory of Natural Products Chemistry. In the period 2012-2017 he served as Dean of the Inter-Faculty Studies in Environmental Protection at the University of Warsaw.

In 1987 he was recipient of the International Scientific Exchange Award (Government of Canada) and in 1993 he received the scientific award of the Polish Academy of Sciences. He is a recipient of the Golden Cross of Merit (by the President of the Republic of Poland, 2005) and the Świętosławski Award (2009). His scientific awards also include several invited lectureships around the globe.

He is a member of the American Chemical Society, the International Society for Tryptophan Research, and the Athens Institute for Education and Research. He was a member of the editorial boards of the *Journal of Amino Acids* till 2017 and *ChronoPhysiology and Therapy* till 2018. He is currently on the board of *Modern Chemistry & Applications, Mediterranean Journal of Chemistry,* and the *Arkivoc*-board of reviewers.

Zbigniew Czarnocki mentored 20 Ph.D. students and supervised over 65 M.Sc. theses. Three highly talented post-doctoral fellows have recently trained under his guidance. He has authored over 150 publications in peer-reviewed journals, 8 review articles, 2 book chapters, 1 academic handbook and 6 patents. His publications have received over 2100 independent citations to date.

His research interests focus on the stereoselective synthesis of natural products, modern catalytic reactions and the pharmacochemistry of various heterocyclic compounds.

Overview of research achievements

During his 43-years of academic activity, Zbigniew Czarnocki and his collaborators have contributed to various fields of organic chemistry, in particular asymmetric synthesis, heterocyclic chemistry, and the chemistry of natural products. His group has also been involved in the development of novel catalytic methods, organocatalysis, physical chemistry of axially chiral molecules and bioorganic chemistry of enzyme inhibitors. The following provides a brief summary of selected topics elaborated by the Zbigniew Czarnocki group over the time span of his career.

Early work on diastereoselective synthesis of isoquinoline alkaloids

It has been proven many times that a postdoctoral internship is an opportunity for a fruitful exchange of research ideas and a significant broadening of scientific horizons. This also happened in the case of Zbigniew Czarnocki. During his several years at McMaster University (Hamilton, Canada), he observed that simple sugars can be effective chiral building blocks in the diastereoselective synthesis of nitrogen heterocycles. Being inspired by this finding he implemented the idea of the use of other simple, naturally occurring sources of

chirality to the asymmetric synthesis of alkaloids and related compounds. It was proved that L-(+)-tartaric acid, among others substrates, may lead to enantiomerically pure natural heterocycles. The key intermediate **1** can be transformed into surprisingly stable aldehyde **2** that in turn may serve as a starting material for subsequent transformations leading to a variety of products (Figure 1).[1,2]

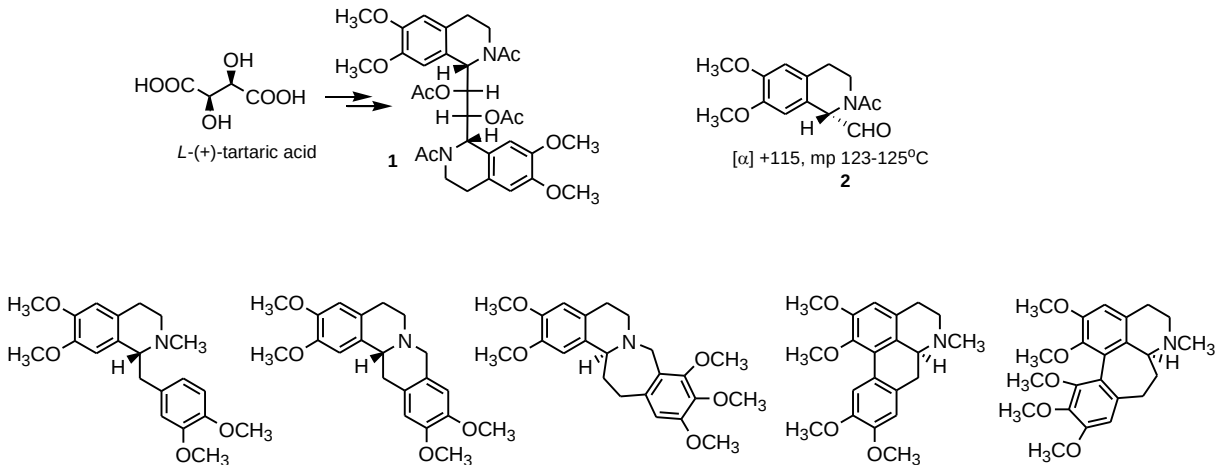
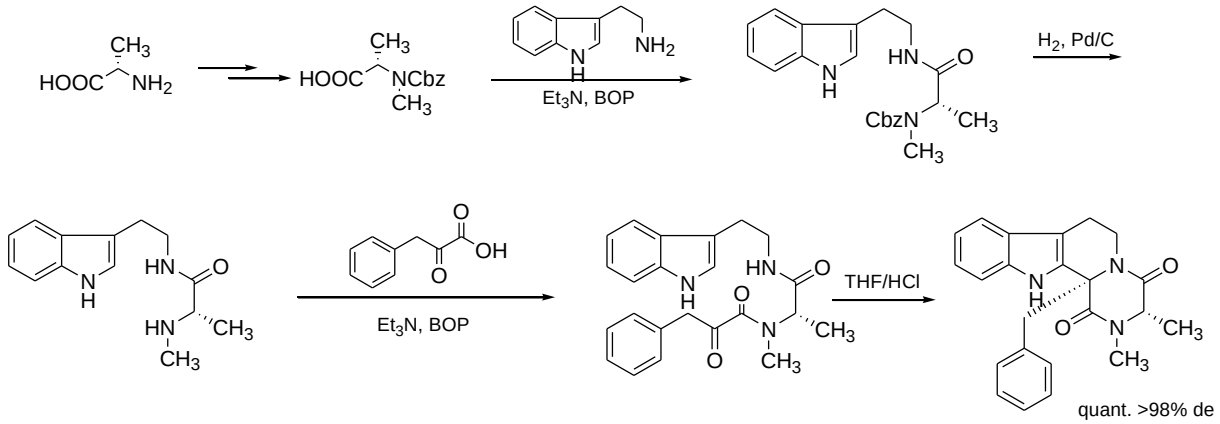


