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Development of new methods in modern selective organic synthesis: preparation of functionalized molecules with atomic precision

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The challenges of the modern society and the growing demand of high-technology sectors of industrial production bring about a new phase in the development of organic synthesis. A cutting edge of modern synthetic methods is introduction of functional groups and more complex structural units into organic molecules with unprecedented control over the course of chemical transformation. Analysis of the state-of-the-art achievements in selective organic synthesis indicates the appearance of a new trend — the synthesis of organic molecules, biologically active compounds, pharmaceutical substances and smart materials with absolute selectivity. Most advanced approaches to organic synthesis anticipated in the near future can be defined as 'atomic precision' in chemical reactions. The present review considers selective methods of organic synthesis suitable for transformation of complex functionalized molecules under mild conditions. Selected key trends in the modern organic synthesis are considered including the preparation of organofluorine compounds, catalytic cross-coupling and oxidative cross-coupling reactions, atom-economic addition reactions, methathesis processes, oxidation and reduction reactions, synthesis of heterocyclic compounds, design of new homogeneous and heterogeneous catalytic systems, application of photocatalysis, scaling up synthetic procedures to industrial level and development of new approaches to investigation of mechanisms of catalytic reactions.
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I. Introduction

Increasing demands of the modern society facilitated development of new industrial solutions and innovative products, thus changing the concept of organic synthesis in the last decade.[1] Of fundamental importance are the primary development of waste-free and non-toxic chemical transformations based on natural raw materials and the use of environmentally friendly chemical modification procedures (sustainable chemistry) in combination with high efficiency (e-factor) and low cost of synthetic methods.[2–6] From the standpoint of construction of chemical process, a synthetic transformation must furnish only the desired product (full selectivity), have high productivity (highly active catalysts and reactants), function for long periods (stable catalysts) and give the possibility to regenerate the reactants and the catalysts for reuse.[7–12] These unprecedentedly high requirements, *i.e.*, in essence, the necessity of creating 'ideal'

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chemical processes, gave rise to a set of new approaches of organic synthesis. This work was markedly stimulated by understanding of the reaction mechanisms at the molecular level coming from application of advanced hardware and analytic tools.[13–18]

Apart from studies aimed at systematic development of the strategy of classical organic synthesis, new approaches in this field appear and rapidly develop giving rise to whole areas of modern chemistry (microwave-assisted reactions, ultrasonic treatment, microreactor processes, processes in ionic liquids and gels, reactions in supercritical media and some other).

A special place among the promising approaches to increasing the efficiency of organic synthesis is occupied by implementation of catalytic reaction pathways for desired chemical transformations. The use of catalytic reactions makes it possible to replace chemicals that are responsible for the formation of hazardous wastes by environmentally safe oxidants (H_2O_2, O_2) and reductants (H_2). Moreover, catalysis can guide the reaction along a shorter and a more efficient pathway (*e.g.* direct synthesis without using protecting groups) with high selectivity to the target products, providing the fulfillment of green chemistry principles such as atomic and energetic efficiency of the chemical reaction.

Catalysis dramatically changed the face of the chemical science in the 21st century and now it plays a leading role in increasing efficiency of modern chemical processes. Most widely used are two types of catalytic processes — homogeneous catalysis by metal complexes (preparation of pharmaceutical substances, drugs and other applications of fine organic synthesis) and the heterogeneous catalysis by metal nanoparticles (processing of hydrocarbons, large-scale syntheses and most of industrial processes). In recent years, organocatalysis has become a new and extremely actively developing area.

Transition metal-catalyzed reactions of carbon–carbon and carbon–heteroatom bond formation have greatly contributed to the production of fine organic synthesis products, pharmaceutical products, natural products, smart materials and synthetic blocks for drug manufacture. The catalytic cross-coupling reactions allowed for the incorporation of diverse aryl, alkenyl, dienyl and alkynyl moieties into organic molecules. High tolerance for the presence of functional groups considerably extended the scope of applicability of these synthetic methods. A milestone in the progress of this line of research is the development of catalytic cross-coupling processes involving heteroatom functional groups aimed at the formation of the carbon–heteroatom bond.

These catalytic reactions, which have quite recently been worked out and optimized on the laboratory scale (< 1 g of the product), are now actively employed in pilot plants (tens or hundreds killogrammes of a product).[14, 19] Of outstanding value is the possibility of targeted transformation of a specified group (atom) in complex functionalized organic molecules. For illustration, several vivid examples can be given, in particular, the Pd-catalyzed Heck reaction at the C(6′) position to give derivative **A**, the Pd–Cu-catalyzed Sonogashira reaction at C(3′) to afford derivative **B**, and the Ru-catalyzed metathesis at C(12′) to form derivative **C** (Fig. 1). The functionalization of a particular carbon atom is successfully accomplished with high precision even in rather complicated molecules containing many functional groups and reaction sites.

For optimization of the cost/efficiency criterion, which is of prime importance for process scaling up, it is necessary to develop new synthetic methods requiring a minimum amount of the catalyst. The continuous search for new catalytic systems carried out in the last decades resulted in the discovery of reactions with ultralow catalyst load (at ppm or ppb level). An exceptionally high activity was found for dynamic catalytic systems with the possibility of adaptive tuning.[20, 21]

Yet another promising approach to increase the efficiency of catalytic reactions in fine organic synthesis is the use of specially developed heterogeneous catalysts in which the active components are immobilized metal complexes or even deposited metal particles. Indeed, heterogeneous catalysts have a number of significant advantages over homogeneous systems and, therefore, they may be considered more valuable for commercialization. In particular, heterogeneous catalysts are non-toxic, can be safely stored and handled, are stable over broad temperature and pressure ranges, have long lifetime and can be easily regenerated and

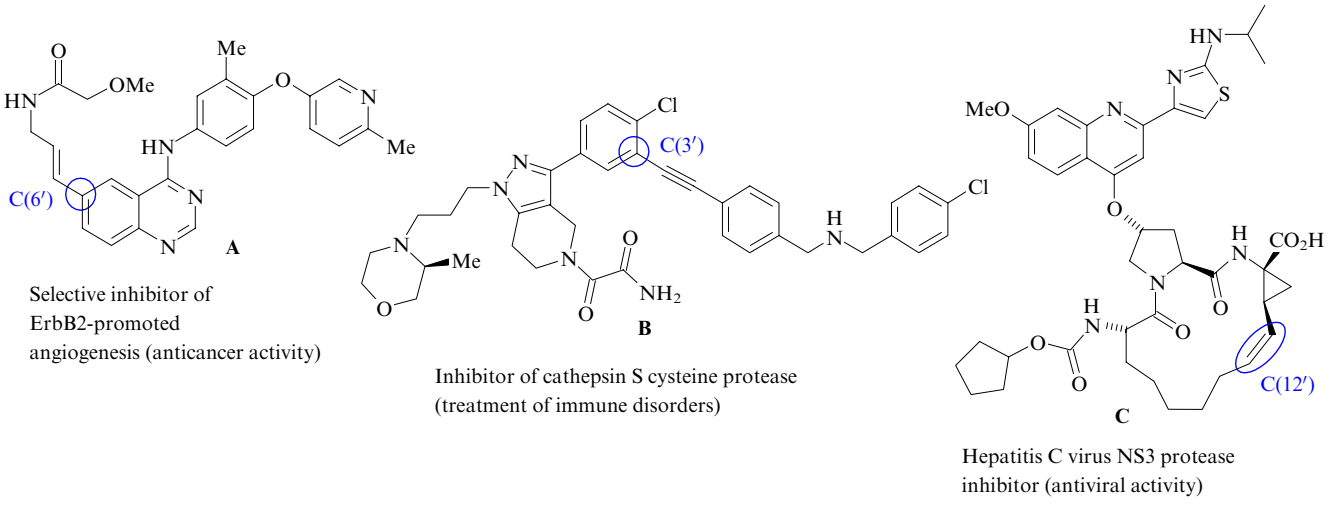


Figure 1. Key role of catalytic Heck, Sonogashira and metathesis reactions in the design of complex organic molecules (**A** , **B** and **C**, respectively) by transformation of specified reaction sites (marked by a circle and an oval).[19]

separated from the reaction medium by filtration or centrifugation. Furthermore, the use of heterogeneous catalysts opens up prospects for conduction of organic synthesis in flow type systems, which are more productive and cost effective.

The present review presents a brief analysis of some modern trends of selective organic synthesis in the relevant fields. Each Section starts with brief highlight of the general trends in the considered subject matter, which is followed by analysis of particular cases of practical implementation and use in organic chemistry.

The review starts with discussion of selective methods for the formation of carbon–heteroatom bonds and transformation processes of heteroatomic functional groups. These functional groups are crucial for organic molecules to exhibit biological activities (for design of new drugs) and practically useful properties (for the development of new materials).

Section II considers the fine organic synthesis of fluorine compounds, which has lately faced new challenges calling for fundamentally new approaches. Analysis of the state of the art of this field demonstrates that known reagents and non-catalytic processes are currently successfully combined with new metal-catalyzed and organocatalytic reactions (Section II.1). A vivid example of introduction of a new catalytic approach into the everyday practice of organic synthesis is metathesis (Section III), the implementation of which is considered in detail in relation to the preparation of biologically active organofluorine derivatives (Section III.1).

The oxidative cross-coupling (Section IV) and atom-economic addition reactions (Section V) represent new strategic approaches to the formation of carbon– heteroatom bonds. Particular implementation of the practically demanded reactions is discussed by the examples of C–O (Section IV.1) and C–P (Section V.1) bond formation. The primary attention is paid to the possibility of tuning catalytic systems by selecting the catalyst and the ligands for controlling the reaction selectivity.

As shown by practice, the design of new ligands is a way of developing versatile metal/ligand structural units, which then serve as the basis for various catalysts. In this case, it is possible to manufacture versatile catalysts for the formation of not only carbon–heteroatom bonds but also carbon–carbon bonds. Most successful along this line are N-heterocyclic carbene ligands (Section VI). A particular application of a class of these ligands — diaminocarbenes with expanded rings — resulted in the development of a series of catalysts for cross-coupling, hydrogenation, hydrosilylation, hydroboration, hydroamination, arylation, polymerization and for asymmetric synthesis (Sections VI.1 and VI.2).

Not surprisingly, the modern chemistry of heterocyclic compounds is actively developing along two lines, the first one being targeted synthesis of demanded heterocyclic compounds (Section VII) and the second one being the preparation of ligands for catalytic reactions. Particular methodological approaches to the former line are considered in Section VII.1, while ligand systems are discussed in Section VI.

A significant methodological achievement of recent years that affected the formation reactions of carbon–heteroatom and carbon–carbon bonds is the design of a new generation of photocatalysts and a convenient practical implementation of photocatalysis reactors (light-emitting diode matrices and solar light). For the goals of selective organic synthesis, noteworthy are visible light-activated hybrid inorganic semiconductor nanophotocatalysts, which proved to be good for selective oxidation of organic compounds (Section VIII).

Recent studies revealed exceptionally high activities of transition metal clusters and nanoparticles in catalytic reactions of selective organic synthesis. Until recently, this boundary area between the homogeneous and heterogeneous catalysis has remained virtually unexplored. Meanwhile, it is in this area that one should expect the next upturn in the development of catalysis and the creation of a new generation of high-performance catalysts (active, selective, stable and regenerable catalysts). Investigation of the prospects of this trend starts with considering special approaches to the design of new heterogeneous catalytic systems for the synthesis of organic compounds (beginning of Section IX); then experimental details are considered (Section IX.1) and particular examples of practical implementation of catalytic processes are discussed (Section IX.2).

The discovery of high activity and selectivity of bimetallic systems (Section X), which have already proved to be efficient in cross-coupling, oxidation and reduction (Sections X.1 and X.2), was highly important for fine organic synthesis. Scaling-up of fine organic synthesis methods for commercialization of industrially significant processes requires special approaches to the development of catalysts (Sections XI and XII) and elaboration of new methods for real-time monitoring of catalytic systems and investigation of the reaction mechanisms (Section XIII).

The preparation of biologically active compounds and application of organic synthesis to solve problems of pharmaceutical industry are discussed in several sections of the review (Sections II –XII). Yet another practically significant application of fine organic synthesis methods is the fabrication of molecular building blocks for the design of new-generation smart materials. The catalytic cross-coupling reactions and transformations of heteroatomic functional groups have already become irreplaceable tools for the design of materials for organic electronics (Section XIV). The development of advanced organic and metal-organic materials is also a practically important application (Section XV).

The present review considers selective methods of organic synthesis suitable for transformation of complex organic molecules without affecting the functional groups and asymmetric centres already present in the molecule. Therefore, the range of covered reactions is limited to those proceeding under mild conditions (as a rule at $\leqslant 200$ °C), which have been already shown to be tolerant to the functional groups present in the molecule and applicable in asymmetric synthesis.

II. Present-day methods for the synthesis of organofluorine compounds

The key specific feature of the fluorine atom, which is largely responsible for organofluorine chemistry being a separate research area, is the ability to crucially change the properties of compounds. Indeed, one or several fluorine atoms being introduced into an organic molecule were found to induce pronounced changes in the chemical and

physicochemical properties of the compound. In turn, the unusual or even unique properties of fluorine compounds open up a broad scope of practical applications.[22,23]

Starting from the mid-20th century, fluorine has played an important role in materials science (fluorinated polymers), and chlorofluoroalkanes have been popular as refrigerants (in particular, in household refrigerators). Somewhat later, fluorinated ethers were introduced into medical practice as general anesthetics. Since the late 1980s, organofluorine compounds have been a necessary component of liquid crystals, which are widely used to manufacture flat monitors and TV screens.[24]

However, the most remarkable feature of fluorine is the ability to modify the biological activity profiles of organic compounds.[25,26] Indeed, there are numerous examples where one or several fluorine atoms or a fluorinated group being introduced in a potential drug molecule substantially enhance the therapeutic effect or give rise to new types of activity.[27–30] Some structures of commercially successful fluorine-containing drugs[31–34] are shown in Fig. 2.

There is no general answer to the question of how fluorine works. For each particular compound, there are own causes among which mention may be made of the effect of fluorine on the metabolism rate, a change in the lipophilicity and an increase in the drug–enzyme binding constant. Currently, ~20% of the pharmaceutical agents permitted for commercial use contain one or several fluorine atoms. This percentage is even higher for agricultural chemicals (about 30%).[35]

In recent years, a field of diagnostic medicine tightly related to fluorine — positron emission tomography — has been vigorously developing.[36,37] The most important parameter for effective use of this method is the quickness of production and isolation of radioactive fluorinated products, which represents an additional challenge for synthetic chemists

It is evident that the design of new drugs requires that preparation methods for diverse fluorine-containing compounds be available. The conventional reactions used to prepare chloro-, bromo- and iodo-derivatives are, most often, inapplicable for fluorination. The synthesis of fluorinated compounds often requires unusual approaches, and studies of the reactivity of these compounds are of fundamental interest.

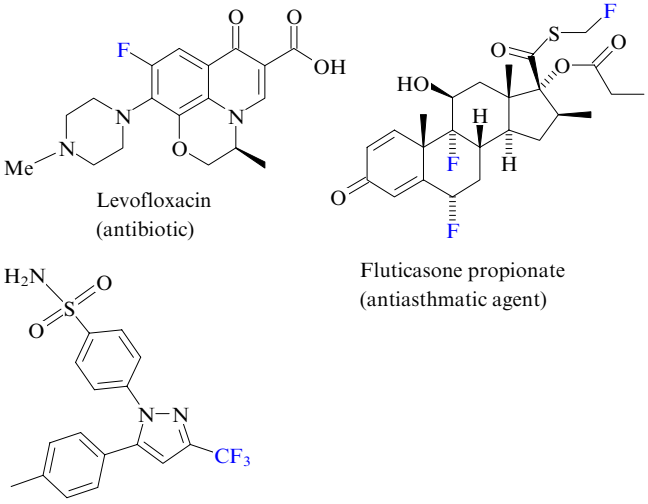


Figure 2. Examples of fluorinated medical drugs.

Fluorine is rather abundant in nature as inorganic fluorides (the fluorine content in the Earth crust is markedly higher than the chlorine content!). In view of the high strength of the C–F bond, which is the strongest bond formed by a carbon atom, it is surprising that only a few natural fluorinated organic compounds are known.[38] This fact implies that the formation of the C–F bonds under natural conditions is difficult and generally defines the problem of using available and convenient metal fluorides for the introduction of fluorine.

