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REVIEW PAPER

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MODERN CATALYSIS IN THE SYNTHESIS OF SOME PHARMACEUTICALS AND FINE CHEMICALS

Catalysis in the synthesis of pharmaceuticals and fine chemicals nowadays becomes more and more important. Synthesis that minimizes wastes is important from the economical aspect, as well as from the environmental aspect. "Green chemistry" or "green technology" is an effort to protect the environment by increasing the efficiency of the overall synthetic processes in the chemical industry by minimizing or eliminating wasteful by–products.
Modern catalytic methods in the synthesis of some pharmaceuticals and fine chemicals are discussed such as phase–transfer catalysis, biocatalysis, asymmetric catalysis and, generally, solid–phase chemistry.

Research and development in pharmaceutical and fine chemicals production is primarily concerned with the synthesis and recognition of new drugs, but also of important intermediates for drug production and a wide variety of other products. This also necessarily includes the development of new catalysts and catalytical procedures for optimal performances in organic synthesis. In the bulk production of organic chemicals the requirements for better and more efficient catalytic methodology are concerned with process optimisation in view of increased yields and energy savings and with the no less important neccessity for environmentally "friendly" processes. Together with these, in pharmaceutical and fine chemicals production there are different, sometimes more severe requirements, considering the high price and the end use of these products. Synthetic drugs are mostly complicated organic molecules, frequently identical to natural compounds or are their modifications, synthesized because of costly extraction procedures from natural substrates. Their synthesis is as a rule a multistep process which needs stereospecific catalysts and the avoidance of costly and time consuming purification and separation steps. The same applies to a large number of fine and speciality chemicals, which are auxiliary pharmaceutical products, additives for food, feed and cosmetics preparations, agrochemicals and electronic components [1–3].

Our own investigations of the use of different catalytic procedures and catalysts at the Department of Organic Chemistry, Faculty of Technology and Metallurgy, Belgrade University, included in the last 10 years the application of strongly acid ion exchangers in the esterification [4] and synthesis of isopropylene glycerol [5], phase transfer catalysis (PTC) in a selective alkylation reaction in two and three–phase processes [6], glycidyl ester synthesis [7] and in the alkylation of variuos N–substituted–2–phenylacetamides [8]. The effect of various catalysts including PTC in the synthesis of 2,4–substituted–3–cyano–2–pyridones was also investigated [9]. The same reaction was also investigated as a biocatalytic process using the enzyme lipase, which was more promising than PTC, where regioselectivity has been established [10,11]. The kinetics and mechanism of this reaction were determined and discussed [12]. Biocatalysis was also used for the production of 6–aminopenicillanic acid [13,14], the hydrolysis of β–D–glycosepentaacetate [15] and n–butyl acetate [16] and the esterification of caproic acid with n–butanol [17]. Also, the immobilization of enzymes on solid supports and their use in reactions has been investigated, as well as the corresponding kinetics and conversion [13–15,17]. Where it was relevant, mathematical models for the conversion were established [13,14].

New Catalysts and New Catalytic Procedures

Traditionally, fine and specialty chemicals are produced using predominantly non–catalytic organic synthesis. In recent years the situation is slowly changing because both production costs and the problem of waste minimization are of increasing concern even for high value pharmaceuticals and agro chemicals.

Catalytic methods can open up new routes for solving a given synthetic problem that were previously not available. Information and guidelines to solutions are given in Table 1 [18].

The search for new catalysts and new catalytic systems has very intensified in the last decade. The trends in that direction are as follows:

– Improvements in traditional homogenous and heterogeneous catalytic procedures.

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Paper accepted: November 26, 2001
Paper presented at Third International Seminar: New Challenges in Catalysis, Belgrade, 2001, organized by Serbian Academy of Sciences and Arts

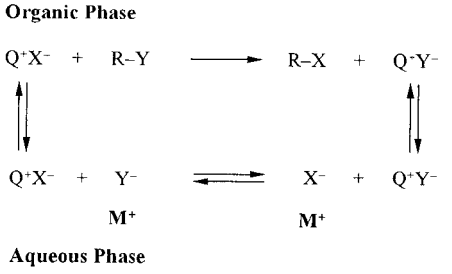
Table 1. Some characteristics of fine and specialty chemicals

The molecules	The synthesis	Requirements for catalysis
• relatively complex (isomers, stereochemistry etc.) • several functional groups • limited thermal stability • short development time • low volume (1–10'000 t/y)	• multistep • classical organic reactions • batch processes in solution • multi purpose equipment • catalysis often key step	• highly chemo–, regio– and stereoselective • fit to overall synthesis • good activity at low T • simple technology • specialists necessary

– A search for new, more specific catalysts and catalytic systems, such as phase–transfer catalysis, asymmetric catalysis and biocatalysis. There have been remarkable advances in the use of solid–supported catalysts and, generally, solid phase synthesis, very important from the point of view of environmental protection.