Figure 1. The application of L-(+)-tartaric acid in diastereoselective synthesis of isoquinoline heterocycles.

Interestingly, other natural hydroxy compounds, like L-(+)-ascorbic acid, may also be used in an analogous sequence.[2]

Natural amino acids as chiral promoters in asymmetric synthesis

In recent decades several highly interesting bioactive natural tetrahydroisoquinolines and tetrahydro-β-carbolines having a quaternary stereocenter have been isolated and investigated. Unfortunately, the synthesis of such substituted skeletons is not straightforward by classical methods such as the Pictet-Spengler condensation, Bischler-Napieralski and Pomeranz-Fritsch reactions. Therefore, Zbigniew Czarnocki and his collaborators developed a general method for their synthesis starting from L-amino acids. A representative synthetic sequence is shown in Scheme 1.



Scheme 1. Representative reaction sequence leading to the formation of a quaternary stereocenter.

All reactions proceeded under mild conditions giving crystalline products in high yields. Comparable results were obtained in the case of L-series amino acids namely valine and phenylalanine, both for

tetrahydroisoquinolines and tetrahydro-β-carbolines. Interestingly, when L-proline was used as the substrate, the absolute configuration at the quaternary stereocenter was reversed in all cases.[3-5]

Asymmetric transfer hydrogenation (ATH) in the synthesis of natural products

The isoquinoline and β-carboline motives are present in numerous natural products and compounds of pharmacological importance and therefore many synthetic approaches were developed in this field. Several target compounds are chiral molecules that require their stereoselective synthesis. In many cases this task could be accomplished by an enantioselective reduction of the imine double bond present in the substrate that in turn can be obtained by Bischler-Napieralski or related methods. The catalytic procedure developed by Professor Noyori[6] may effectively be used for this purpose. Several [$Ru^{II}Cl(\eta^6$-arene)diamine] complexes were proved to be highly efficient catalysts for the ATH reactions. Moreover, the presence of a chiral diamine ligand in the catalyst molecule allows for efficient chirality transfer to the product which makes this reaction a most important synthetic procedure.[7] Zbigniew Czarnocki and his collaborators took advantage of this method, performing several syntheses of natural products and pharmacologically important derivatives in an enantio-selective manner (Figure 2).