The organofluorine chemistry has developed during the whole 20th century and the obtained results formed the foundation of this area.[22,39] However, in the last 10–15 years, the number of publications on this topic has increased like an avalanche, which is reflected in a number of recent reviews.[40–44] Section II.1 presents the key approaches, methods and reagents determining the modern level of organofluorine synthesis. The processes characterized by high selectivity and allowing the use of substrates with a broad range of functional groups are considered. However, this Section does not cover the reactions involving highly reactive reagents such as fluorine or hydrogen fluoride, which are, on the one hand, highly dangerous and, on the other hand, can react with almost any functional group.[45,46]

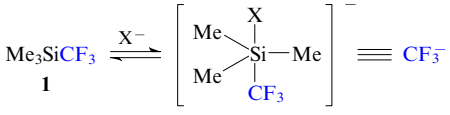
II.1. Comparative analysis of methods for the synthesis of compounds with CF_3, CF_2 and CF groups

The known methods for the preparation of fluorine compounds can be divided into two types. One type of methods, which is discussed in this Section, is based on the direct introduction of a fluorine atom or a fluorinated group into a molecule. The development of these methods requires new reactions, reagents, catalysts, ligands and, in some cases, fundamentally new approaches. The second type includes reactions involving building blocks that already contain fluorine, in some cases, remote from the reaction centre. These processes are described in more detail in Section III.

II.1.a. Methods for the introduction of a CF_3 group

A popular method for the introduction of a trifluoromethyl group is nucleophilic trifluoromethylation.[47] Unlike classical organomagnesium and -lithium reagents, the trifluoromethylated analogues (for example, F_3CLi, F_3CMgBr) are unstable even at reduced temperatures (−78 °C). The most convenient synthetic equivalent of the CF_3 carbanion is trimethyl(trifluoromethyl)silane (**1**) (Ruppert–Prakash reagent). Treatment of silane **1** with basic activating reagents (fluoride, carboxylate and alkoxide anions) results in the generation of a pentacoordinate intermediate, which serves as the source of the trifluoromethyl anion (Scheme 1).

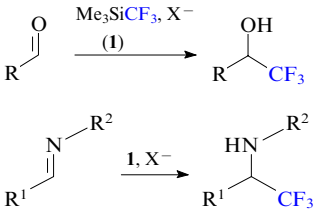
Scheme 1



$X^- = F^-, AcO^-, Bu^tO^-$

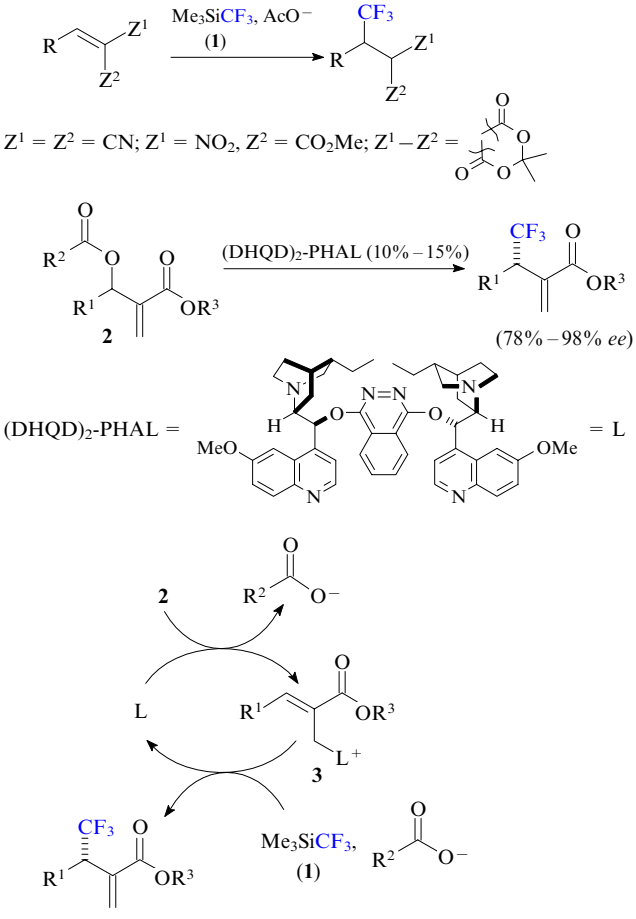
Using silane **1**, carbonyl compounds[47–49] and imines[50] (and many other compounds with the C=N bond)[51] can be easily converted to the corresponding CF_3-substituted alcohols and amines — useful building blocks for medicinal chemistry (Scheme 2). (Some schemes in the review are presented in the general form reflecting the possibility of the processes; excessive detailing was considered inexpedient.) Examples of the asymmetric addition of the trifluoromethyl group to aldehydes using the fluoride anion for activation in combination with the chiral ammonium counter-ion based on cinchona alkaloids were described.[52]

Scheme 2



Nucleophilic addition of the trifluoromethyl anion to Michael acceptors was also studied using several examples. High yields of conjugate addition products were obtained only for substrates with a highly electrophilic double bond (Scheme 3).[53–55] However, the addition to classical α,β-unsaturated aldehydes, ketones, esters and nitro compounds has not yet been performed. Using the acylated Baylis–Hillman adducts **2** in combination with a chiral catalyst, the asymmetric nucleophilic substitution of the acyloxy group

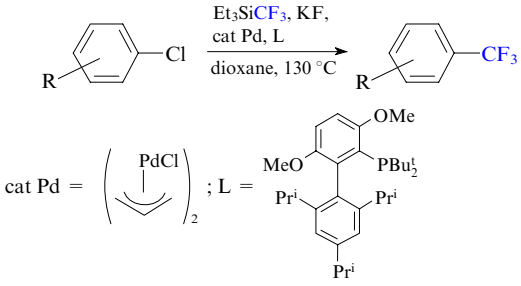
Scheme 3



was carried out. This process includes a double allylic substitution: first, the chiral nitrogen-based nucleophile (L) attacks substrate **2** at the double bond thus generating chiral electrophilic intermediate **3**, which reacts with silane **1** under activation by the released carboxylate anion.[56, 57]

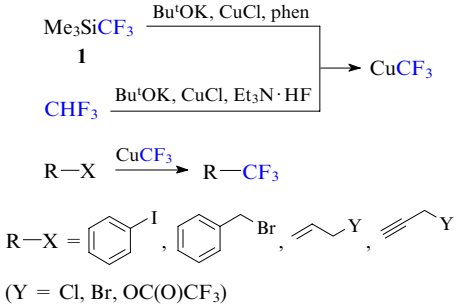
A lot of attention was paid to the cross-coupling of aryl halides with nucleophilic trifluoromethylating reagents catalyzed by transition metal complexes.[41] In the case of catalysis by palladium complexes, there is a problem of slow reductive elimination from $RPd(L)CF_3$. This problem was solved only in 2010 by using monophosphine biphenyl ligands in the reaction of aryl chlorides with a silicon reagent (Scheme 4).[58] Later, this cross-coupling reaction was extended to vinyl triflates and vinyl nonaflates.[59]

Scheme 4



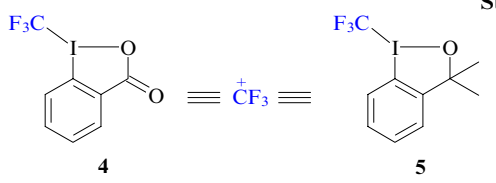
Trifluoromethylation reactions promoted by copper(I) salts were intensively studied.[41] Trifluoromethylcopper can be prepared from silane **1** (see Ref. 60) or from fluoroform on treatment with potassium di(*tert*-butoxy)cuprate generated *in situ* from potassium *tert*-butoxide and copper(I) chloride (Scheme 5).[61] Note that the copper complex with 1,10-phenanthroline (phen), $CF_3Cu(phen)$, has become commercially available. It was shown that trifluoromethylcopper can act as an efficient trifluoromethylating reagent for aromatic, benzyl, allyl and propargyl substrates.[62] Conditions for conducting the trifluoromethylation in the presence of catalytic amounts of copper salts were also found.[63]

Scheme 5



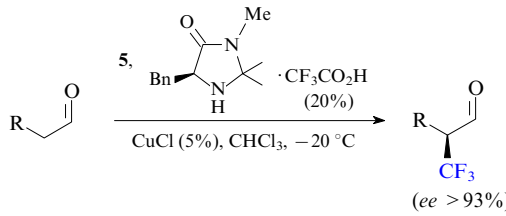
The conduction of electrophilic trifluoromethylation is a very difficult task. The presence of three fluorine atoms at the reaction centre hampers classical S_N1 and S_N2 reaction

Structures 4, 5



mechanisms. In 2006, reagents **4** and **5** based on trivalent iodine — Togni reagents — were proposed (Scheme 6).[64, 65]

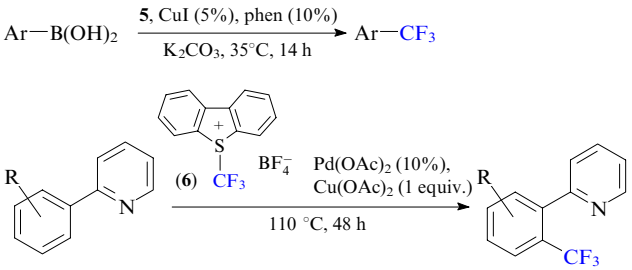
Scheme 6



These reagents proved to be efficient for electrophilic trifluoromethylation of a very broad range of substrates. Besides C-nucleophiles (1,3-dicarbonyl compounds, α-nitroesters, aromatic compounds), this reaction may involve thiols, phosphines, alcohols and azoles. Scheme 6 depicts an example of asymmetric trifluoromethylation of aldehydes with compound **5** in the presence of the MacMillan catalyst.[66]

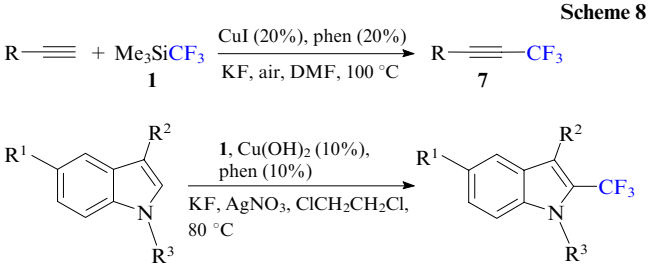
A new direction is related to the ability of some electrophilic trifluoromethylating reagents to transfer a cationic CF_3 group to a transition metal. This increases the oxidation state of the metal, which considerably promotes the reductive elimination. Presumably, the trifluoromethylation of boronic acids with **5** in the presence of copper salts occurs by this mechanism (Scheme 7).[67, 68] In the palladium chemistry, a cycle based on the Pd^{II}/Pd^{IV} pair was also proposed for CH-trifluoromethylation of aromatic compounds.[69] In the latter case, the Umemoto reagent was used as the source of the CF_3 cation (**6**) (see Scheme 7).

Scheme 7



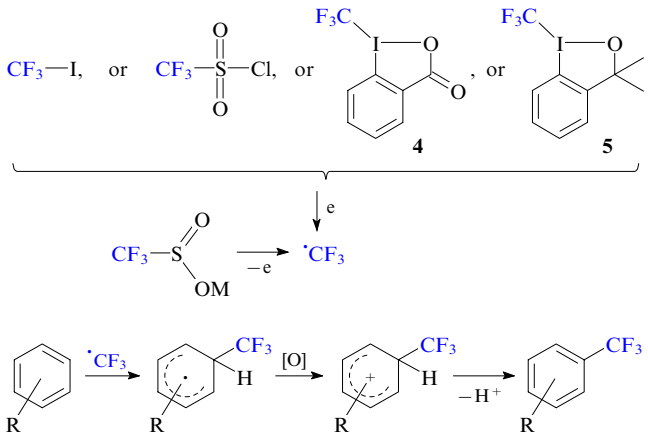
Starting from 2010, studies of reactions involving cross-coupling of a nucleophilic component with a nucleophilic trifluoromethylation reagent in the presence of an oxidant (additional reagent or air oxygen) have been rapidly developing (Scheme 8). For example, a combination of simple terminal acetylenes with silane **1** in the presence of KF and oxygen affords, in one step, CF_3-substituted acetylenes **7**, which are very difficult to prepare by any other method.[70] Similarly, heterocyclic compounds containing a relatively acidic hydrogen atom can be trifluoromethylated in the presence of a silver salt as an oxidant (see Scheme 8).[71]

Scheme 8



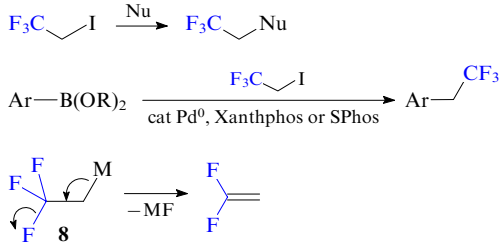
In recent years, the interest in free radical trifluoromethylation processes has substantially increased.[42] Indeed, unlike the carbocation or carbanion, the trifluoromethyl radical is generated rather easily. This can be done under either oxidative or reductive conditions (Scheme 9). The trifluoromethyl radical can react with various π-nucleophiles (alkenes, aromatic compounds) to give products of CF_3-group substitution for hydrogen. Thus, CF_3-containing compounds can be prepared without preliminary functionalization of the substrate. However, the problem of low regioselectivity of the radical trifluoromethylation of substituted aromatic compounds remains unsolved in most cases.

Scheme 9



A special but still important case of synthesis of CF_3-containing compounds is the introduction of the 2,2,2-trifluoroethyl substituent, which can be performed by a nucleophilic substitution reaction (Scheme 10). Methods of Pd-catalyzed cross-coupling involving boronic acids or pinacolyl boronates and trifluoroethyl iodide were proposed; for this reaction to occur, the presence of a sterically hindered phosphine ligand, either bidentate Xanthphos or monodentate SPhos, is required.[72, 73] However, reactions involving 2,2,2-trifluoroethyl organometallic reagents **8**, which are prone to β-elimination, are still unknown. Just recently, stable organoboron compounds of this type [**8**, M = $B(OR)_2$] were obtained but cross-coupling reactions with these reagents have not been studied as yet.[74]

Scheme 10

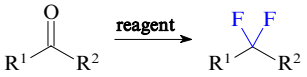


II.1.b. Methods for the preparation of compounds with a CF_2 group

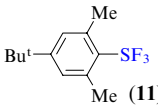
The most general approach to the formation of a CF_2 moiety is direct transformation of a carbonyl compound (aldehyde or ketone) according to the deoxofluorination reaction (Scheme 11).[75] However, a considerable drawback of this process is difficulty of handling of fluorine reagents (toxicity of sulfur tetrafluoride; detonation susceptibility of

sulfotrifluorides **9**). Recently, less hazardous reagents **10**[76] and **11**[77] were proposed. Nevertheless, deoxofluorination implies, by its nature, fairly drastic reaction conditions, which narrows down the range of functional groups that may be present in the substrate.

Scheme 11



The reagent is SF_4-HF, R_2NSF_3 (**9**), $R_2\overset{+}{N}{=}SF_2BF_4^-$ (**10**),

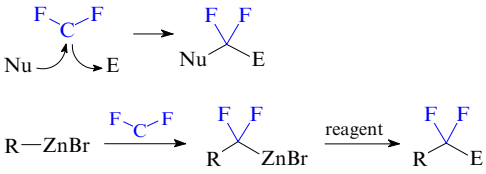


(**11**)

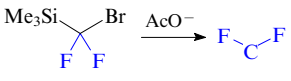
Often, the target compounds are prepared by functionalization of accessible compounds that already have a CF_2 group.[78,79] As simple examples, of note are halodifluoroacetic acids (XCF_2CO_2H; X = Cl, Br) and their derivatives and some difluoroalkanes (CF_2Br_2, $ClCHF_2$), although the availability of the latter compounds can be considerably restricted by the Montreal Protocol due to ozone layer depletion.

