

Vitomir Šunjić and Krunoslav Kovačević

# Organic Stereochemistry in Croatia and Prelog School

Editor: Danijel Namjesnik

Published by: Croatian Chemical Society, Zagreb, 2020

ISBN 978-953-8334-00-9 (Hardcover) • ISBN 978-953-8334-01-6 (pdf)

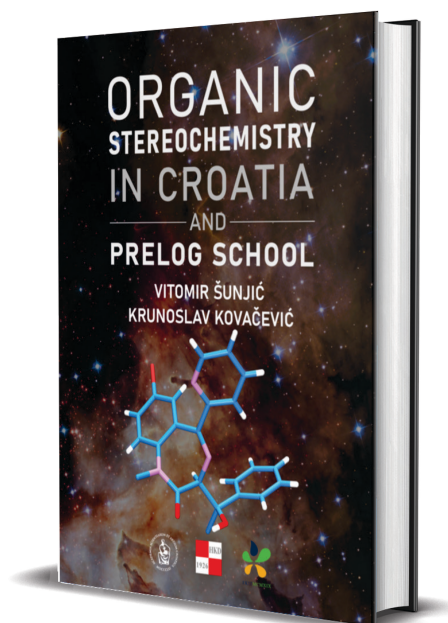
310 pages • Open access: <https://prelog.hkd.hr/>

Review by: Mladen Žinić

This excellent book, printed in a very limited number of hard copies but available online in open access, was written with a very important and ambitious goal to review the achievements of Croatian chemists in the field of stereochemistry during the last 70 years. The second objective was to accentuate intensive and fruitful scientific bonds between the Swiss Nobel Prize winner of Croatian origin, Professor Vlado Prelog, and several generations of Croatian chemists from academia and industry (known in Croatia as Prelog school) during 1936–1992 period and enlighten its influence on the development of organic chemistry in Croatia. To my opinion, both goals have been more than accomplished.

In the introductory Chapter 1, containing several paragraphs, a brief survey of Prelog's contribution to asymmetric synthesis was presented together with historically important data on early organic chemistry and first stereoselective transformations reported by Croatian chemists in 1893–1952. The introductory chapters also provide a brief outline of the basic principles of stereoselective reactions, including kinetic control, the effect of a chiral catalyst on the energy of transition state and for the practitioners' important relationship between Gibbs free energy change ( $\Delta\Delta G^\ddagger$ ) and the enantiomeric excess (ee/%).

In the following Chapter 2, entitled **Asymmetric catalytic reactions**, a plethora of the asymmetric catalytic transformations is described. It starts with hydrogenations of selected prochiral substrates catalyzed by various originally developed organometallic chiral catalysts such as bidentate diphosphate and diphosphine ligands prepared from monosaccharides, Rh(I)-norbornadiene and camphoric acid based catalysts, bioinspired Rh(I) catalysts with “back door” induced chirality by folding of short



peptide chains and Ir(I) catalysts with monodentate axially chiral P-ligands derived from binaphthol. In some examples, very high enantioselectivity and conversion yields were achieved. The use of centrally and axially chiral catalysts in allylic substitutions is also described. The catalytic complex formed from an alkylamine,  $[\text{Ir}(\text{COD})\text{-Cl}]_2$ , and axially chiral phosphoramidite binaphthol ligand appears very efficient in several enantioselective allylic substitution reactions. Asymmetric cyclopropanation reactions caught the interest of Croatian chemists since chiral cyclopropane rings could be found in many synthetic and natural compounds. Extensive studies of the asymmetric catalytic cyclopropanations started, for the first time in Croatia, in the early

nineties, at the Laboratory for stereoselective catalysis and biocatalysis (CATBIO) at the Ruđer Bošković Institute (RBI), headed by one of the authors (V. Š.). A series of original bidentate nitrogen ligands incorporating the center of chirality was synthesized and applied in Cu(I) catalyzed cyclopropanations of styrene with methyl diazoacetate. The acquired knowledge was used in the synthesis of optically pure fungicides, (S)-fenpropidin, and (S)-fenpropimorph. High “cumulative stereoselectivity”, (enantio- and diastereo-, cis/trans -selectivity), was accomplished by the originally designed C2-chiral macrocyclic ligands which upon Cu(I) complexation endow helical reaction space where the catalytic transformation is taking place.

In this Chapter, also many examples of organocatalytic transformations are provided which are characterized by small organic molecule catalysis in the absence of any metal ion. Systematic research on asymmetric organocatalysis in Croatia commenced in CATBIO with the project on kinetic resolution and desymmetrization by organocatalysis. The approach was based on the use of quinin and pseudo-enantiomeric cinchona alkaloids, quinine, and quinidine, as catalysts in the desymmetrization of anhydrides, and successfully applied in the preparation of some known drugs and fragrances in the optically pure form. Some of the described projects were realized in collaboration with the Croatian pharmaceutical and cosmetic industry.