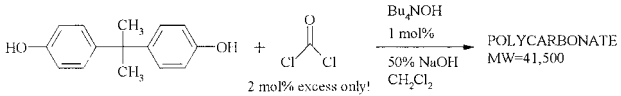
Phase–Transfer Catalysis (PTC) [19, 20]

Cost reduction and pollution prevention are the main reason for the development and use of PTC. This type of catalysis is particularly favourable in the reaction of anions or neutral molecules soluble in water with substrates soluble in organic solvents. It has been applied in major organic reaction, alkylations, esterifications, substitution, additions, condensations, etc. Phase transfer catalysed reactions have been performed in two– and three phase systems, the latter operating with solid supported catalyst [20]. The catalysts are most frequently quaternary ammonium salts, which in three–phase systems are immobilized on a solid support, usually polymers. The catalyst "transfers" the anion or neutral molecule from the aqueous into the organic phase, where it reacts with the organic substrate. This is shown in Scheme 1, explaining the PTC extraction mechanism, which is most frequently used to explain the unique performances of phase transfer catalysis.



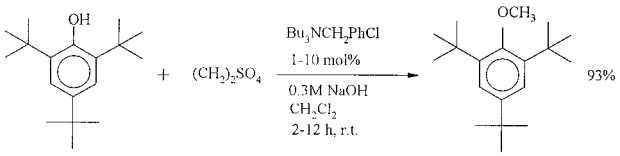
Scheme 1. The extraction mechanism for PTC

The variety of processes which could be catalysed by PTC with an advantage are best visualized by the examples which follow.



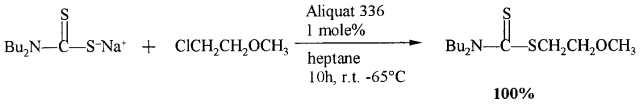
Advantage: Improvement in safety, environmental control.

Scheme 2. Outstanding reduction of excess hazardous high volume raw material

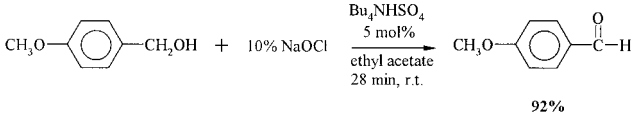


Advantage: High yield etherifications, non–dry mild conditions, no need for alkoxide, easy work–up.

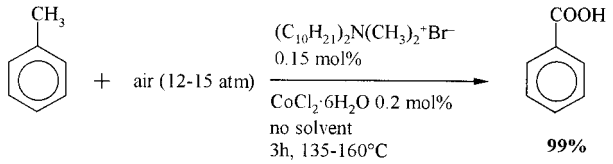
Scheme 3. Etherification (O–alkylation)



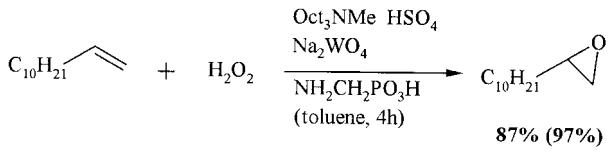
Scheme 4. Thioesterifiaction for lubricant



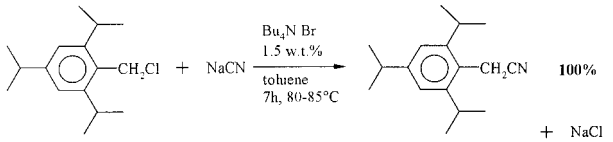
Scheme 5. Oxidation (hypochlorite)



Scheme 6. Oxidation with air

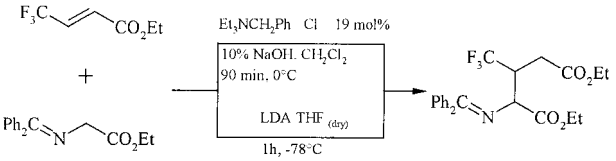


Scheme 7. Epoxidation and chiral epoxidation



Achieved: Yield increase, solvent recycle, less excess of cyanide, less work–up operations, less waste