Methods based on difluorocarbene reactions are rather efficient.[44] In particular, an approach to the synthesis of difluoromethylene compounds from three components — a nucleophile, difluorocarbene and an electrophile — has been proposed recently (Scheme 12).[80] The possibility of independent variation of the nucleophile and the electrophile makes this method quite versatile. This approach was demonstrated by a number of examples where organozinc compounds served as nucleophiles and bromine, iodine, proton and allyl halide were the electrophiles. Note that with an allylic electrophile, three-component coupling furnished two C–C bonds.[81] In the reactions with organozinc reagents, (bromodifluoromethyl)trimethylsilane (**12**) in the presence of the acetate anion was used to generate difluorocarbene.

Scheme 12



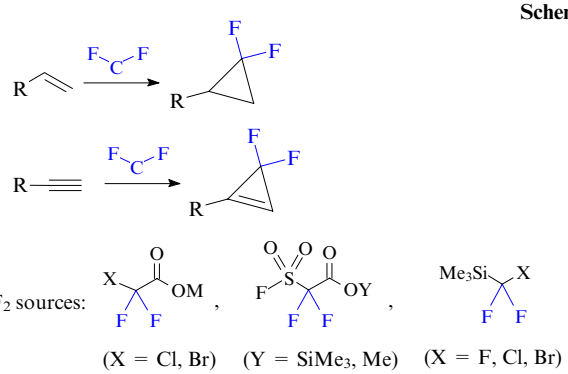
The reagent is I_2, Br_2, AcOH, AllBr; E = I, Br, H, All



12

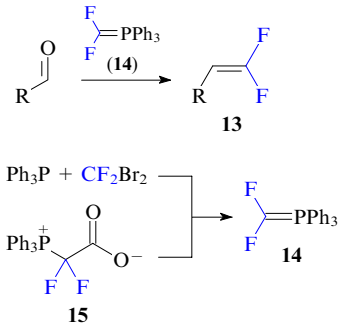
gem-Difluoro-substituted cyclopropanes and cyclopropenes represent a separate class of compounds that are usually synthesized by 1,2-cycloaddition of difluorocarbene (Scheme 13).[82] The suitable sources of carbene include salts of halodifluoroacetic acids, perfluoropropylene oxide, difluorohaloalkanes, difluoro(fluorosulfonyl)acetic acid derivatives[83] or fluorosilicon and fluoromercury reagents.[84,85] Difluorocarbene is an electrophilic carbene; therefore, it readily reacts with electron-enriched double bonds, whereas the addition to electron-deficient alkenes is less efficient.

Scheme 13



1,1-Difluoroalkenes **13** are prepared most often by the Wittig reaction (Scheme 14). However, the corresponding phosphonium ylide **14** is unstable and is generated *in situ* from dibromodifluoromethane[86] or from zwitter-ionic reagent **15**, which is easily formed from bromodifluoroacetic acid.[87]

Scheme 14



For the preparation of functionalized compounds with a CF_2 group, a series of heteroorganic (including organometallic) reagents containing both standard carbon functional groups (ester,[88] nitrile[89]) and substituents based on chalcogenides,[90] phosphorus[91] and even silicon[92] have been devised (Fig. 3). The presence of these substituents opens up prospects for the subsequent activation of the carbon–heteroatom bond (C–S, C–P, C–Si) by heterolytic and

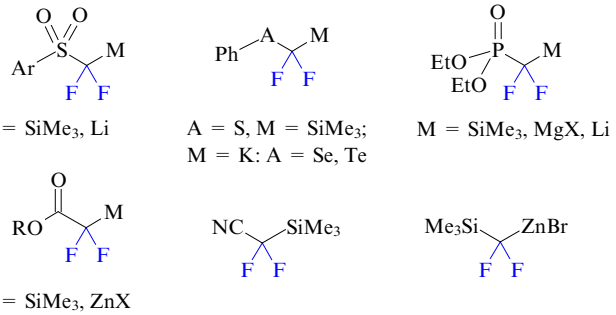


Figure 3. Reagents for the synthesis of compounds with a CF_2 group.

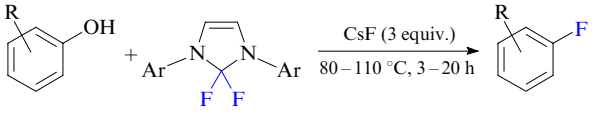
homolytic mechanisms, which provides a broad range of difluoro-substituted products.

II.1.c. Methods for the preparation of compounds with a C–F group

A classical method for the introduction of a fluorine atom into the aromatic ring is thermolysis of diazonium tetrafluoroborates (Schiemann reaction).[93] However, this method is potentially hazardous especially on an industrial scale due to low stability of diazonium salts. Meanwhile, the direct nucleophilic substitution of fluoride ion for the chloride ion, so-called Halex process is applicable only to a narrow range of substrates.[94]

Replacement of the phenolic hydroxy group by a fluorine atom by deoxofluorination is difficult to implement, and standard fluorine–sulfur reagents used for aliphatic alcohols prove to be inefficient. The most reactive reagent for the deoxofluorination of phenols is difluoroimidazoline **16**, which is suitable only for phenols containing electron-donating substituents in the ring (Scheme 15).[95]

Scheme 15

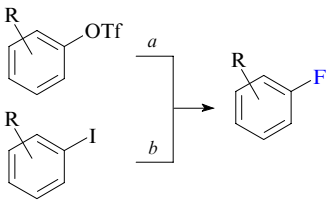


16

Ar = 2,6-$Pr^i_2C_6H_3$

In the last five years, methods for C–F bond formation based on the transition metal chemistry have been rapidly developed.[96] The fluorine atom substitution for the triflate leaving group was accomplished under palladium catalysis in the presence of sterically crowded monodentate phosphines (Scheme 16).[97] An alternative method includes replacement of the iodine atom by fluorine on treatment with an excess of copper(I) triflate and silver(I) fluoride at high temperature.[98]

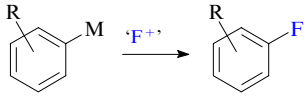
Scheme 16



(*a*) CsF, cat. Pd^0–R_3P, 80–130 °C, 14 h;
(*b*) $(Bu^tCN)_2CuOTf$ (3 equiv.), AgF (2 equiv.), DMF, 140 °C, 22 h

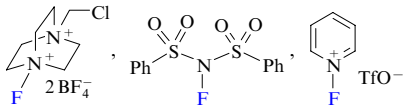
A new, in principle, method for the preparation of aromatic fluorides comprises electrophilic fluorination of the nucleophilic carbon–element bond (Scheme 17). Originally, quite expensive xenon difluoride was used. A substantial progress along this line is related to the appearance of reagents with a nitrogen–fluorine bond,[99] although they are prepared using elemental fluorine. The Selectfluor and NFSI reagents are stable crystalline compounds convenient for handling and are sold by many companies at reasonable prices. The reaction of the organometallic substrate with an N-fluorinating reagent can occur as a direct nucleophilic attack on the fluorine atom (for M = Li, MgX). However, in some cases (for boron and tin compounds), the reaction is catalyzed by transition metal complexes (palladium, nickel, copper and silver) and, probably, includes the initial formation of the bond between the fluorine atom and the transition metal followed by reductive elimination.

Scheme 17



M = Li, MgX, $B(OR)_2$, SnR_3;

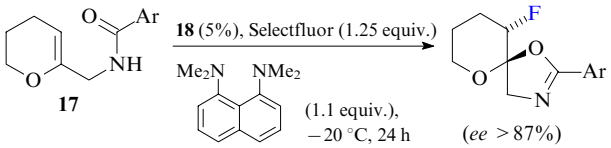
'F^+' = XeF_2,



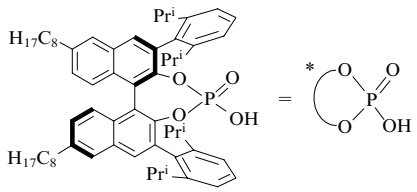
Selectfluor NFSI

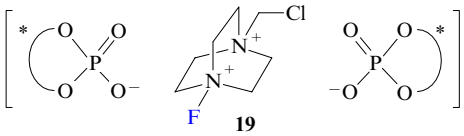
Electrophilic fluorinating reagents have started to be used in enantioselective processes catalyzed by transition metals or under organocatalysis. Scheme 18 shows the electrophilic fluorination of substrates **17** with chiral phosphoric acid **18** functioning as the asymmetric inductor. Presumably, salt **19** containing an achiral N–F group and two chiral counter-ions serves as the enantioselective reagent.[100] In this reaction, high enantiomeric excess values can be achieved, although the chiral inductor has no covalent bond with either substrate **17** or the fluorinating reagent.

Scheme 18



18 =

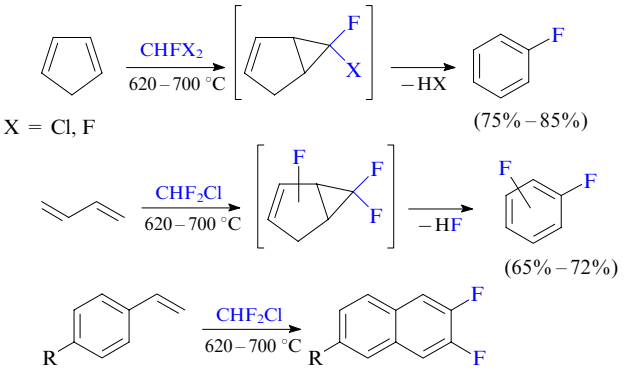




19

Academician O M Nefedov and co-workers[101–104] proposed an interesting approach to the synthesis of fluoroaromatic compounds, fluoroalkenes and fluorodienes, comprising the cycloaddition of fluorine-substituted carbenes to unsaturated substrates and the subsequent skeletal rearrangement of cyclopropanes involving three-membered ring opening, resulting in new structures with the fluorine–carbon bond being retained. The process is conducted in the flow mode. This method can be efficiently used to prepare fluoroaromatic compounds (aromatization is attained upon elimination of hydrogen halide) (Scheme 19).[101] Indeed, various mono- and difluoroarene products (including 2,3-difluoronaphthalenes inaccessible by other methods) can be obtained from readily available starting compounds.

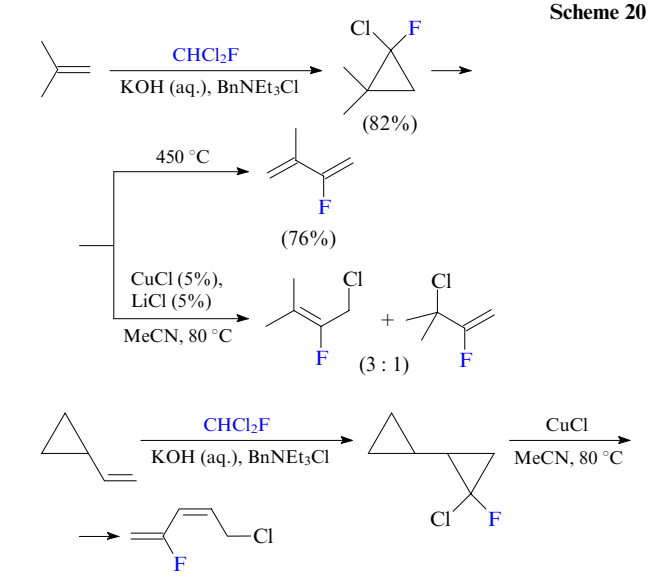
Scheme 19



Carbene syntheses of fluoroarenes can also be arranged for liquid-phase processes with generation of fluorochlorocarbene by treatment with aqueous alkali under phase transfer catalysis (at ~0 °C). In this reaction, relatively labile spiro derivatives of cyclopentadiene and fulvenes can be used as substrates, apart from alkylcyclopentadienes and indenes.[101]

This approach is also rather efficient for the synthesis of fluoro-substituted dienes and alkenes. For example, cyclopropanation can be carried out under mild conditions of carbene decomposition of fluorodichloromethane giving rise to fluorochlorocyclopropanes in good yields (Scheme 20). The subsequent rearrangement of the fluorochlorocyclopropane moiety can be induced not only by thermolysis (300–500 °C) but also on moderate heating (80 °C) in the presence of a catalytic amount of copper(I) chloride or a CuCl and LiCl mixture in acetonitrile.[103, 104]

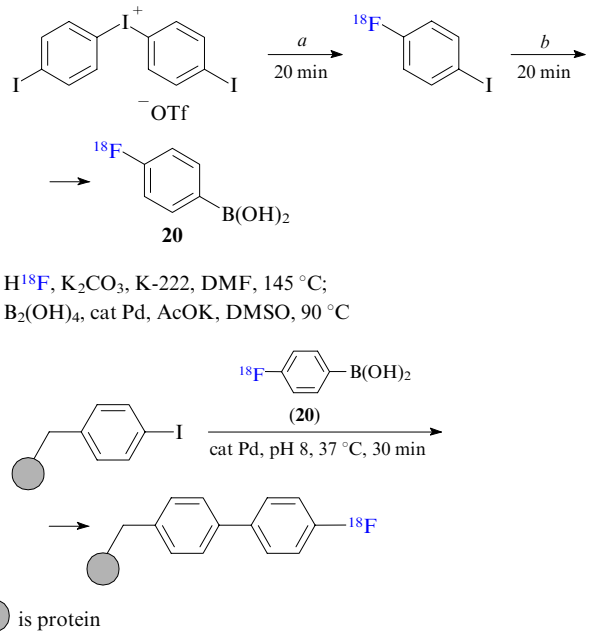
Scheme 20



Skeletal rearrangements of methoxy-substituted *gem*-fluorochlorocyclopropanes can also be used to prepare fluorine-substituted α,β-unsaturated aldehydes, ketones and methoxy-substituted fluorodienes.[105, 106]

The fluorine chemistry has started to play an important role in the positron emission tomography (PET) based on the use of isotopes that decay to give off positrons.[36, 37] Among these isotopes, ^{18}F with the half-life of 109.7 min is most convenient. After injection of a substance containing ^{18}F into the blood, it is possible to determine the exact distribution pattern of this substance in the body by means of the detection equipment. Fast decay of the ^{18}F isotope imposes substantial restrictions on the method used: the synthesis, isolation and purification of the desired compound should not require long time. In addition, the ^{18}F isotope is formed in the cyclotron as either elemental fluorine or a solution of hydrofluoric acid in water (*i.e.*, as the fluoride anion). The latter alternative is, on the one hand, more practical and, on the other hand, more complicated as regards the introduction of fluorine into an organic molecule. This is why effective methods for the introduction of fluorine as the fluoride anion (especially into the aromatic ring) are highly demanded. Scheme 21 shows an example[107] in which ^{18}F-containing boronic acid **20** is attached to a protein containing a iodophenyl substituent *via* the Suzuki reaction. Reagent **20** is prepared in two steps using nucleophilic aromatic substitution to introduce the fluorine atom by the reaction of the iodonium salt with the fluoride anion in the presence of cryptand K-222 (the cryptand strongly binds the potassium ion thus transferring the fluoride anion into the organic solvent).

Scheme 21



Thus, unlike the CF_3 group, which can be introduced into the molecule by a variety of reported methods, there only a few methods for the precise and highly selective introduction of fluoro- and difluoro-substituents. Conduction of nucleophilic substitution by the S_N2 mechanism using fluorine-containing nucleophilic reagents remains an unsolved problem.

A separate topical direction is synthesis of compounds with a CF_2 group. For example, it is difficult to prepare compounds containing a halodifluoromethyl group (CF_2X, X = Cl, Br, I) using existing reactions, and the corresponding carbanions are quite unstable.

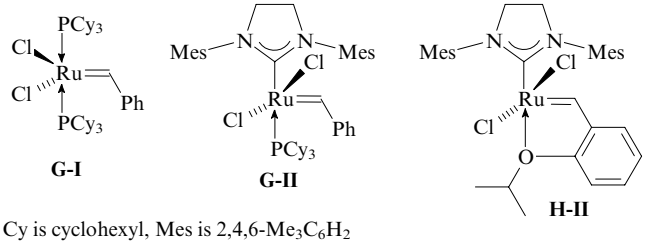
III. Metathesis reaction catalyzed by ruthenium complexes

The previous Section gives comparative analysis of various methods for the introduction of fluorine-containing groups

into organic molecules. The present part of the review considers the catalytic methods of transformation of building blocks, which already contain fluorine. Extremely broad possibilities for the conversion of fluorine-containing organic molecules are provided by metathesis.