Significant results on the mechanochemical approach to asymmetric C–C bond formation by using axially chiral tiourea derivatives as the catalyst and also the series of asymmetric reactions catalyzed by chiral Brønsted acids (chiral quaternary ammonium salts, ammonium salts of chinchona alkaloids, chiral organophosphoric acids) were accomplished by young RBI researchers. The latter catalytic system was shown to be very efficient in the synthesis of some important biologically active compounds including HIV-1 reverse transcriptase inhibitors. B. List and I. Čorić from the Max Planck Institute für Kohlenforschung have shown that highly enantioselective  $\alpha$ -alkylations of aldehydes could be realized by organocatalysis with L-proline or 1,1,3,3-tetramethylguanidine. Asymmetric acetalizations with non-symmetric diols catalyzed by axially chiral binaphthyl-phosphoric acid open the highly efficient route to chiral *O,O*-acetals, *N,O*-acetals, and spiroacetals.

Asymmetric biocatalytic transformations comprise biocatalytic kinetic resolution of a racemic mixture, biocatalytic desymmetrization of meso-compounds, and biocatalysed asymmetric synthesis. This type of research did not exist in Croatia until its development started in 1992 within the CATBIO laboratory at RBI. The impressive research comprising over 20 projects where the lipase-catalyzed resolution of racemates was the key step was described. A considerable part of the research targeting commercially important compounds is conceived in collaboration with

pharmaceutical and chemical companies, PLIVA (CRO), CRC, Caffaro (IT). Successful synthetic results often triggered research on the origin and mechanism of stereoselectivity, in particular on the structure of the productive enzyme/substrate complex.

Studies on the kinetics and the mechanism of hydrolysis or acylation by butyrylcholinesterase (BChE) started in Croatia in the early sixties. The project is later extended to the systematic study of the mechanism and stereochemistry of inhibition of BChE by the enantiomers of some known inhibitors and their congeners by the teams located at the Institute for Medicinal Research (IMI, Zagreb) and the Department of Chemistry, Faculty of Science, University of Zagreb (PMF, Zagreb). Biocatalytic asymmetric reduction of ketones using baker's yeast as biocatalyst was studied also by the CATBIO group as a potentially useful synthetic method for the development of the large scale synthesis of optically pure carbinols. An extensive study of activity and enantioselectivity of wild-type and genetically modified halohydrin dehalogenase (HHDHs) contributed to a deeper understanding of the stereochemistry of enzyme promoted biocatalytic reactions. M. M. Elenkov from CATBIO, as a postdoctoral student with professor D. B. Janssen at Groningen University significantly contributed to the understanding of HHDHs enantioselectivity in the ring-opening of racemic epoxides and broad acceptance of various nucleophiles.

Chapter 3, Chiral separations, starts with a discussion of chiral resolution of racemates by partition between aqueous and organic phase containing esters of tartaric acid as chiral selectors and describes the synthesis of chiral crown ethers incorporating axially chiral spirobisfluorene unit and their use in enantioselective extractions of racemic amino acid ammonium salts. This research based on chiral recognition through weak non-covalent interactions thus, conceptually belonging to just emerging supramolecular chemistry field, was mostly performed by Croatian PhD or postdoctoral students in Prelog's laboratory at ETH in the 1975–1985 period. The major part of the Chapter is related to the development of chiral chromatography methods in the separation of racemates. The research in this field, set in Croatia in 1979 describes chromatographic separations of optically unstable racemates possessing central and axial chirality. Next, the development of original chiral stationary phases (CSPs) named “brush-type” CSPs was described by the CATBIO group in the mid-1990s. Later, by careful structural modifications, a series of very efficient brush-type CSPs were prepared and successfully applied in chiral chromatographic separation of the racemates of various drugs and ligands for organometallic catalysts. Excellent chiral separation properties of brush-type CSPs resulted in patent protection and their commercialization.

The last, 4th Chapter, **Chiral molecular and supra-molecular structures** describe research at Croatian academic institutions and industrial R&D laboratories covering various themes of organic, polymer and supra-molecular chemistry being less focused to the preparation of optically pure compounds but more directed toward studies of the impact of chirality on their properties and applications.

A systematic study of stereoselective addition of ammonia and hydrogenation of cyclohexene carboxylic acid, uridine, and thymidine derivatives describes the formation and identification of various stereoisomers and products of intramolecular cyclization and explains stereo-, chemo- and regio-selectivity observed in such transformations. The collaborative research by INA R&D Institute and Technical faculty of the University of Zagreb was focused on the preparation of optically pure monomers (for example (S)-4-methyl-caprolactame, optically pure butadiene, toluene-sulphonamido- $\beta$ -propiothiolactone, and 1,3-hexadiene) and their polymerization into homochiral polymeric materials.

Studies on CNS active, worldwide known drugs, 1,4-benzodiazepines, started in Croatia in the seventies. Very intense and highly fruitful research on the synthesis and stereochemistry of benzodiazepines extended to the next 30 years and generated 60 research papers and several international patents. The paragraph describes excellent synthetic, stereochemical, and in vitro biological studies on chiral 1,4-benzodiazepines which contributed to high international recognition of the Croatian research group.