Scheme 8. Cyanation



Achieved: Eliminated very expensive hazardous organic strong base (LDA) at very expensive very low temperature with 19% yield increase! Multiple Michael addition to acrylates used for lubricants also reported

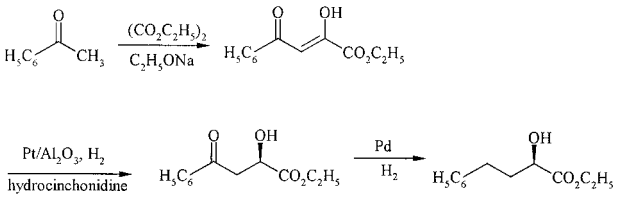
Scheme 9. Michael addition

Asymmetric Catalysis and Biocatalysis

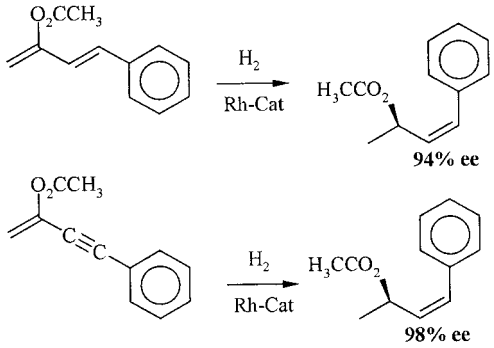
A large number of organic compounds used as drugs are chiral molecules. Considering that the tissues and biochemical processes occurring in living organisms are strictly stereospecific, it is understandable that only one enantiomer will show the desired physiological action [1, 21–23]. Drugs originating in nature or those obtained by biocatalytic processes are normally pure single enantiomers, while those from organic synthesis, without a stereoselective catalyst in the chiral reaction sequence are racemic mixtures. They were used as such for many years, until the awareness in the last three decades of the potential danger of that practice, prompted the development of separation processes and efforts toward enantioselective synthesis employing the corresponding catalysts. It is the fact that the other enantiomer is usually not active at all, is much less active or active in some other sense which might be unfavourable or even have tragic consequence. The development of new catalysts for asymmetric synthesis has intensified in the last ten years, considering that traditional methods for enantiomer separations are costly and lengthy multistep procedures, unsuitable for industrial application [21,22]. For asymmetric synthesis there are two general approaches: (I) The use of chiral intermediates, small chiral "building blocks" designed to give the desired molecule by combinations and/or modification with achiral or other chiral molecules. (II) A much more practical approach is to use asymmetric catalysts in the total synthesis of a single enantiomer. Two general types of asymmetric catalysts are being used, transition metal complexes and enzymes as biocatalysts [1, 21–24].

Asymmetric catalysts based on transition metals could be metals or metal oxides modified by chiral molecules or chiral organometalic complexes immobilised by covalent bonds or adsorption at organic polymers or metal oxides. Heterogenisation or immobilisation of these metal complexes could be a promising strategy by combination of the best features of homogenous and heterogeneous catalysis [20, 23, 24]. This type of catalysis is shown in Schemes 10–14.

Enzymes are natural catalysts which participate in the synthesis of practically all molecules built in the tissues of living organisms and interact in their metabolic

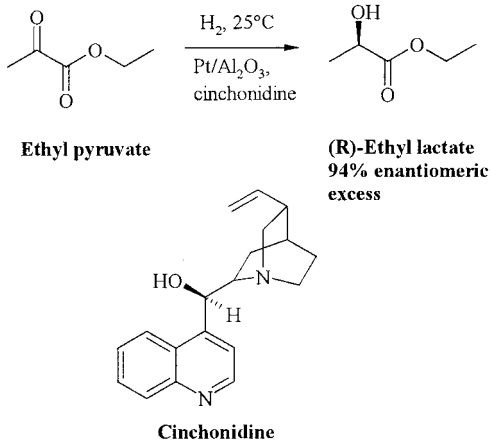


Scheme 10. An improved route to a drug intermediate



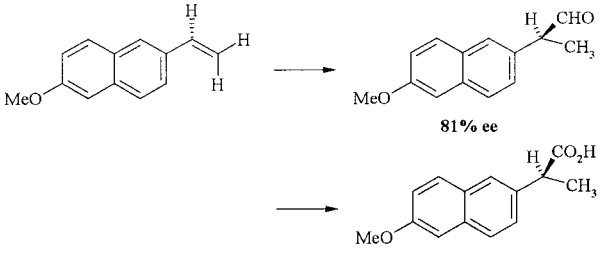
Rh–Cat = 1,2–bis[(2R,5R) – dimethylphospholano]benzene complexed with Rh(I)