During the last decade, the metathesis of alkenes as a significant method for the formation of new carbon–carbon bonds has become one of the most swiftly developing fields of organic chemistry. This process, which was rewarded by the Nobel Prize in 2005, has already made an inestimable contribution to the synthesis of physiologically active natural compounds, drugs, diverse functional materials and polymers.[108–113]

The discovery of effective ruthenium carbene complexes distinguished by high stability with respect to air moisture and oxygen and to various functional groups resulted in elaboration of a number of important synthetic processes such as ring closing metathesis (RCM), cross metathesis (CM), ring opening metathesis polymerization (ROMP), acyclic diene metathesis (ADMET) and alkene–acetylene metathesis.[114–117] The use of Grubbs ruthenium catalysts (Fig. 4) provided the unique possibility to predict and embody innovative and environmentally friendly synthetic strategies with minimum time, energy and money expenditures.



Cy is cyclohexyl, Mes is 2,4,6-$Me_3C_6H_2$

Figure 4. Commercially available catalysts for alkene metathesis: Grubbs catalysts of generations I (**G-I**) and II (**G-II**), Hoveyda–Grubbs catalyst of generation II (**H-II**).

In the chemistry of amino acids and peptides, the use of intramolecular metathesis resulted in effective synthesis of cyclic derivatives, which are currently widely used in the design of new potential drugs.[111] First of all, this is due to the fact that the introduction of cyclic α-amino acids into strategic sites of peptides secures the amide bonds in unique conformations needed to maximize the biological activity.[118]

Meanwhile, it is well known that fluorine-containing analogues of natural biologically active compounds often demonstrate unique physiological activity.[22, 32, 119] In the last decade, modification of peptides and proteins by introducing fluorine-containing α-amino acids and their functional derivatives has been successfully performed. These modifications lead, most often, to higher lipophilicity, proteolytic and conformational stability, considerably improving the transport characteristics of potential drugs.[120] Moreover, owing to the presence of fluorine atoms, it is possible to monitor the chemical environment of fluorine-containing residues and to perform conformational analysis and study the metabolism of peptides by ^{19}F NMR spectroscopy. In addition, α-amino acids containing fluorine atoms in the β-position attract attention due to their unique ability to selectively inhibit several important enzymes, while exhibiting various types of biological activity.[121]

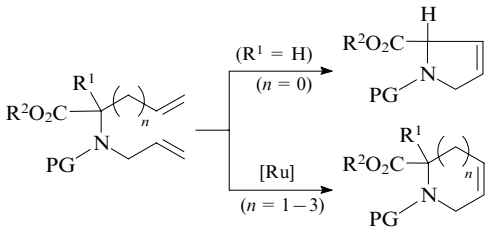
Thus, development of selective methods for the synthesis of new fluorine-containing α-amino acids of cyclic structure by intramolecular metal-catalyzed metathesis transformations is of considerable fundamental and applied value.

III.1. Intramolecular metathesis in the synthesis of cyclic fluorine-containing α-amino acids and their derivatives

III.1.a. Metathesis of fluorinated dienes

The metathesis of linear 1,7-dienes containing an α-amino acid skeleton was first employed by Grubbs[122] in 1996 to prepare dehydropipecolic acid ($n = 1$, Scheme 22). It was found that the corresponding five-membered derivatives — dehydroprolines — cannot be synthesized with catalysis by the carbene complex **G-I** (see Fig. 4): due to the acidic nature of the α-proton in the initial 1,6-dienes ($n = 0$, see Scheme 22), the reactions afford only linear α,β-unsaturated oligomers. More recently, this strategy was successfully used by other research teams to prepare six-, seven- and eight-membered amino acid derivatives ($n = 1–3$, see Scheme 22).[123, 124]

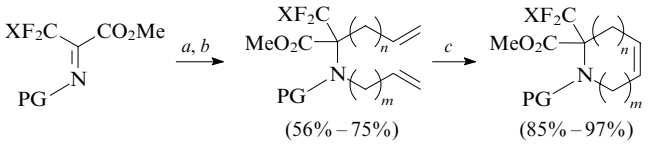
Scheme 22



PG is protecting group; [Ru] = **G-I**, **G-II**, **H-II**

Ring closing metathesis was first used in the synthesis of fluorine-containing cyclic α-amino acids in 1998.[125] The starting di- and trifluoromethyl dienes were prepared under mild conditions by amidoalkylation of the corresponding C-nucleophiles with highly electrophilic fluorinated methyl pyruvate imines. The subsequent cyclization was easily accomplished at room temperature in the presence of 5 mol.% catalyst **G-I** to give metathesis products in high yields. The absence of the α-proton ensured the formation of previously inaccessible five-membered proline derivatives ($n = 0$, $m = 1$, Scheme 23).[126]

Scheme 23

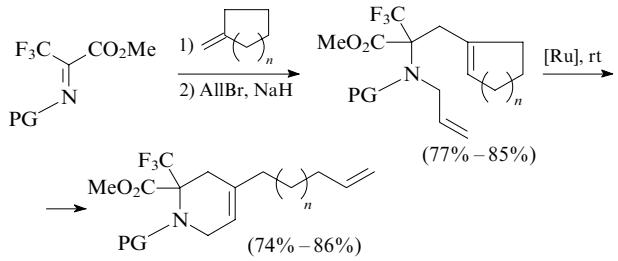


X = F, Cl; PG = Cbz, Boc, SO_2Ph (Cbz is benzyloxycarbonyl, Boc is *tert*-butoxycarbonyl); $n = 0–2$; $m = 1, 2$;
(*a*) RMgBr (R is vinyl, allyl, homoallyl), THF, −78 °C;
(*b*) RBr (R is allyl, homoallyl), DMF, 0 °C;
(*c*) **G-I** or **G-II** (3 mol.%–5 mol.%), CH_2Cl_2, 20 °C

2-Trifluoromethyl-substituted 4,5-dehydropipecolic acids containing additionally an alkenyl substituent in the 4-position can be prepared by combined ring opening—

ring closing metathesis (ROM–RCM).[127] The synthesis of the starting aza-1,7-dienes containing one of the double bonds in the ring comprises the ene reaction of methyl trifluoropyruvate imine with methylidenecycloalkanes and subsequent N-allyllation with sodium hydride-induced deprotonation. The aza-1,7-dienes obtained in this way readily undergo carbene complex **G-I**-catalyzed rearrangement of the carbon skeleton, which includes opening of cycloalkene and closure of a new heterocycle, resulting in the desired dehydropipecolinates with an alkenyl substituent the length of which can be controlled by varying the ring size in the starting methylidenecycloalkane (Scheme 24).

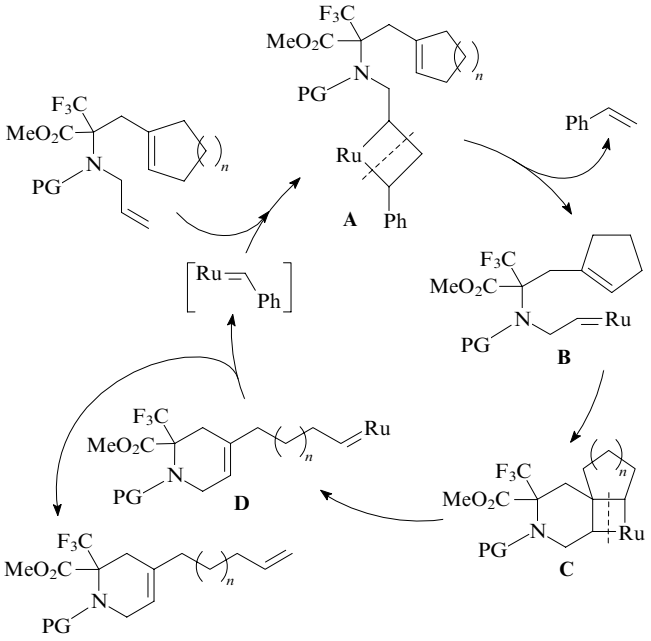
Scheme 24



PG = Cbz, Boc, SO_2Ph; n = 1, 2

The catalytic cycle, resulting in the rearrangement of the carbon skeleton occurs, apparently, in the following way: four-membered metal ring **A** formed initially is fragmented with evolution of a styrene molecule to give carbene complex **B**, which undergoes intramolecular cyclization to give unstable [2 + 2]-cycloadduct **C**. The latter rearranges into a new ruthenium complex **D**, which in turn undergoes cross-metathesis with a styrene molecule occurring in the reaction area to give stable reaction products and a catalyst molecule for a new catalytic cycle (Scheme 25).

Scheme 25



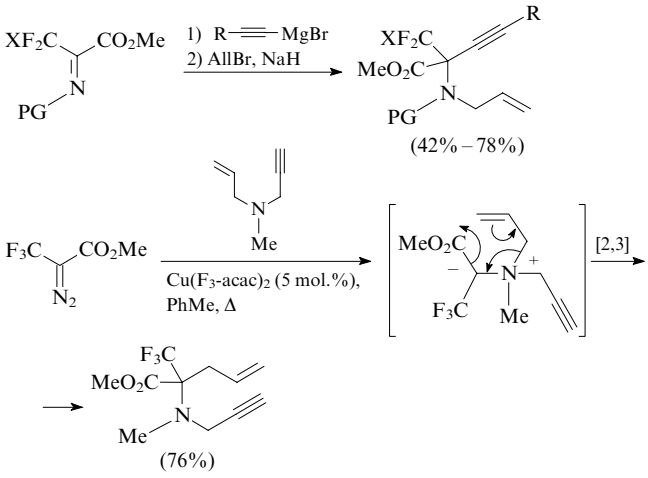
III.1.b. Metathesis of fluorinated enynes

Ring closing enyne metathesis (RCEYM), like diene metathesis, has been rapidly developed in recent years and has acquired importance in the synthesis of carbo-, hetero- and macrocyclic compounds and other biologically important derivatives.[128, 129] A characteristic feature of intramolecular ring closing enyne metathesis is that the formation of a new C–C bond occurs without the loss of the carbon skeleton and results in cyclic 1,3-dienes with one double bond in the ring, which are widely used to form polycyclic systems.

However, the RCEYM synthesis of cyclic 1,3-diene-containing α-amino acids often gives unsatisfactory results. On the one hand, this may be due to catalyst inhibition upon coordination of the nucleophilic nitrogen atom to the metal centre. On the other hand, metathesis of terminal enynes often gives low product yields due to poisoning of the active catalytic species in the secondary metathesis processes of diene intermediates.[130]

Taking into account the above-indicated features, we studied metathesis of 1,6- and 1,7-enynes containing α-XCF_2-α-amino acid moieties. The starting enynes can be obtained either from the corresponding imines[131] similarly to dienes or from fluorinated diazocarbonyl compounds by [2,3]-sigmatropic rearrangement of the allyl group in nitrogen CF_3 ylides (Scheme 26).[132]

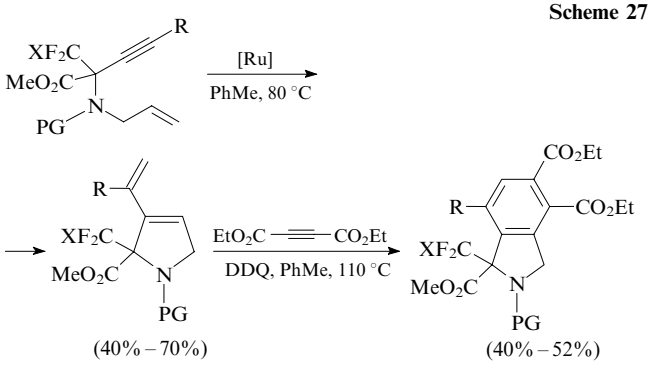
Scheme 26



F_3-acac is 1,1,1-trifluoroacetylacetonate

As a result, it was found that aza-1,6-enynes cyclize only in the presence of 5 mol.%–8 mol.% of the allenylidene ruthenium complex [Ru=C=C=CPh_2(Cl)(PCy_3)(*p*-cymene)]$^+$TfO$^-$, which was deliberately synthesized from the readily accessible precursor [RuCl(PCy_3)(*p*-cymene)]$^+$TfO$^-$ and the alcohol HC≡$CCPh_2OH$. The metathesis products obtained in moderate and good yields were

Scheme 27

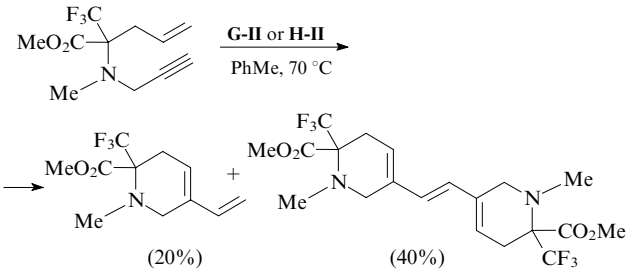


X = F, Cl; PG = Cbz, Boc, SO_2Ph; R = H, Bu^n, CH_2OMe; [Ru] = [Ru=C=C=CPh_2(Cl)(PCy_3)(*p*-cymene)]$^+$TfO$^-$

then introduced into the Diels–Alder reaction followed by oxidation with 2,3-dichloro-4,5-dicyanobenzoquinone (DDQ), which resulted in the corresponding functionally substituted benzoprolines (Scheme 27).[131]

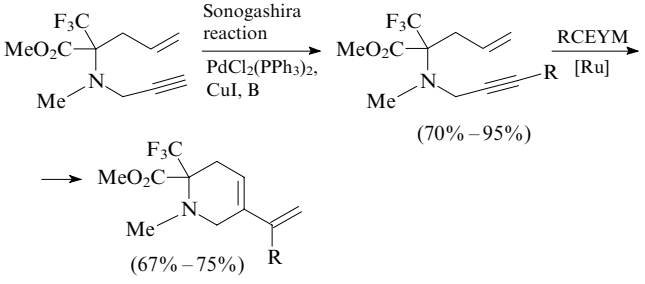
As expected, in the case of terminal aza-1,7-enyne, the desired metathesis product is formed in a moderate yield when the reaction is catalyzed by commercially available Grubbs (**G-II**) or Hoveyda–Grubbs (**H-II**) catalysts. Even an increased catalyst loading and long-term heating in toluene produced mainly the product of homo-cross-metathesis of cyclic 1,3-diene (Scheme 28).[133]

Scheme 28



Since cross-metathesis of 1,1-disubstituted alkenes is known to be a challenging task requiring either drastic conditions or more active catalytic systems,[117] the decision was made to introduce an additional substituent to the aza-1,7-enyne triple bond; then the RCEYM step will give 1,1-disubstituted alkene, which will suppress the undesirable side homo-cross-metathesis reaction. A number of new aza-1,7-enynes containing an internal triple bond were prepared by the Pd-catalyzed Sonogashira reaction and subjected to ring closing metathesis. In all cases, aza-1,7-enynes smoothly cyclized on heating in toluene, which resulted in the selective formation of cyclic 1,3-dienes in high yields (Scheme 29).[133]

Scheme 29

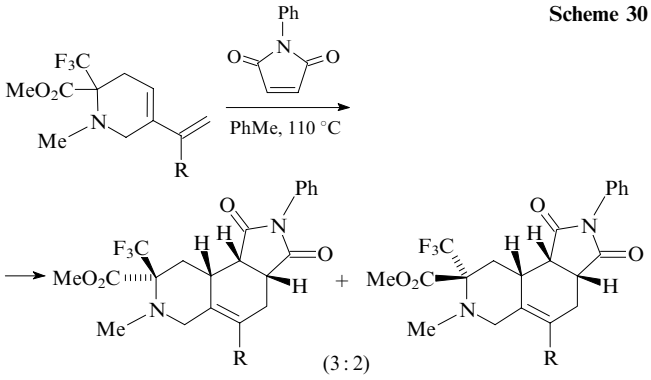


R = Ar, Aroyl, Acyl; [Ru] = **G-I**, **G-II**, **H-II**; B is base

In order to demonstrate the synthetic potential of the obtained conjugated dienes in the design of functionally substituted polycyclic systems, tricyclic α-amino acid derivatives were synthesized by a procedure based on [4 + 2]-cycloaddition of cyclic 1,3-dienes to *N*-phenylmaleimide (Scheme 30).