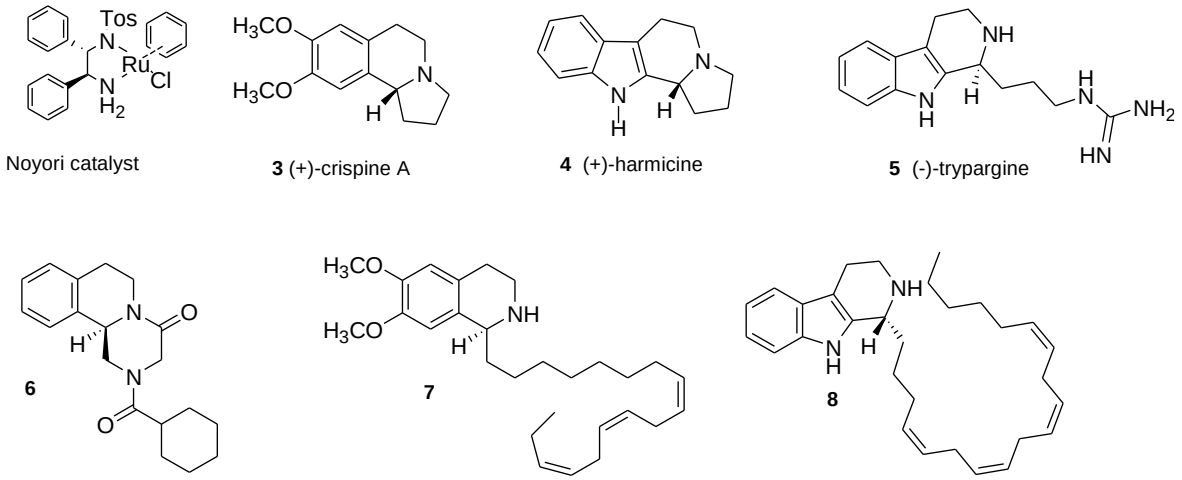


Figure 2. Chemical structure of the Noyori catalyst and selected bioactive compounds obtained with its use.

In several cases the structure of the catalyst was optimized to afford high efficiency by varying the diamine structure, arene part or by the use of different conditions. Among many published examples, should be mentioned i) the first enantioselective synthesis of (+)-cryspine **3**[8], ii) an alkaloid with antitumor properties from *Carduus crispus* plant, and iii) (+)-harmicine **4**[8] of strong anti-leishmanial activity from *Kopsia griffithi* (Thailand) and (-)-trypargine **5**[9] a highly potent neurotoxin found in the African poisonous frog *Kassina senegalensis*. Other enantiomerically pure bioactive molecules were prepared by Czarnocki's group that included the anti-malarial drug praziquantel **6**[10] and a novel class of lipophilic dopamine and serotonin analogues **7** and **8**.[11] In some cases classic Noyori catalysts turned out to be less effective. Therefore, a search for alternative catalysts was performed resulting in the discovery of new complexes derived from natural monoterpenes *1S*-(+)-carene **9** and *R*-(+)-limonene **10**. They were found useful in the synthesis of e.g. tetracyclic antidepressant aptazepine **11** (Figure 3).[12,13]

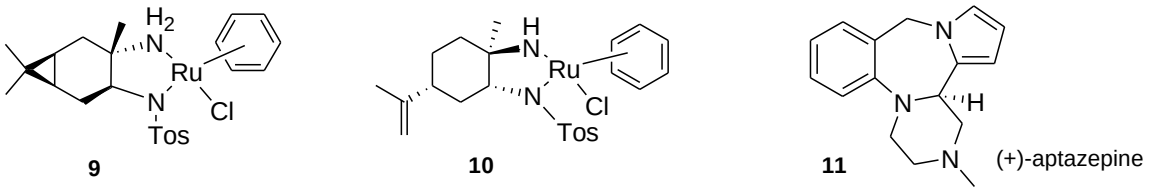


Figure 3. Chemical structures of new catalysts **9** and **10** and antidepressant aptazepine **11**.

Atropisomerism in arylpyridine derivatives

The Laboratory of Natural Products Chemistry has been involved in a more than decade-long formal collaboration with the Internal Security Agency (Poland) in the field of forensic chemistry of illegal drugs. In particular, they were interested in profiling minor by-products present in illegally produced amphetamine analogues, which is crucial to gathering court evidence. As a result of this collaboration, more than 200 new oligo-aryl substituted pyridine and pyrazine derivatives were synthesized and fully characterized.[14,15] The Suzuki-Miyaura cross coupling reaction proved to be extremely effective in the synthesis of these compounds. While working on this research topic, relatively stable atropisomeric derivatives were formed. They were isolated, their structure established by X-ray analysis and their dynamic stereochemistry thoroughly studied (Figure 4).[16,17]

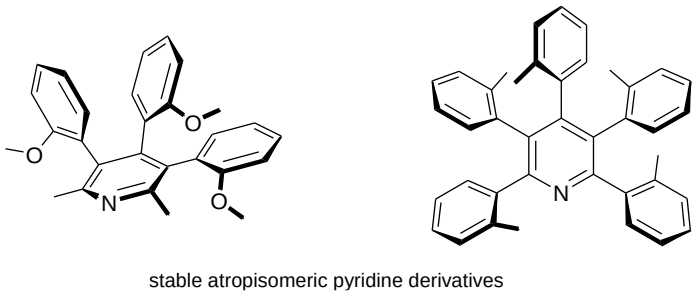


Figure 4. Examples of configurationally stable atropisomeric pyridines.