Scheme 11. Asymmetric hydrogenation

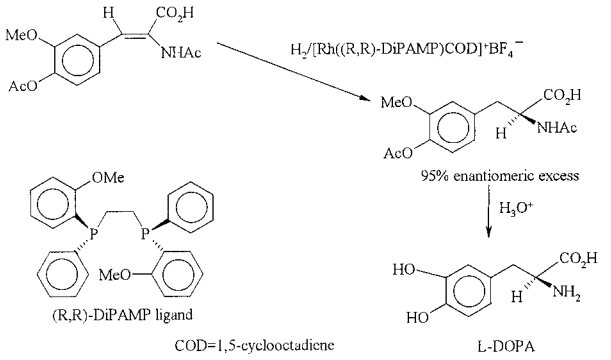


Using cinchonidine as a chiral template, while maintaining an optimum cinchonidine–to–platinum ratio throughout the course of the reaction, yields (R)–ethyl lactate in large enantiomeric excess

Scheme 12. Metal catalyst with a chiral template



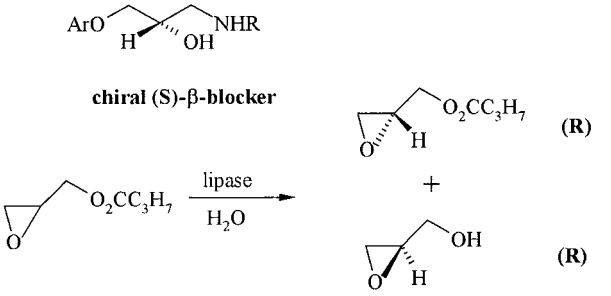
Scheme 13. Naproxen synthesis by hydrogenation in the presence of the catalyst ruthenium[2,2–bis–(diarylphosphino–1,1–binaphtyl]diacetate



Scheme 14. Asymmetric synthesis of L–DOPA

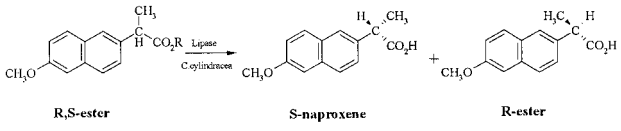
processes. The most important natural polymers are composed of chiral compounds, pure enantiomers or stereoisomers. It is evident that enzymes are highly enantioselective catalysts and it is logical that they would be investigated as catalysts for enantioselective reactions in organic synthesis [25].

Active chiral forms of (S)–β–blockers (Scheme 15) are conveniently synthesized from chiral intermediates, which could be obtained by enzymatic resolution from the corresponding (R,S)–glycidyl esters as shown in Scheme 15 [21,22].



Scheme 15. Synthesis of chiral intermediates for (S)–β–blockers

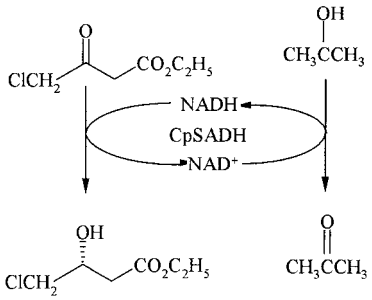
Naproxene, an important analgetic and antireumatic drug, active only in its (S) form, could also be synthesized by an enzymatic process (Scheme 16) [22].



Scheme 16. Naproxene synthesized by an enzymatic procedure

From the point of view of environmental protection enzymes are more acceptable than many chemical catalysts. However, the initial euphoria about the use of enzymes as an entioselective catalysts is somewhat subdued, probably because numerous investigations performed on various substrates helped to visualize the limitations of enzymatic catalysis. At the same time this effort helped to overcome certain disadvantages by the use of new techniques, like work in organic solvents, immobilization on solid supports, entrapping in natural and synthetic gels, encapsulation, etc. Other disadvantages, like the inhibition or reversibility of enzymatic reactions could be controlled by the detailed study of the kinetics and appropriate adjustment of reaction parameters [1,25]. Some of the enzymes require a co–factor to demonstrate catalytic ability [25].