In addition, a new metathesis reaction involving aza-1,6- and 1,7-enynes was discovered. In the presence of 5 mol.% ruthenium complex Cp*Ru(cod)Cl (Cp* = η^5-C_5Me_5; cod is cycloocta-1,5-diene) and an equimolar amount of substituted diazoalkane, the starting enynes undergo combined cyclization–cyclopropanation reaction to give the corresponding bicyclic products (Scheme 31). The products formed in reactions with trimethylsilyldiazomethane have

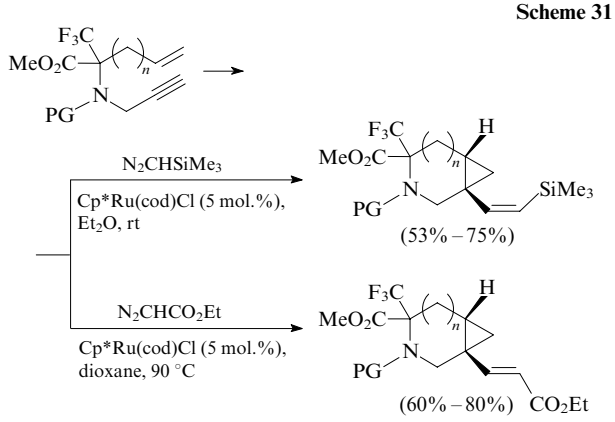
Scheme 30



R = Ph (78% overall yield), 4-MeC_6H_4 (74%)

the alkenyl group exclusively in the *Z*-configuration, whereas reactions with ethyl diazoacetate give products with the *E*-configured alkenyl group.[134]

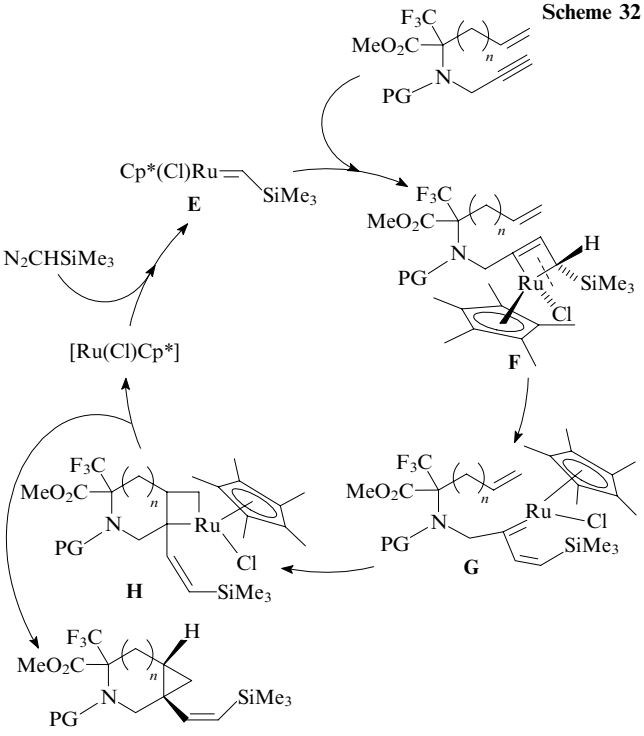
Scheme 31



PG = Boc, Cbz, Ts; *n* = 0, 1

The presumed mechanism of this unusual transformation comprises the primary reaction of a diazo compound

Scheme 32



with the catalyst to give carbene complex **E**, which reacts with the substrate by the classical enyne metathesis mechanism up to the formation of intermediate **H** (**E** → **F** → **G** → **H**), and after that, the pathway becomes different. In particular, intermediate **H** does not give off the corresponding carbene complex (as in the enyne metathesis) but undergoes instead reductive elimination to give unusual bicyclic products. The observed stereochemistry of the alkenyl moiety may be related to the sterically more favourable arrangement of the trimethylsilyl (TMS) and pentamethylcyclopentadiene groups in intermediate **F**, namely, in *anti*-positions relative to each other. Meanwhile, it cannot be ruled out that the interaction between the neighbouring chlorine atom and the TMS group can also be responsible for the reaction stereochemistry (Scheme 32).

III.1.c. Metathesis transformations of fluorinated diynes. Co-trimerization of diynes with acetylenes in the synthesis of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives

The intra- and intermolecular cyclotrimerizations of acetylenes catalyzed by transition metal complexes have been widely spread during the last two decades as a versatile method for the synthesis of substituted aromatic and heteroaromatic compounds. Catalysts based on transition metal complexes, most often, cobalt and rhodium, were successfully used in the alkyne cyclotrimerization serving as the key step for the synthesis of a series of biologically important structures, including natural compounds.[135] However, only a few examples of application of this strategy to prepare α-amino acid derivatives were reported, and data on the synthesis of fluorine-containing amino acids and their phosphorus analogues are totally absent.

It is known that the tetrahydroisoquinoline moiety is encountered in many organic compounds that exhibit various types of biological activity including antihypertensive, antimalarial and antitumour activities. Among these, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (TIC), being a conformationally rigid analogue of phenylalanine, attracts particular attention as an important component of highly selective enzyme inhibitors and integrin and δ-opioid receptor antagonists with a broad spectrum of pharmacological activity.[136, 137] The most vivid example of using the TIC pharmacophore for the drug design is the discovery of Accupril®,[138] which is currently used to treat hypertension and congestive heart failure (Fig. 5). Therefore, the development of efficient catalytic processes for the synthesis of new TIC derivatives is of obvious fundamental and applied interest.

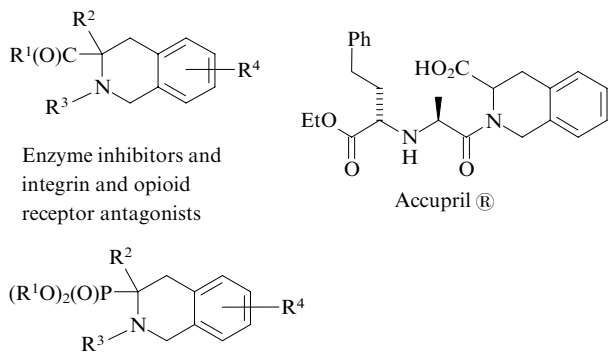
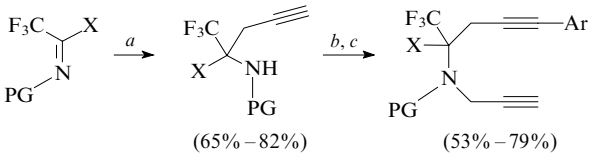


Figure 5. 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid derivative.

An original approach was proposed to the synthesis of CF_3-TIC derivatives [139] and their phosphorus analogues [140] comprising regioselective co-trimerization of aza-1,7-diynes with terminal acetylenes catalyzed by the Grubbs ruthenium complex (**G-II**). The starting trifluoromethyl-aza-1,7-diynes were prepared from the imines $CF_3(X)C{=}N-PG$ [X = CO_2Me, $P(O)(OEt)_2$)] [141] using the following synthetic sequence: (i) the reaction of the imine with propargylmagnesium bromide; (ii) the introduction of the aryl substituent at the terminal triple bond by means of Pd-catalyzed cross-coupling with aryl iodides; (iii) N-propargylation of the Sonogashira reaction products during deprotonation of sodium hydride (Scheme 33).

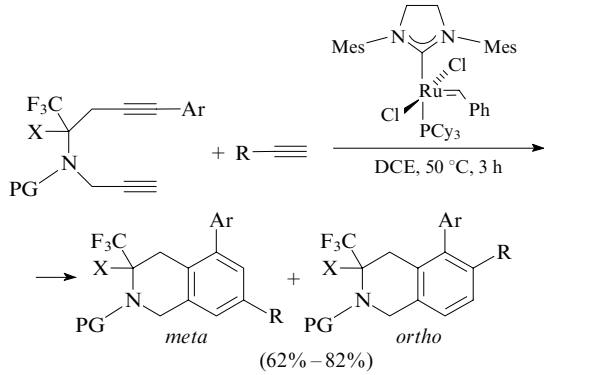
Scheme 33



X = CO_2Me, $P(O)(OEt)_2$; PG = Boc, Cbz, Ts;
Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$;
(*a*) — $HC{\equiv}CCH_2Br$, Mg, $HgCl_2$, Et_2O, −78 °C;
(*b*) ArI, $PdCl_2(PPh_3)_2$ – CuI (5 mol.%), organic base, rt;
(*c*) NaH, $HC{\equiv}CCH_2Br$, DMF, 0 °C

A study of the Ru-catalyzed cyclotrimerization of aza-1,7-diynes with various alkynes (acetylene, hex-1-yne, oct-1-yne and phenylacetylene) ascertained that reactions with terminal acetylenes occur on moderate heating in dichloroethane (DCE) in the presence of 5 mol.% of the second-generation Grubbs catalyst (**G-II**) and lead to the corresponding bicyclic derivatives with high *meta*-selectivity and in good yields (Scheme 34). In all cases, the content of the *meta*-isomer was above 92%, and in the case of the 2-MeO-phenyl substituent, it was >97%.

Scheme 34

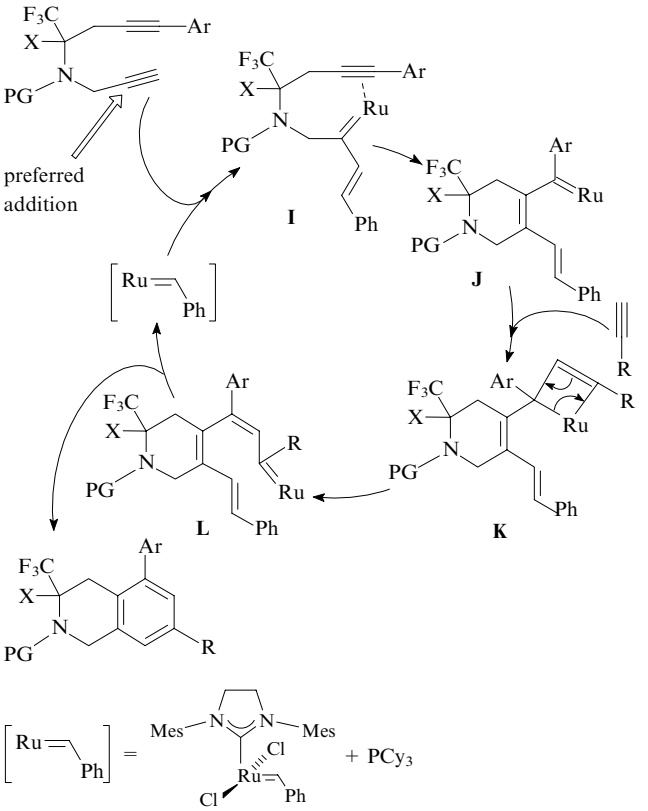


PG = Boc, Cbz, Ts; Ar = H, Ph, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$O_2NC_6H_4$; X = CO_2Me, $P(O)(OEt)_2$; R = H, Ph, Bu^n, n-C_6H_{13}

The presumptive mechanism of cyclotrimerization includes the preferred addition of the ruthenium carbene complex to the terminal triple bond of aza-1,7-diyne to afford intermediate **I**, this step being facilitated by the coordination of ruthenium to the remaining triple bond.

This is followed by a cascade of well-known intra- and intermolecular metathesis steps **J** → **K** → **L**, which ends in the release of the ruthenium benzylidene active species and predominant formation of the *meta*-isomer. The selective [2 + 2]-addition of the terminal acetylene to the Ru=C bond of intermediate **J**, resulting in the formation of ruthenacyclobutene **K**, is responsible for the observed chemo- and regioselectivity of the process (Scheme 35).

Scheme 35



Note that new fluorine-containing α-amino acids and their derivatives prepared by ring closing metathesis hold good promise for the use in bioorganic and medicinal chemistry for modification of biologically active peptides and are of interest by themselves for biological activity assays.

Generally, despite the substantial achievements in the metathesis, some problems of intra- and intermolecular metathesis transformations remain unsolved. First of all, this concerns the regio- and stereoselectivity of reactions, especially in the metathesis involving polyfunctional unsaturated compounds containing internal double (RCM process) and terminal triple (RCEYM process) bonds. Furthermore, due to the thermodynamic nature of metathesis, the *Z*-selective alkene metathesis is still a highly problematic reaction. The use of most of commercially available catalysts usually furnishes a difficult-to-separate *Z*- and *E*-alkene mixture in which the more thermodynamically favourable *E*-isomer predominates.[142] This fundamental problem of the alkene metathesis markedly restricts its industrial implementation. Solution of this problem can lead to creation of industrially important processes for utilization of by-products of petroleum cracking,[143, 144] alternative energy sources based on bioresources[145, 146] and new stereoregular polymers with unique properties.[147, 148] Therefore, the search for new, in principle, ruthenium-based catalytic systems with enhanced characteristics,[149, 150] first of all the activity and selectivity, is a highly topical line of research of modern chemical science.

IV. Oxidative cross-coupling

Currently, there is no universal way of C–F bond formation; furthermore, the classical cross-coupling reactions proved inapplicable for this purpose. It is worth noting that for a number of other carbon–heteroatom bond formation reactions, versatile synthetic procedures were elaborated within a general approach. This Section discusses the coupling reactions giving C–O bonds. This is followed by discussion of atom-economic addition reactions (Section V) and versatile catalytic systems based on N-heterocyclic carbenes as ligands (Section VI).

The study of oxidative cross-coupling (cross-dehydrogenative coupling, CDC reaction) is among the key lines of research in organic chemistry. As a rule, these are reactions in which two different molecules are linked by a new bond, each giving off a hydrogen atom. The oxidative cross-coupling provides the formation of a new bond with almost the maximum possible atom efficiency and does not require additional synthetic steps of introduction of functional groups that are necessary for other approaches to cross-coupling (Hal, OTf, BR_2, SiR_3, SnR_3, ZnHal). Thus, oxidative coupling is a promising approach to decreasing the amount of by-products and decreasing the number of steps of the organic synthesis.[151–154] The key problem faced by implementation of the oxidative coupling is to ensure the process selectivity and minimize the side oxidation reactions.

The oxidative coupling processes are of not only practical but also of considerable fundamental interest for research. Implementation of these processes requires the discovery of new aspects of reactivity of organic compounds, invention of new oxidative systems and study of their properties, and accurate choice of reaction conditions.

Among oxidative cross-coupling reactions, C–C coupling has been studied most comprehensively, while C–O coupling has been less studied.[151–154] Performing the oxidative C–O cross-coupling is a challenging task due to some features of the chemical behaviour of the O-components used for coupling. A new C–O bond may be formed from O-nucleophile, O-electrophile or O-radical. Most compounds containing an OH group (O-components) have rather low nucleophilicity, especially in neutral or acidic medium in which most oxidative systems used for coupling are reactive. O-Electrophiles are rarely used in reactions giving a C–O bond between two molecules, being represented by peroxides having specific structure such as (*p*-nitrophenyl)sulfonyl peroxide[155] and benzoyl peroxide[156] — reactions with these compounds are beyond the scope of this Section of the review. O-Radicals are usually generated under drastic conditions, they are highly reactive and unstable; reactions involving O-radicals are often nonselective and are accompanied by the formation of alcohols, carbonyl compounds and fragmentation products.

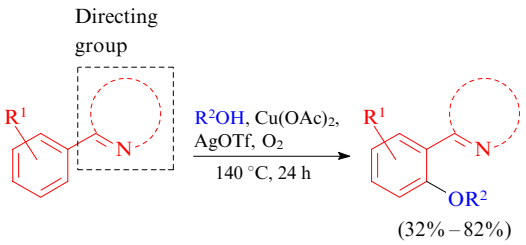
IV.1. Formation of the carbon–oxygen bond

Alcohols or carboxylic acids are used most often as the O-components for the C–O coupling; coupling reactions with sulfonic acids, hydroxylamine derivatives and perox-

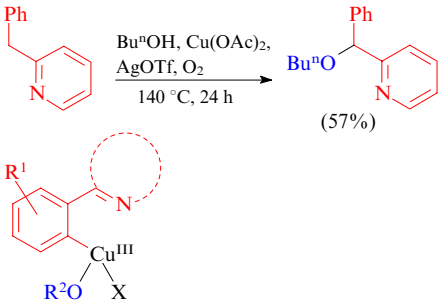
ides are also encountered. The C-components are represented by compounds containing directing functional groups (amide, nitrile, heteroaromatic, oxime or azo group) and by substrates containing activated C–H bonds (carbonyl compounds, ethers, compounds with benzyl or allyl moiety). By directing group is meant a functional group that facilitates the oxidative coupling and determines its regioselectivity (for example, by means of complexation with the metal catalyst) but is not changed itself during the reaction.