In a search for alternative and more effective catalysts in the Suzuki-Miyaura reaction, a novel L-prolinal dithioacetal ligand was constructed. Surprisingly, it was not only useful for the Suzuki coupling, but also proved to be quite efficient in the stereoselective aldol reaction serving as an organocatalyst (Figure 5).[18]

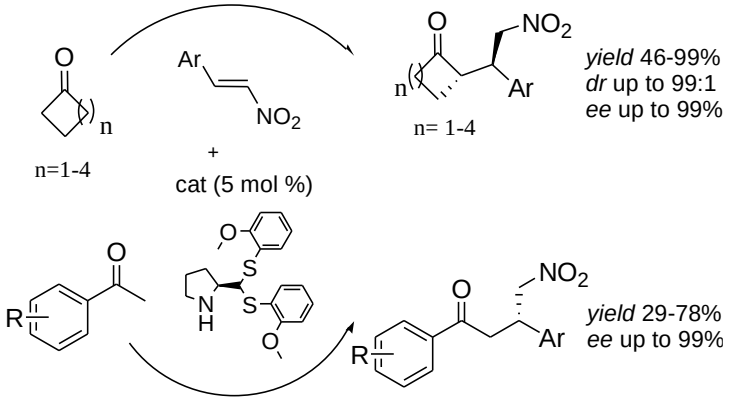


Figure 5. The novel L-prolinal dithioacetal ligand for aldol reactions.

Stereoselective synthesis of lignans

The Czarnocki's group also presented a general method for diastereoselective synthesis of cyclolignans. The synthetic sequence started with a double Stobbe condensation of the succinate ester and appropriate aromatic aldehydes. In subsequent steps L-prolinol was used as a chiral auxiliary. In the crucial step, photochemical cyclization was employed. Finally, (-)-podophyllotoxin and several its analogues were obtained.[19] It was also found that an in-flow procedure was superior compared to the bath type process. This was proven by further synthesis of another cyclolignan (+)-epigalcatin.[20] 1*R*,2*R*-*cis*-podophyllic aldehyde, an important intermediate during the synthesis of (-)-podophyllotoxin, was converted to the first known heterodimer of podophyllotoxin and benzothiazole. This compound was much more active against the majority of the tested tumor cell lines than podophyllotoxin itself.[21]

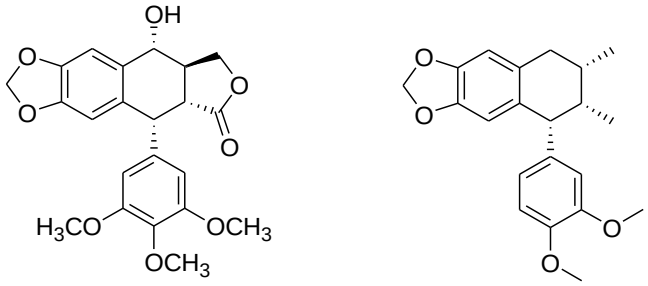


Figure 6. The chemical structures of podophyllotoxin **12** and epigalcatin **13**.

Search for novel cholinesterase inhibitors

Melatonin **14** is an example of a unique natural compound playing a highly diverse and important role in living systems. A very fruitful cooperation with the group of Professor Russel J. Reiter (University of Texas, USA) initiated studies in which the group of Prof. Czarnocki intensively conducted research on the chemistry and biochemistry of melatonin and its derivatives.[23]

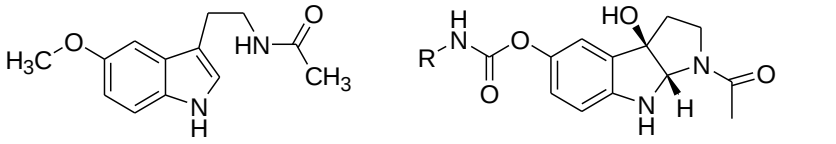


Figure 7. Chemical structure of melatonin and a general structure of cholinesterase inhibitors.

In vitro studies have shown that some of the melatonin derivatives exhibit potent inhibitory activity towards acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) enzymes.[23] An exemplary general structure of such inhibitors is shown in Figure 7 (structure **15**). Compounds with a general structure **15**, as well as a number of others obtained in Prof. Czarnocki's group are being considered as potential drugs in the treatment of Alzheimer disease. It has been shown recently that they may influence the autophagy process which opens new prospects in this area of research.[24]

Teaching

During his career, Prof. Czarnocki has been a dedicated teacher. He currently teaches courses at various levels, ranging from lectures on basic organic chemistry and biochemistry to courses for PhD students on stereochemistry and asymmetric transformations. As was mentioned earlier, Prof. Czarnocki has graduated 20 Ph.D. students and supervised over 65 M.Sc. theses. Three highly talented post-doctoral fellows have recently trained under his guidance. Finally, 20 international Erasmus students (from Croatia, Germany, France, Spain, South Africa, and others) have worked in his group each for periods of up to 6 months internship.

Joanna Szawkało

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