The synthesis of a new synthon is an example of the use of an enzyme with a co–factor catalysed reaction of a fine chemical building block (Scheme 17) [2].



NADH, NAD^+ = reduced and oxidized forms of nicotinamide adenine dinucleotide
CpSDH = Candida parapsilosis secondary alcohol dehydrogenase

Scheme 17. Asymmetric reduction yields new synthon

However the question arises, why use enzymes at all and abandon the well established techniques and procedures of synthetic organic branches of science? The answer is simple – new synthetic and catalytic methods are necessary to deal with the new classes of compounds that have become targets in medicinal and biological chemistry. The enzymatic catalyses provide the routes for synthetic transformations that are otherwise impossible or impractical, especially in key areas of biochemistry [25].

Solid Phase Catalysis

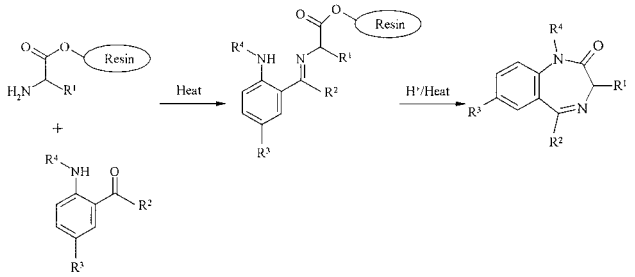
Catalysts supported on solid carriers needs to be discussed in the general context of organic synthesis supported by inorganic or organic solid phases. There are three aspects of supported chemistry: (I) solid supported substrates, (II) supported reagents (III) solid catalysts. The technical side in all three is very much the same, and the most important improvements lie in reactivity, selectivity and isolation [26]. Generally speaking, solid phase chemistry is not a new approach, as it has been playing an important part in chemistry and biology in the last three decades, since the Merrifield solid phase synthesis of peptides and easy use of polymer supported ion exchangers as catalysts. Solid inorganic catalysts have been extensively used in the petroleum industry [22, 23], and polymer production (Ziegler–Natta catalysts).

By the functionalization of several types of polymer resins, mostly Merrifield, it is possible to immobilize various catalysts, directly or with the help of a linker. Many reactions could be performed in such a manner, the examples being presented in the Schemes which follow.

Supported systems offer the following advantages to both research and process chemistry:

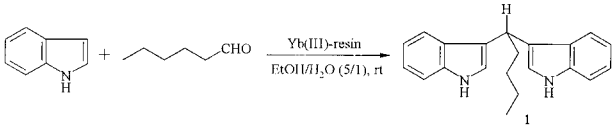
– Ease of work–up
– Ease of recovery of ligand for reuse
– Ease of product isolation
– High product purity
– Application to batch reactors and continuous flow systems for high throughput.

A very good example for solid state chemistry is the synthesis of an important class of tranquilizers – substituted benzodiazepines given in Scheme 18 [27].

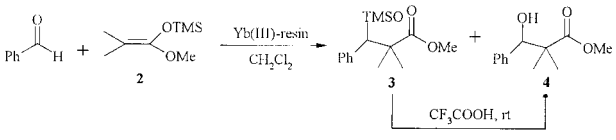


Scheme 18. Benzodiazepine solid phase synthesis

In the two examples which follow the use of lanthanide (III) catalysts supported on ion exchange resins, which have been demonstrated to be effective in a number of important organic transformations such as condensation (Scheme 19) and aldol condensation (Scheme 20) and others is shown. The advantage of lanthanide catalysed processes are mild reaction conditions and non–dry media [26].