An example of using the pyridine moiety as the directing group for oxidative alkoxylation of aryl and benzyl CH groups is presented in Scheme 36.[157] Presumably, the copper ion is inserted into the C–H bond of the aromatic ring, the Cu^{II} complex thus formed is oxidized by silver(I) ions to a Cu^{III} complex and the C–O bond is formed upon reductive elimination. The drawbacks of the method are the use of large amounts of silver triflate and alcohol (serving as the solvent) and high temperature of the synthesis.

Scheme 36



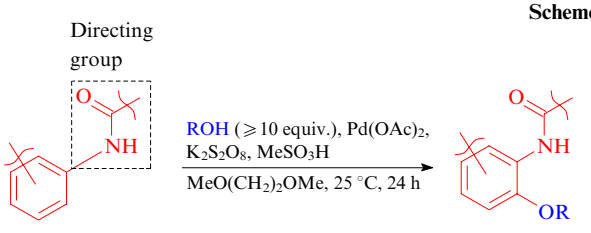
R^2 = Et, Bu^n, Pr^i, CH_2All, CH_2Bn, $(CH_2)_2OMe$, *etc.*



Presumed intermediate

Some reactions of arene acetoxylation and alkoxylation are catalyzed by $Pd(OAc)_2$, suitable oxidants include $K_2S_2O_8$, potassium peroxymonosulfate (oxone, $KHSO_5 \cdot 0.5\ KHSO_4 \cdot 0.5\ K_2SO_4$), $PhI(OAc)_2$, and an oxime, amide, *N*-alkoxyamide, nitrile or azo moiety can serve as the directing group. For example, oxidative coupling of anilides with alcohols has been performed under the action of the $Pd(OAc)_2 - MeSO_3H - K_2S_2O_8$ system

Scheme 37

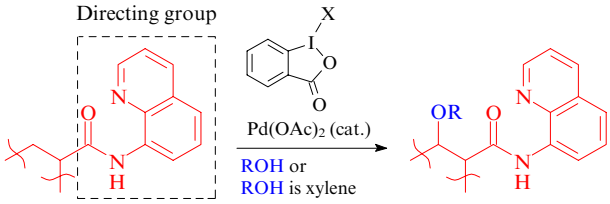


R = n-Alk, cyclo-Alk, $(CH_2)_2Cl$, $(CH_2)_2OMe$

(Scheme 37, here and below in this Section, fragments of reactant and product molecules are shown).[158] Presumably, reactions proceed through the formation of intermediates with the C–Pd–OR moiety, which undergo reductive elimination to give the C–O coupling product. A general drawback of the method is the use of an excess of the O-component of coupling, which makes this approach unsuitable for coupling involving alcohols or acids with complex structures.

In the presence of directing groups, the alkyl groups of the molecule can be involved in oxidative coupling with alcohols or carboxylic acids. An example is alkoxylation of *N*-(quinolin-8-yl)amides under the action of iodine(III) catalyzed by palladium acetate (Scheme 38).[159] Primary, secondary and tertiary alcohols, including those containing functional groups can be involved in this reaction, the yields being up to 91%. A drawback of the method is the use of an excess of the alcohol and the directing group of a complex structure.

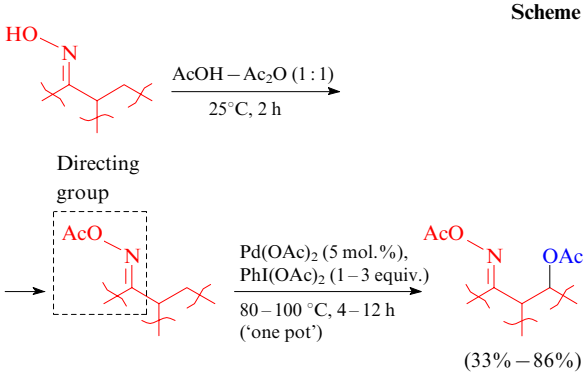
Scheme 38



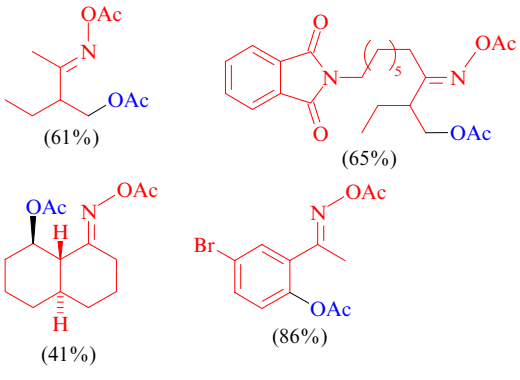
X = OMe, OAc

Related acetoxylation of alkyl and aryl CH fragments of *O*-acetyl oximes is induced by the $Pd(OAc)_2 - PhI(OAc)_2$ system in an $AcOH - Ac_2O$ mixture (Scheme 39).[160] The acylation of the oxime and CH-acetoxylation are conducted

Scheme 39



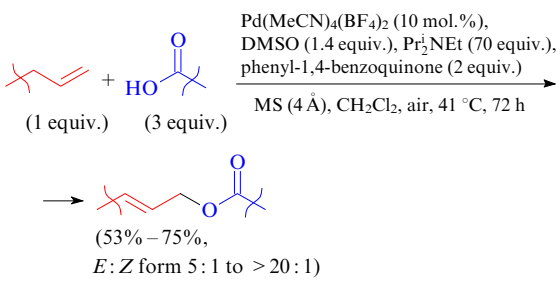
Examples of obtained products (in parentheses are the yields)



as a one-pot process without isolation of the intermediate product. In the acetoxylation of alkyl groups, the CH_3 group is more reactive.

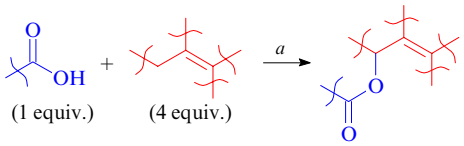
A large series of studies are devoted to the oxidative coupling of alkenes and carboxylic acids catalyzed by palladium complexes to give allyl esters. Presumably, this reaction proceeds *via* a π-allylic palladium complex; simple acids (*e.g.*, acetic) in a large excess with respect to the alkene are used for coupling. Selective synthesis of linear allylic esters by coupling of terminal alkenes with complex carboxylic acids was reported (Scheme 40).[161] The *Z*-isomer of the linear ester and branched allylic ester are formed as by-products.

Scheme 40



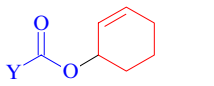
The oxidative C–O coupling of alkenes with carboxylic acids can also be performed by the $Bu^n_4NI-Bu^tOOH$ system (Scheme 41).[162] Apparently, the reaction proceeds by a radical mechanism comprising abstraction of a hydrogen atom from the allylic position of the alkene by *tert*-butylperoxyl or *tert*-butoxyl radical. The reaction is carried out with an excess of alkene; similarly to the coupling of alkenes, coupling involving the benzylic position of alkylarenes also takes place.[162, 163]

Scheme 41

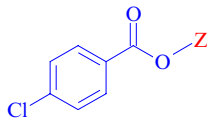


(*a*) Bu^n_4NI (20 mol.%), Bu^tOOH (70% aq.) (1.5 equiv.), PhH, 80 °C, 8 h

Examples of obtained products



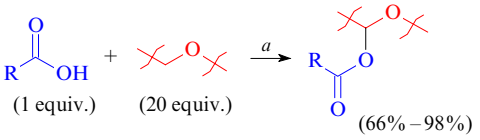
Y = 2-MeC_6H_4 (89%), cyclo-C_3H_5 (79%), CH_2Bn (80%), CH_2NHBoc (67%)



Z = Bn (23%), thNaph (85%), $CH_2C(Me)=CPh_2$ (98%), $CH_2CH=C_6H_{10}$-cyclo (72%)
(thNaph is 1,2,3,4-tetrahydro-1-naphthyl)

The $Bu^n_4NI-Bu^tOOH$ system proved to be also efficient in the oxidative C–O coupling of ethers with carboxylic acids (Scheme 42).[164] The coupling was carried out with low-molecular-mass ethers taken in a 20-fold excess with respect to the acid. It is assumed that the *tert*-butoxyl radical generated in the $Bu^n_4NI-Bu^tOOH$ system detaches a hydrogen atom from the α-position of the ether; the C-radical thus formed is oxidized to the carbocation, which reacts with the carboxylate anion to give the coupling product.

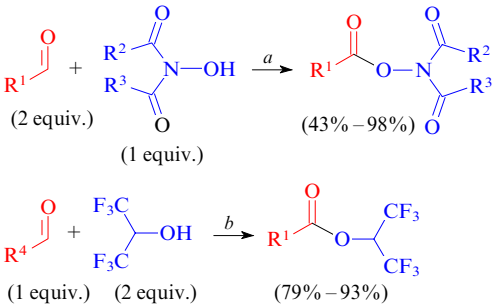
Scheme 42



R = Ar, Het, PhCH=CH, $BnCH_2$, n-$C_{15}H_{31}$;
(*a*) Bu^n_4NI (20 mol.%), Bu^tOOH (70% aq.) (2.2 equiv.), EtOAc, 80°C, 12 h

In many oxidative coupling reactions, aldehydes are used as the C-components. For example, C–O coupling of aldehydes with *N*-hydroxyimides and hexafluoroisopropyl alcohol induced by $Bu^n_4NHal-Bu^tOOH$ systems (Hal = I or Br, Scheme 43) was reported;[165] the coupling products readily react under mild conditions with alcohols or amines to give esters or amides, respectively. One of the coupling components is used in a twofold excess. In other publications, I_2, iodine(III) organic compounds, systems based on transition metal salts or N-heterocyclic carbenes served as oxidants to perform these transformations with aldehydes or alcohols giving esters.

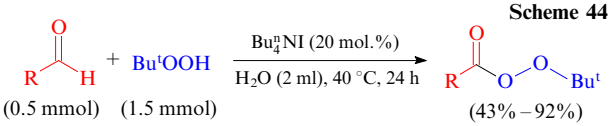
Scheme 43



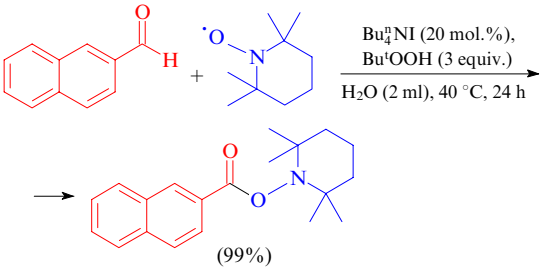
R^1 = Ar, Het, 4-$ClC_6H_4CH=CH$, PhCH=CBr, Bu^t;
R^2-R^3 = CH_2CH_2, *o*-phenylene; R^4 = Ar, PhCH=CBr;
(*a*) Bu^n_4NI (10 mol.%) or Bu^n_4NBr (10 mol.%), Bu^tOOH (5.5 M decane solution) (2 equiv); EtOAc, 70 °C, 7–12 h;
(*b*) Bu^n_4NI (10 mol.%), Bu^tOOH (5.5 M decane solution) (2 equiv.), EtOAc, 70 °C, 6 h

The $Bu^n_4NI-Bu^tOOH$ system can also serve for the oxidative coupling of aldehydes with Bu^tOOH (Scheme 44). The *tert*-butyl peroxy esters thus formed find use in the functionalization of the allylic position of alkenes to give

Scheme 44

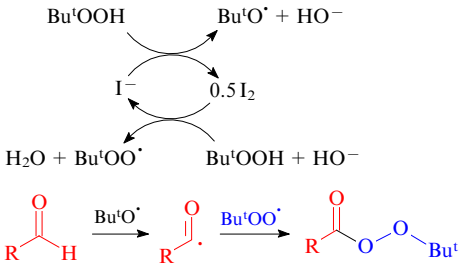


R = Ar, Cy



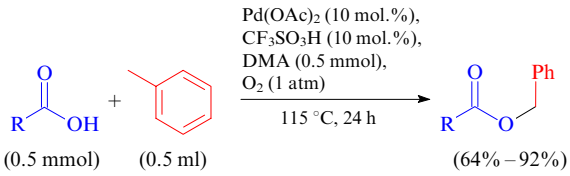
allylic esters by the Kharasch–Sosnovsky reaction.[166] Presumably, *tert*-butylperoxy esters are formed upon recombination of acyl and *tert*-butylperoxyl radicals (Scheme 45). The radical reaction mechanism is confirmed by the experiment in which the acyl radicals were trapped by TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl radical) (see Scheme 44).

Scheme 45



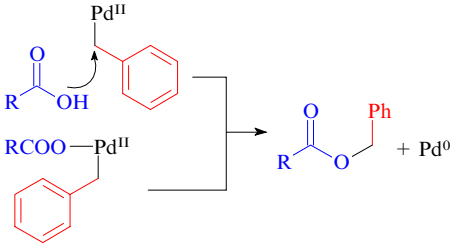
Yet another class of C-components used in the oxidative C–O coupling are alkylarenes. Under the action of the Pd(OAc)$_2$–CF$_3$SO$_3$H–DMA–O$_2$ system (DMA is dimethylacetamide), benzylation of aryl-, alkyl- and cycloalkylcarboxylic acids takes place; the reaction is carried out in toluene (Scheme 46).[167] Probably, the process occurs by an ionic mechanism in which the toluene C–H bond is cleaved under the action of Pd^{II}. The product is formed either upon nucleophilic attack of the Pd^{II} complex by the carboxylic acid or upon reductive elimination (see Scheme 46). Presumably, the role of dimethylacetamide is reduced to promotion of Pd^0 reoxidation to Pd^{II} with oxygen and suppression of Pd^0 aggregation, while trifluorometanesulfonic acid facilitates the C–H bond cleavage in toluene *via* the formation of Pd^{II} cationic compounds.[167]

Scheme 46



R = Ar, PhCH=CH, 4-FC$_6$H$_4$CH$_2$, n-C$_7$H$_{15}$, cyclo-C$_3$H$_5$, Cy

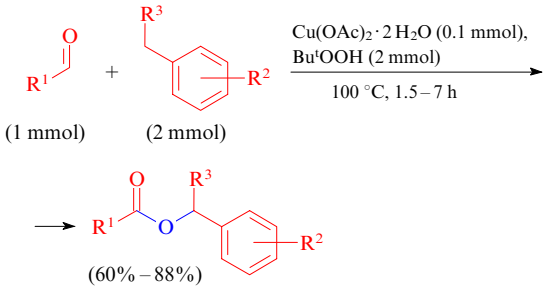
Possible ways of C–O bond formation



The oxidative coupling of diarylmetthanes with carboxylic acids is induced by MnO$_2$ in the presence of a catalytic amount of DDQ. It is assumed that DDQ oxidizes diarylmethanes to diarylmethyl cations, which react with carboxylic acids to give esters. Manganese dioxide serves for oxidation of the reduced form of the catalyst to DDQ. A drawback of the method is that it requires the presence of two aryl moieties at the reaction centre of the C-component of coupling and the use of a four-fold excess of the carboxylic acid (O-component).[168] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone is used in some other oxidative C–O coupling reactions involving alcohols, phenols, thiols, carboxylic acids[168] and oximes as nucleophilic O-components and ArCH=CHCH$_2$R or ArC≡CCH$_2$ R with the activated allylic or propargylic position as C-components.