Asymmetric synthesis of the  $\beta$ -lactam ring represents a highly important theme due to its appearance in many biologically active compounds, antibiotics in particular. An excellent asymmetric synthesis of  $\beta$ -lactam is described by Iwao Ojima from Stony Brook University and his post-doctoral student at that time, Ivo Habuš. This approach was later used in the preparation of an enantiomerically pure taxol side chain. I. Habuš upon his return to RBI continued the studies which resulted in the preparation of  $\beta$ -lactam containing ferrocene derivatives and bioisosters of ezetimibe, a cholesterol absorption inhibitor. Ferrocene derived peptide biomimetics was the topic extensively studied by the group at the Faculty of Food Technology and Biotechnology, University of Zagreb.

In the next paragraph, the supramolecular chemistry research introduced by the Laboratory of supramolecular chemistry at RBI is described. The group pioneered the research on chiral gelators comprising synthesis, studies of gelling properties, self-assembly motifs, and the chirality effects appearing at the supramolecular level. The outline of that research ends with nano-chemistry results on the chiral ordering of gold nanorods adsorbed on helical gel fibers resulting in a strong Cotton effect at the position of

the longitudinal localized surface-plasmon resonance (LSPR). Another group at RBI contributes with fine synthetic, stereo- and photo-chemistry of chiral adamantane and polyadamantane derivatives.

A considerable part of 80 years, continuous chemistry research at PLIVA Co. resulted in impressive achievements in the preparation of original and generic drugs in optically pure form. They include laboratory and large scale synthesis of many well-known drugs such as optically pure chloramphenicol, stereochemical studies on epimerization in the  $\beta$ -lactam series, D-penicillamine, industrial process for the synthesis of L-Me-DOPA, ethambutol used in the treatment of tuberculosis, processes for the production of 6-APA, Vitamin C and B6 and many others with the world-class achievement by the discovery of original antibiotic Azithromycin.

The research at another Croatian pharmaceutical company, BELUPO, comprises the development of novel synthetic routes to benzodiazepines, oxazepam and lorazepam and asymmetric synthesis of atenolol, an important  $\beta$ -blocker, improved synthetic approach to world-known drug sildenafil (Viagra) and synthetic studies of antihypertensive dihydropyrimidine drug.

The research directed toward new drug entities, including synthetic chemistry and stereochemistry of macrolides and some small target molecules, was conducted at Galapagos Co. becoming later Fidelta Company. The excellent in-depth macrolide chemistry research includes stereoselective transformations of oleandomycin and azithromycin.

The liquid crystal research is started by the CATBIO group in 1996. The research comprises the synthesis and mesomorphic properties of achiral alkoxyphenacylpyridines and their copper (II) complexes and extends to the studies of selected chiral dopand effects on chiral induction. Transfer of molecular chirality from molecular to supramolecular level was studied on composite supramolecular systems consisting of gel and liquid crystal. Using selected achiral bent molecules it was shown that despite achiral molecules from which the phase is composed the chiral helicoidal structure of the phase is strongly implicated.

The Chapter ends with an overview of the research on chiral interactions of small molecules with nucleic acids, the topic of high biomedical importance and wide interest. This topic was initiated by the group at RBI and endowed extensive international collaboration. Designed positively charged dye molecules, functionalized with amino acid, spermine, adenine, etc., possessing large aromatic surface were used as ligands for DNA/RNA ds- and ss-oligonucleotides. The results show that binding of such small molecules to helically chiral nucleic acid oligomers results in the induced Cotton effect. Hence, the chiroptical spectroscopy methods offer a toolbox of techniques useful to characterize

not only nucleic acids but also to identify the mode and determine the strength of their interactions with small molecules.

After the first reading of the book, it occurred to me that if it was not written it should necessarily be written since this book appears very important from multiple and different reasons. It is undoubtedly important from the historical point of view since it sheds light on the development of organic chemistry of chiral compounds in Croatia realized in academic institutions and industry during the 70 years. It can be concluded that the advance in organic chemistry research in that period seems quite impressive for a small country, considering its limited resources and often unfavorable historical, economic, and political circumstances. The book content clearly shows that a new knowledge accumulated both, at academic institutions and pharmaceutical industry R&D laboratories in the covered period provides more than solid fundament for the future development of organic chemistry and related industry in Croatia. Secondly, the described research demonstrates the influence of V. Prelog on the development of Croatian organic chemistry, not only

through his persistent care, mentoring, and collaboration with Croatian chemists, but also through described scientific contributions of his students working at universities, institutes or industry. The latter fully justifies the second part of the book title. The book delivers very fine organic chemistry research covering topics from organometallic, organo- and bio-catalytic asymmetric transformations and chiral resolution to stereochemical studies at the molecular, polymer, supramolecular and nanochemistry levels. It should be emphasized that the additional value of the book arises from a detailed explanation of described stereochemical transformations and related mechanisms which makes it highly valuable as the advanced chemistry textbook. Considering all the above-listed values of the book it can be concluded that it represents true masterpiece, which will undoubtedly arouse interest both, at the national and the international level. Therefore, all the compliments go to the authors and publishers for their most valuable effort.

*Mladen Žinić*