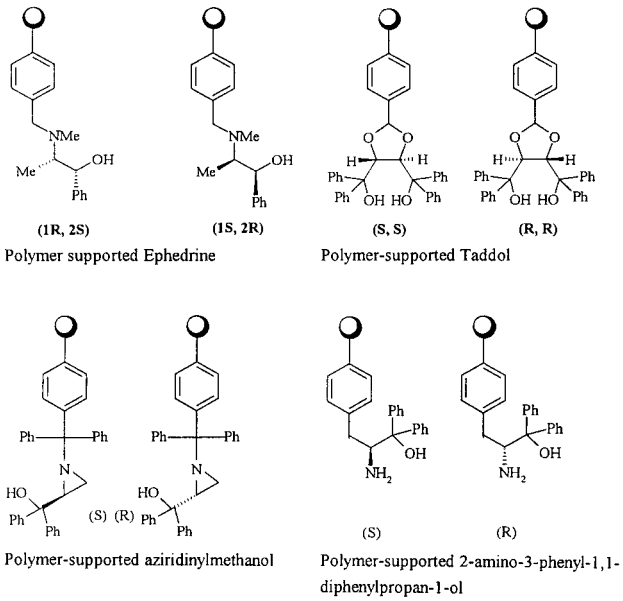


Scheme 19. Reaction of indole with hexanal catalyzed by Yb(III)–resins

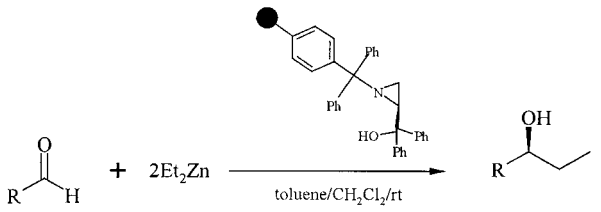


Scheme 20. Aldol reaction catalyzed by Yb(III)–resins in dichloromethane

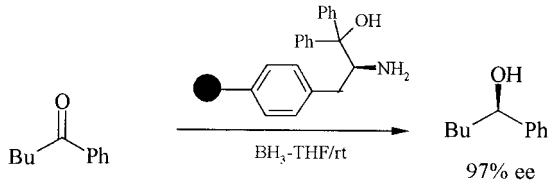
In the last few years several firms specializing in catalysts production, offer ready–made supported ligands, mostly on polymer supports, intended for asymmetric catalysis [28]. A number of these are shown in Scheme 21. Examples for the corresponding reactions are given in Schemes 22 and 23 [28].



Scheme 21. Supported ligands for asymmetric catalysis



Scheme 22. Asymmetric addition



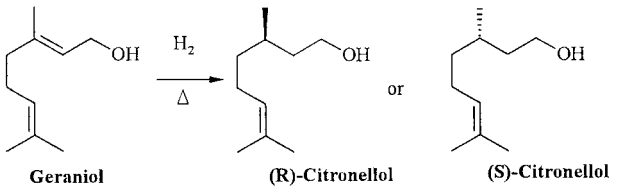
Scheme 23. Asymmetric reduction

The recent initiatives for the use of solid phase chemistry have been largely caused by the increasing pressure of environmental problems on the chemical industry to develop production models based on clean or "green" technologies with reduced hazardous pollution of the environment. Independent of this aspect, the main advantages of solid phase catalysis in organic synthesis are the adjustment of reactivity, improved selectivity, simplified separation, and the recycling of the catalyst [21, 22, 26].

New Trends in Catalysis for Pharmaceuticals and Fine Chemicals

In the current year several communications have been presented which we consider to be of exceptional interest. These are mostly concerned with asymmetric synthesis.

At the 17th meeting of the North American Catalysis Society it was disclosed and later presented in Chem.Eng.News [1] that in the asymmetric hydrogenation of geranoil (Scheme 24) by the use of homogenous chiral ruthenium–phosphine catalyst Ru(II)–S–BINAP, high enantioselectivity could be achieved by employing kinetics to steer a reaction toward a preferred product. By variation of the reaction conditions, pressure and temperature, taking advantage of the different rates of formation of enantiomers, the stereochemical outcome of the reaction could be inverted without switching the catalyst chirality.

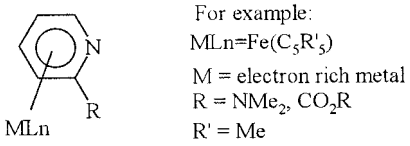


EITHER/OR By choosing the right hydrogen pressure and reaction temperature, researchers can obtain (R)– or (S)–citronellol in 93% enantiomeric excess without changing the chirality of the catalyst

Scheme 24. Enantiomeric control by kinetics

It was also mentioned that enantioselectivity could be obtained by variations of the reaction conditions in heterogenous systems as well [1].