Using the Cu(OAc)$_2$–Bu^{t}OOH system, oxidative C–O coupling of aldehydes with alkylarenes was performed (Scheme 47).[169] A specific feature of this coupling is the formation of two C–O bonds and cleavage of two C–H bonds; the same type of coupling of methyl- and ethylarenes with aromatic aldehydes was accomplished on treatment with the Bu$^n_4$NI–Bu^{t}OOH system using an excess of either alkylarene or aldehyde.[170]

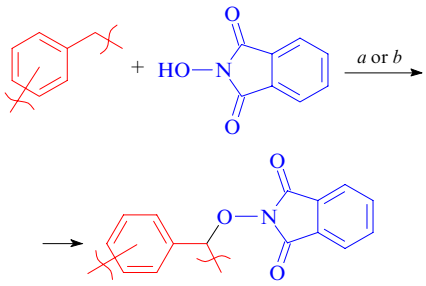
Scheme 47



R^1 = Ar, 2-Th, PhCH=CH, Cy; R^2 = Me, Cl; R^3 = H, Me;
Th is thienyl

The oxidative C–O coupling of alkylarenes and related compounds with *N*-hydroxyphthalimide was carried out with the CuCl–PhI(OAc)$_2$ (Ref. 171) or (NH$_4$)$_2$Ce(NO$_3$)$_6$ (Ref. 172) oxidants (Scheme 48). The CuCl–PhI(OAc)$_2$ system provides somewhat higher yields of coupling products than (NH$_4$)$_2$Ce(NO$_3$)$_6$ but requires higher temperature and longer duration of the synthesis. Apparently, the C–O bond is formed upon recombination of benzyl and phthalimide-*N*-oxyl radicals, while side recombination of the benzyl radicals with each other and oxidation of benzyl radicals to give alcohols and carbonyl compounds can be avoided; however, for attaining high yields, alkylarenes are taken in excess. Coupling of *N*-hydroxyphthalimide with ethers and alkenes proceeds in a similar way.[171]

Scheme 48

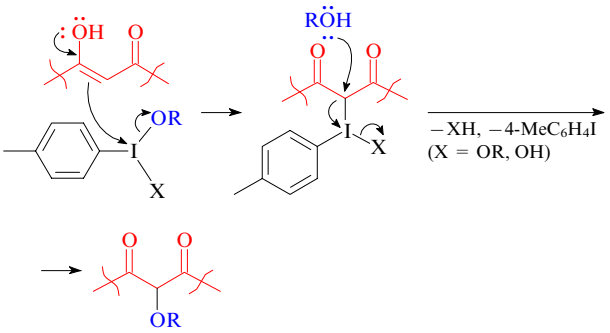


(*a*) CuCl–PhI(OAc)$_2$, 70 °C, 12 h;
(*b*) (NH$_4$)$_2$Ce(NO$_3$)$_6$, 20–25 °C, 30 min

Most of oxidative C–O coupling reactions involving the α-position of carbonyl compounds utilize iodo-containing oxidants. Most often, organic compounds of iodine(III) are used, including those generated *in situ* from aryl iodides and carboxylic peroxyacids such as *m*-chloroperoxybenzoic

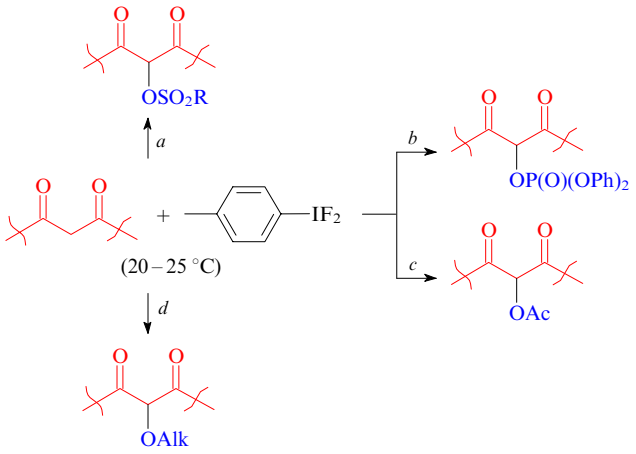
and peroxyacetic acids. These processes follow an ionic mechanism: the electrophilic iodine atom attacks the enol derived from the dicarbonyl compound; then the O-nucleophile replaces the iodine-containing group to give the C–O-coupling product (Scheme 49).

Scheme 49



Indeed, *p*-(difluoroiodo)toluene induces the oxidative coupling of β-dicarbonyl compounds with various OH-reagents: sulfonic and carboxylic acids, diphenyl hydrogen phosphate and alcohols (Scheme 50).[173]

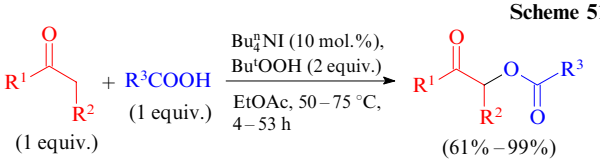
Scheme 50



(*a*) RSO_3H (R = Me, 4-MeC_6H_4), 5–30 min; (*b*) $(PhO)_2P(O)OH$, 15–20 min; (*c*) AcOH, 15–80 min; (*d*) AlkOH (Alk = Me, Et, Pr^i), 0.5–24 h

Good results were obtained in the oxidative C–O coupling of ketones or aldehydes with carboxylic acids induced by the Bu^n_4NI–Bu^tOOH system (Scheme 51).[174] *tert*-Butyl hydroperoxide is a convenient and safe oxidant, the coupling reaction proceeding with high yields for a broad range of substrates; the C- and O-components for the coupling are taken in 1 : 1 ratio. Aldehydes react similarly to ketones, the proper aldehyde group being retained unchanged. The reaction is assumed to follow a radical mechanism.[174]

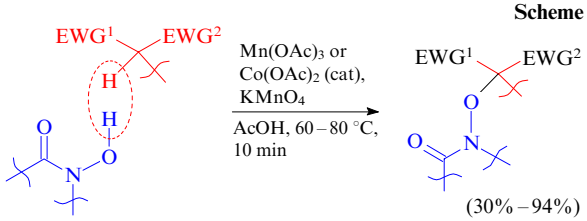
Scheme 51



R^1 = H, Ar, Het, Me, OMe; R^2 $$ Alk, Ph, Bn, Ac, CO_2Alk, *etc.*; R^3 = Me, Ar, alkenyl

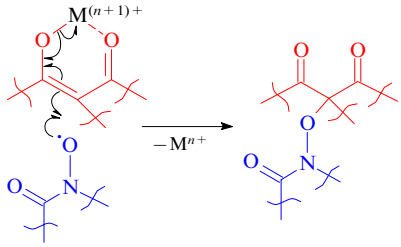
N-Hydroxyimides and *N*-hydroxyamides enter into the oxidative C–O coupling with 1,3-dicarbonyl compounds and their heteroanalogues, 2-substituted malononitriles and ethyl cyanoacetates, under the action of manganese-, cobalt- and cerium-based oxidants.[175] The best results were obtained with $Mn(OAc)_3$ and the $Co(OAc)_2$(cat.)–$KMnO_4$ system; the product yields are up to 94% without the need of using excesses of reactants (Scheme 52). The formation of imide-*N*-oxyl radicals during oxidative coupling was detected by EPR spectroscopy. Presumably, the oxidizing metal performs two functions: generation of the *N*-oxyl radicals from *N*-hydroxyimides or *N*-hydroxyamides and one-electron oxidation of 1,3-dicarbonyl compounds.

Scheme 52



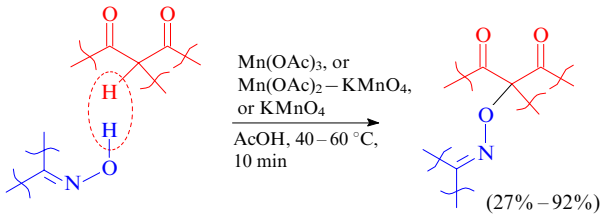
EWG^1, EWG^2 = CO_2Et, Ac, CN

Presumed pathway of C–O bond formation

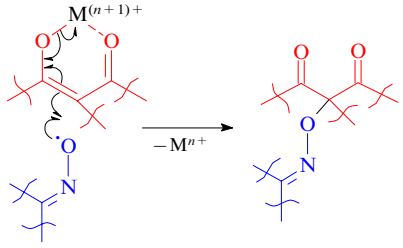


Recently, oxidative coupling of 1,3-dicarbonyl compounds with oximes, which apparently follows a similar mechanism, was documented (Scheme 53).[176] The reaction is induced by the oxidants $KMnO_4$, $Mn(OAc)_2$–$KMnO_4$, $Mn(OAc)_3 \cdot 2H_2O$, MnO_2, $Mn(acac)_3$ (acac is acetylacetonate), $Fe(ClO_4)_3$, $Cu(ClO_4)_2 \cdot 6H_2O$, $Cu(NO_3)_2 \cdot 2.5H_2O$ or $(NH_4)_2Ce(NO_3)_6$. Using $KMnO_4$, $Mn(OAc)_3 \cdot 2H_2O$ or the

Scheme 53



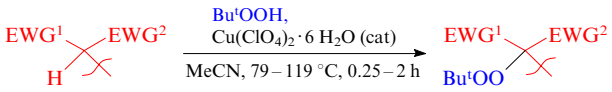
Presumed pathway of C–O bond formation



$Mn(OAc)_2-KMnO_4$ system, twenty coupling products were synthesized in 27%–92% yields. The formation of iminoxyl radicals from oximes was proved by EPR spectroscopy. This reaction is the first example of a selective intermolecular reaction involving unstable iminoxyl radicals generated *in situ*.

Apparently, the oxidative coupling of 1,3-dicarbonyl compounds[177] and their heteroanalogues[178] with *tert*-butyl hydroperoxide catalyzed by transition metal (Cu, Fe, Co, Mn) salts proceeds by a similar mechanism. *tert*-Butyl hydroperoxide functions as an oxidant and the O-component for coupling, and the best results were achieved using $Cu(ClO_4)_2\cdot 6H_2O$ as the catalyst (Scheme 54).

Scheme 54

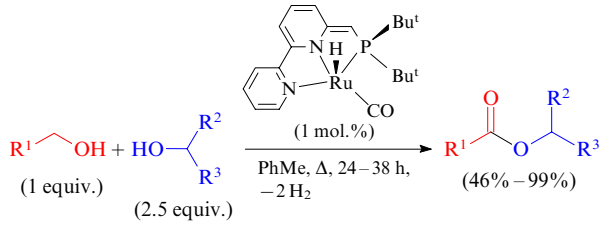


(37%–94%)

EWG^1, EWG^2 = CO_2Et, Ac, CN

Unusual oxidative C–O cross-coupling of primary alcohols with secondary alcohols to give esters without using an oxidant was performed with a ruthenium complex as the catalyst and was accompanied by evolution of molecular hydrogen (Scheme 55).[179]

Scheme 55



(46%–99%)

The cross-coupling products were obtained in high yields despite the possibility of homocoupling of primary alcohols to give symmetric esters and dehydrogenation of secondary alcohols to give ketones.

Thus, the oxidative cross-coupling is currently one of the most actively developing areas of organic chemistry. The oxidative C–O cross-coupling is now relatively little studied, although the C–O–R group is encountered in organic molecules of a variety of classes and a lot of structurally diverse possible O-components for the coupling are known.

The key drawback of most of the existing methods of oxidative C–O coupling is the use of an excess of one of the reactants, either the C- or O-component. These methods are inapplicable for coupling of two valuable complex compounds. Moreover, the reaction is usually conducted at elevated temperatures for long periods of time.

The major tasks in the strategy of the oxidative C–O coupling are to extend the range of eligible substrates; develop methods based on accessible, convenient and safe oxidative systems; develop methods for coupling of C- and O-components without using an excess of either of them; lower the reaction temperature and decrease the reaction time.

V. Catalytic atom-economic addition reactions

As has already been noted, the modern trends of planning organic synthesis are directed at the development of effective, practically convenient and environmentally friendly methods for the preparation of new organic compounds. Particular attention is paid to waste disposal problems and purification of the desired products, decrease in the amounts of catalysts used and search for alternatives to traditional organic solvents. Therefore, most promising are methods for the synthesis of organic compounds that have 100% atom efficiency (atom-economic reactions)[4,180] where all atoms of the starting compounds constitute the product. The use of both homogeneous and heterogeneous catalysts increases the yield of the desired product and makes chemical transformations highly selective.

Catalytic atom-economic addition reactions are currently a versatile synthetic approach for the formation of C–B, C–O, C–N, C– Si, C–P, C–Se, C–Sn, C–Te and some other bonds.[181–183] As a particular example of the development of this strategy, we will consider the preparation of organophosphorus compounds, which are of high demand in modern organic and biomedical chemistry.

Among methods for the synthesis of compounds with carbon–phosphorus bonds,[184–186] the atom-economic addition reactions of substrates with a phosphorus–hydrogen bond to unsaturated compounds (alkenes, dienes, alkynes, diynes) are now significant.

Some early investigations in this field were devoted to non-catalytic addition reactions to triple bonds of alkynes resulting in the formation of a mixture of isomeric (*Z* and *E*) linear adducts.[187,188] Unfortunately, low yields of the desired products, drastic reaction conditions and moderate selectivity inevitably deteriorate the versatility of this synthetic approach. The use of transition metal complexes (Pd, Ni, Rh and so on) to catalyze the addition reactions has become the turning point that laid the firm foundation for a new promising strategy of the synthesis of various adducts with the C–P bond. Using catalytic amounts of these complexes (< 10 mol.%), it is possible to perform these reactions under mild conditions with quantitative yields of desired products and high regio- and stereoselectivity. Studies of these processes in Russian and foreign laboratories brought about considerable progress in the development of effective methods for the synthesis of new phosphorus compounds.[183,189–193] Thus, development of new multipurpose highly effective catalytic systems is a topical primary task, the solution of which determines the success of application of this synthetic approach for selective synthesis of compounds with a $C-P^V$ bond.

As a conceptual example, we survey the addition of H-phosphonates $(RO)_2P(O)H$, secondary phosphine oxides $R_2P(O)H$, hypophosphites $(RO)P(O)H_2$ and H-phosphinates $(RO)(R')P(O)H$ to alkynes. Comparative analysis of phosphorus substrates with the P–H bond clearly demonstrates the possibility of fine optimization of catalytic systems to control the process selectivity.

V.1. Selective hydrophosphorylation, hydrophosphinylation and hydrophosphonylation of alkynes

V.1.a. The addition of H-phosphonates $(RO)_2P(O)H$ (hydrophosphorylation)

The first example of catalytic alkyne hydrophosphorylation has been known since 1996 and implies the use of palladium

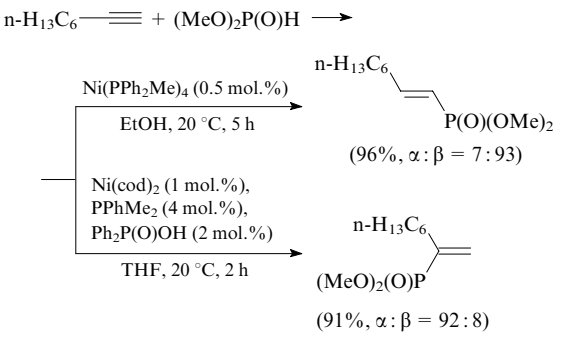
phosphine complexes.[194] A considerable part of synthetic procedures published later also used various Pd phosphine complexes as catalysts and provided branched alkenylphosphonates (α-isomers).[195–197]

Successful use of rhodium complexes for catalytic hydrophosphorylation of alkynes giving selectively only the linear β-*E*-isomer was demonstrated for some examples. This difference of the selectivity of addition in the presence of complexes of different metals (Pd and Rh) was attributed to differences at the step of alkyne insertion, which involves the Pd–P bond in one case and the Rh–H bond in the other case. However, in both cases, the reaction proceeds as *syn*-addition. Thus, Pd- and Rh-catalyzed hydrophosphorylations of alkynes supplement each other, thus enabling the selective synthesis of isomeric α- and β-*E*-alkenylphosphonates, respectively.[198, 199]

A recently developed procedure allows controlling the selectivity of Pd-catalyzed reaction, which can be used to synthesize both branched (α-) and linear (β-*E*-) products.[200] The control of the selectivity was achieved by deliberate modification of the coordination sphere of palladium intermediates by choosing the appropriate ligand out of the series $P\{(MeO)_nC_6H_{5-n}\}_3$.[200] This approach to the regioselectivity control has no analogues among reactions of this type.

In 2004, a study of alkyne hydrophosphorylation catalyzed by nickel complexes was published,[201] being concerned with the effect of diphenylphosphinic acid [$Ph_2P(O)OH$] on the reaction regioselectivity with the use of Ni systems with different phosphorus ligands (Scheme 56). Unfortunately, in this case, it is impossible to identify the key factor responsible for the regioselectivity of addition, because the reactions were carried out in different solvents (THF, ethanol) with addition of the acid [$Ph_2P(O)OH$] and without the acid using various catalyst precursors and ligands of various nature (PPh_2Me and $PPhMe_2$) (see Scheme 56).[201] The authors also did not present the interpretation of the regioselectivity change from the standpoint of the reaction mechanism.