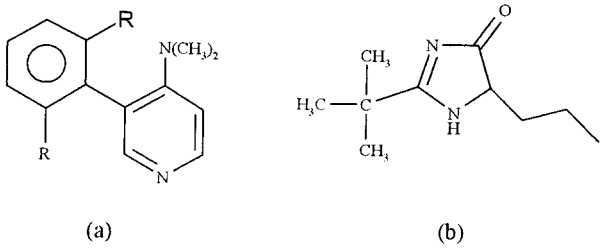
A different approach has been disclosed in several communications presented at the 15th Lakeland Symposium on Heterocyclic Chemistry [29]. Examples of heterocyclic compounds, substituted by appropriate functional groups, which could be used as nucleophilic enantioselecive catalysts were presented. One type of such compounds are "planar–chiral" catalysts, which are essentially p–complexes of heterocycles with transition metals, which show stereochemical delocalization and intervene in the transition state of the reaction.. Metallocenes with heterocyclic ligands were also mentioned in this context.



Scheme 25. Planar–chiral catalyst based on substituted pyridine

It was stated that the chiralester intermediate of the important analgetic and antireumatic drug (S)–ibuprofen has been synthesized with high enantiomeric purity with the help of a "planar–chiral" catalyst.

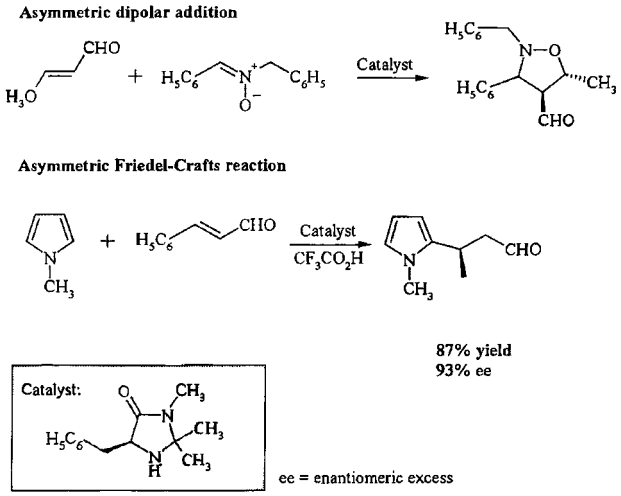
The concern about transition metal residues in drugs or fine chemicals final products, focused the recent developments towards the design and synthesis of "all organic" chiral nucleophilic catalysts. As it could be expected, those so far reported are nitrogen heterocycles shown in Scheme 26 [29].



Scheme 26. New substituted (a) 4–diamethylamino pyridine and (b) imidazolidinone derivatives used as enantioselective catalysts

The derivatives of 3–substituted–4–dimethyl-aminopyridine (Scheme 26a) are stated to be useful as catalysts in the synthesis of chiral β–lactams and β–lactones.

New imidazolidinone catalysts of the type presented in Scheme 26(b) have been introduced as tools in a new strategy of organocatalysis which are broadly useful for a range of enantioselective organocatalytic reactions such as the Diels–Adler reaction, 1,3–dipolar cycloaddition, Michael addition and Friedel–Crafts alkylation [29]. Examples of two of these reactions are presented in Scheme 27 [30].



Scheme 27. New nonmetal catalysts for asymmetric transformations

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IZVOD

SAVREMENA KATALIZA U SINTEZI NEKIH FARMACEUTSKIH SIROVINA I FINIH HEMIKALIJA

(Pregledni rad)

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Kataliza u sintezi farmaceutskih sirovina i finih hemikalija sve više poprima na značaju. Sinteza koja smanjuje količinu otpadnih materija značajna je kako sa ekonomskog tako i sa ekološkog značaja. "Zelena hemija" ili "zelena tehnologija" predstavljajuju pokušaj da se zaštita čovekove okoline dovede na viši nivo povećanjem efikasnosti pri izvođenju sintetskih procesa u hemijskoj industriji, smanjenjem ili eliminisanjem sporednih proizvoda.
U okviru ovoga rada dat je pregled savremenih katalitičkih metoda u sintezi nekih farmaceutskih sirovina i finih hemikalija. U tom cilju dat je pregled sinteza koje uključuju primenu međufazne katalize, biokatalize, asimetrične sinteze, i generalno sinteze na čvrstoj fazi.

Ključne reči: Kataliza • Farmaceutske sirovine • Fine hemikalije • Sinteza • Međufazna–kataliza • Biokataliza • Asimetrična sinteza • Sinteza na čvrstoj fazi • Katalizatori •
Key words: Catalysis • Pharmaceuticals • Fine chemicals • Synthesis • Phase–transfer catalysis • Biocatalysis • Asymmetric catalysis • Solid phase catalysis • Catalysts •