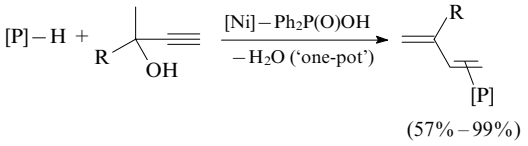
Scheme 56



Note that a similar effect of the $Ph_2P(O)OH$ additive was also observed for the Ni-catalyzed addition to alkynes of other P^V-H substrates — Ph(EtO)P(O)H and $Ph_2P(O)H$.[201] However, in these cases, too, the factor responsible for the control of regioselectivity remained unidentified for the above-indicated reasons. Moreover, commercially available diphenylphosphine oxide [$Ph_2P(O)H$] used by the researchers[201] contains, as a rule, a noticeable amount of the acid $Ph_2P(O)OH$ formed upon oxidation. Therefore, study of the effect of the acid on alkyne hydrophosphinylation with diphenylphosphine oxide requires thorough purification of this P^V-H substrate. Unfortunately, the researchers did not describe the purification of $Ph_2P(O)H$ before the reaction.

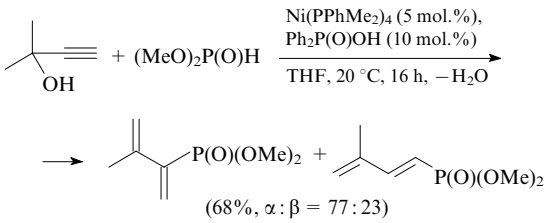
Subsequently, the [Ni]–$Ph_2P(O)OH$ catalytic system was used in the reaction of propargyl alcohols with various P^V-H substrates [H-phosphonates, H-phosphinates and $Ph_2P(O)H$], which made it possible to obtain phosphinoyl-1,3-dienes in high yields (Schemes 57 and 58).[202]

Scheme 57



[P]–H = $(MeO)_2P(O)H$, $Ph_2P(O)H$, Ph(EtO)P(O)H;
R = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$Me_2NC_6H_4$, *etc.*

Scheme 58



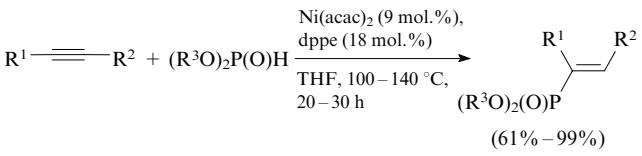
A more detailed comparative analysis of published data (see Schemes 56 and 58)[201, 202] discloses some contradictions in the presented results and brings about some questions. Indeed, earlier the same authors demonstrated[201] the possibility of hydrophosphorylation of oct-1-yne with dimethylphosphite on a nickel catalyst (see Scheme 56); however, only 1 mol.% of the nickel-containing catalyst precursor was used, whereas in the reaction of dimethyl phosphite with 2-methylbut-3-yn-2- ol (see Scheme 58), the amount of the catalyst precursor was 5 mol.%.

In addition, in the latter case, the reaction was carried out for 16 h rather than for 2 h as the reaction with oct-1-yne. It can hardly be conceived that the presence of the hydroxy group in the aliphatic moiety at the triple bond can have so adverse effect on the addition reactions and can require a 5 times greater amount of the catalyst for a 8 times longer reaction time. One more fact is noteworthy, in particular, in this synthetic procedure, the authors use 10 mol.% $Ph_2P(O)OH$ (see Scheme 58) instead of 2 mol.% used earlier (see Scheme 56) but the product yield was much lower in this case: 68% and 91%, respectively. Note that in the presence of 10 mol.% $Ph_2P(O)OH$, the regioselectivity is lower: the content of the α-isomer is only 77%, while in the presence of 2 mol.% $Ph_2P(O)OH$, it is 92% (see Schemes 56 and 58).[201, 202] The use of different amounts of the catalyst precursor and contradictory data on the effect of acid addition on the regioselectivity with the alkyne structure being varied preclude drawing unambiguous conclusions about the general applicability of the [Ni]–$PPhMe_2$–$Ph_2P(O)OH$ system proposed by the authors to hydrophosphorylation of terminal alkynes.

A procedure of alkyne hydrophosphorylation using inexpensive and oxygen- and air moisture-stable $Ni(acac)_2$ as the catalyst precursor was developed in 2010.[203] With this nickel complex, the catalytic reaction can be carried out without addition of the acid with no decrease in the yield or

selectivity. The addition of H-phosphonates with various substituents to terminal and internal alkynes was accomplished with high regio- and stereoselectivity (Scheme 59).

Scheme 59

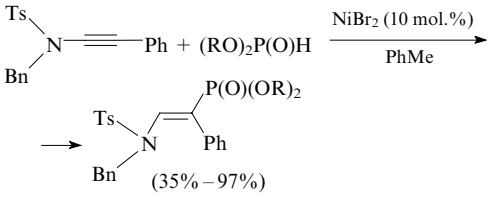


$R^1 = R^2 = Ph$, Et; $R^2 = H$: R^1 = n-C_5H_{11}, $NC(CH_2)_3$, Ph; R^3 = Pr^i, n-$C_{12}H_{25}$, Bn, Ph; R^3-R^3 = CH(Me)CH(Me); dppe = $Ph_2P(CH_2)_2PPh_2$

The mechanism of catalytic hydrophosphorylation of alkynes was examined using quantum chemical calculations.[204] Comparative analysis was done for the two alternative pathways of alkyne insertion either at the metal–phosphorus bond or at the metal–hydrogen bond. It was demonstrated for the first time that alkyne can be inserted much more readily into the M–H bond than into the M–P bond. The same publication [204] demonstrated that the catalytic hydrophosphorylation of internal alkynes can, in principle, occur without a phosphine ligand.

Yet another vivid example of nickel-catalyzed hydrophosphorylation is the addition of H-phosphonates to ynamides.[205] The best result was achieved with $NiBr_2$ (10 mol.%) (Scheme 60).

Scheme 60



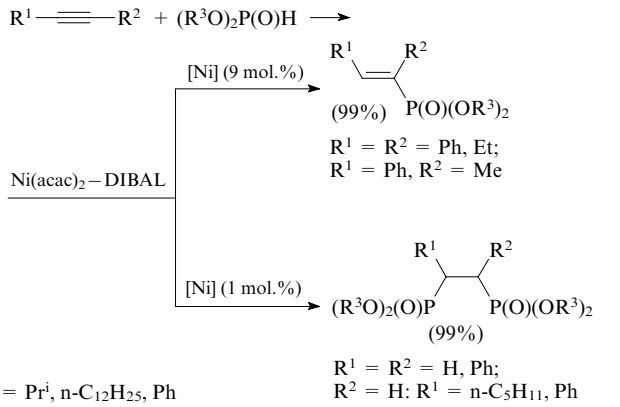
R = Me, Et, Pr^i

The current trend of going from palladium to nickel catalysts is attributable, first of all, to the economic factor, *i.e.*, high cost of palladium compounds. Also, some organic nickel derivatives [for example, $Ni(acac)_2$] are attractive from the practical standpoint, as they are air stable, can be stored for long without the loss of activity, whereas some palladium compounds have low stability even in the solid state [for example, $Pd_2(dba)_3$, dba is dibenzylideneacetone].[206]

Recently, high catalytic activity of the system $Ni(acac)_2$–DIBAL (DIBAL = Bu^i_2AlH) in the hydrophosphorylation of terminal and internal alkynes was found and explored.[207] The hydrophosphorylation proceeds without a solvent and does not require the use of phosphine ligands or acid additives. The $Ni(acac)_2$–DIBAL system provides a unique possibility for controlling the selectivity by changing the amount of $Ni(acac)_2$ (1 mol.% or 9 mol.%): either mono- or 1,2-bis-phosphonate can be obtained in a quantitative yield (Scheme 61).

To date, only a few publications have been devoted to the catalytic hydrophosphorylation of diynes.[194, 198, 208] In the presence of palladium [194, 208] and rhodium [198] catalysts, addition of simple aliphatic H-phosphonates [$(MeO)_2P(O)H$,[194, 208] (cyclo-$OCMe_2CMe_2OP)(O)H$ [198, 208] and $(EtO)_2P(O)H$ [208]] was performed to give α- and β-adducts and cyclic vinylphosphonate derivatives.

Scheme 61

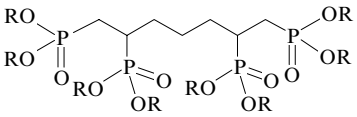


R^3 = Pr^i, n-$C_{12}H_{25}$, Ph

The moderate number of publications is due to low reactivity of diynes in hydrophosphorylation. The $Ni(acac)_2$–dppe-based catalyst, which showed high efficiency in the hydrophosphorylation of hept-1-yne,[203] proved to be inefficient for hepta-1,6-diyne.[209] Evidently, the substantially lower reactivity of diynes compared to alkynes is due to the presence of the second triple bond in the molecule; however, the cause of this unexpected phenomenon is still unclear.

In 2013, hydrophosphorylation of a number of diynes was accomplished in the presence of a nickel catalyst.[209] The $Ni(acac)_2$–DIBAL catalytic system described above [207] provided the formation of alkyltetraphosphonates **21** upon the addition of H-phosphonates of different nature to diynes. The products were obtained in good (up to 91%) yields. This work was the first example of the synthesis of alkyltetraphosphonates by the catalytic reaction of H-phosphonates with diynes.[209]

Structures 21



21

R = Et, Pr^i, Ph

V.1.b. The addition of secondary phosphine oxides $R_2P(O)H$ (hydrophosphinylation)

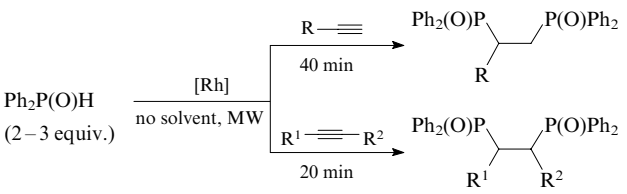
As in the case of hydrophosphorylation, studies of the catalytic hydrophosphinylation of acetylene hydrocarbons were started in the second half of the 1990s. The development of both reactions was pursued in parallel, both similar and distinctive features being revealed in the course of studies.

Commercially available H-phosphonates are represented by a series of inexpensive compounds, while the marketed secondary phosphine oxides are limited to only a few expensive P^V–H substrates of this class. Among these, diphenylphosphine oxide has the lowest cost, but still it is tens and sometimes hundreds times more expensive than H-phosphonates. Furthermore, as has already been noted, commercial $Ph_2P(O)H$ contains, most often, noticeable quantities of the acid $Ph_2P(O)OH$; therefore, thorough preliminary purification of this reagent is required, which

increases the duration and the cost of the whole synthetic procedure. Nevertheless, there are several examples of reported catalytic addition reactions of commercial $Ph_2P(O)H$ to acetylene hydrocarbons.[201, 202, 210–215] Complexes of various metals (Pd, Rh, Ni, Cu) were used as catalysts. Analysis of published data shows that many characteristic features of hydrophosphorylation reactions are also observed for hydrophosphinylation. The use of nickel catalysts for this class of reactions was discussed above.[201, 202]

It was shown that the Rh complex-catalyzed addition of $Ph_2P(O)H$ to alkynes can proceed without a solvent under microwave irradiation (MW),[213] the reaction time in this case being decreased to several minutes. This reaction, like all the processes involving Rh complexes discussed above, gave, with high selectivity, linear β-(*E*)-alkenylphosphine oxides (for terminal alkynes) and *syn*-addition products (for internal alkynes). The possibility of microwave-assisted bis-hydrophosphinylation with 2–3 equivalents of $Ph_2P(O)H$ was demonstrated[213] (Scheme 62).

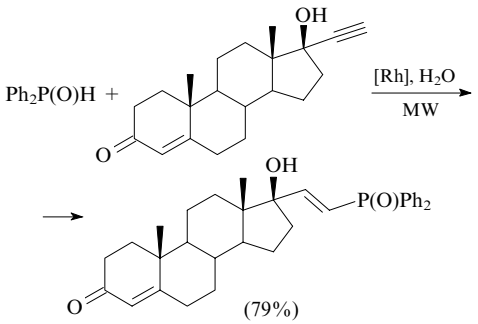
Scheme 62



The same study reports the possibility of using polymer-supported catalysts, which provides regeneration and reuse of the metal complex.[213] This approach to the design of a catalytic system, *i.e.*, the use of microwave radiation, catalyst recycling and the absence of solvent, is consistent with the green chemistry requirements and makes it possible to decrease the expenditures for the synthesis.

Yet another important transformation catalyzed by Rh complexes is the addition of $Ph_2P(O)H$ to the triple bond of ethynylsteroids — microwave-assisted hydrophosphinylation insensitive to air oxygen and moisture.[216] The reaction occurs in water as the solvent and affords a linear (β-*E*-isomer) addition product in good yield (Scheme 63). The use of water is highly untypical for the addition of molecules with a P^V-H bond to alkynes; as a rule, these transformations are adversely sensitive to even traces of water.

Scheme 63

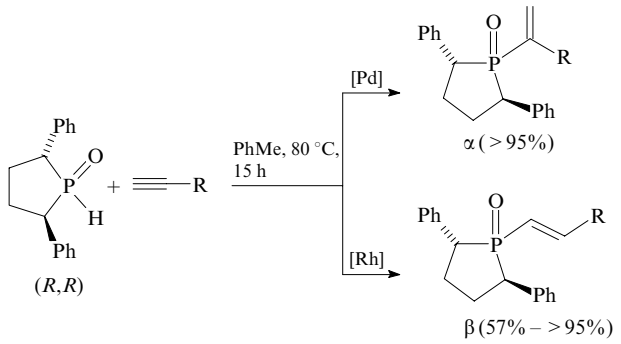


[Rh] = $(Me_2PhP)_3RhMe_3$

Among examples of bis-hydrophosphinylation, mention should be made of the reaction of terminal alkynes with diphenylphosphine oxide in the presence of $Pd(PPh_3)_4$ [217] or binuclear or trinuclear Pd–M catalysts (M = Ti, Zr, Hf); the process occurs under mild conditions (40 °C, 1 h) and gives products in high yields (> 95%).[218]

A recent paper[215] describes the procedure of addition of chiral enantiomerically pure 1*r*-oxo-2c,5*t*-diphenylphospholane to terminal alkynes catalyzed by Pd and Rh complexes. The selective formation of α- and β-*E*-isomers in Pd- and Rh-catalyzed reactions, respectively, was demonstrated (Scheme 64). Unfortunately, although the product yield calculated from NMR data was often higher than 95%, most products were isolated in yields of about 25%–40%, which was attributed by the authors[215] to destruction of the alkenylphosphine oxides on silica gel during chromatography.

Scheme 64

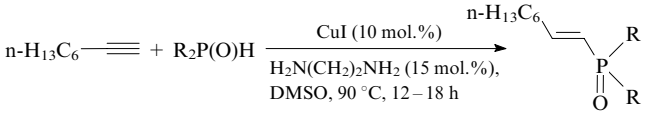


[Pd] = $Pd(PPh_3)_4$, [Rh] = $[Rh(cod)Cl]_2$

The ratio between two alternative processes, namely, regioselective addition to give the α-isomer and bis-hydrophosphinylation, in the reaction of terminal alkynes with $Ph_2P(O)H$ catalyzed by Pd complexes was studied.[219] In the presence of the bidentate dppe ligand, branched α-adducts were formed in good yields (64%–88%) and with high selectivity (95%–99%). When a monodentate ligand was used [P(*o*-Tol)$_2$Ph, *o*-Tol is *o*-tolyl], bis-hydrophosphinylation occurred predominantly to give a reasonable yield (48%) of the corresponding product.

In 2007, alkyne hydrophosphinylation was implemented in the presence of the CuI–1,2-diaminoethane system (Scheme 65).[220] The use of $Ph_2P(O)H$ and $Bn_2P(O)H$ as the P^V-H substrates resulted in the formation of β-alkenylphosphine oxides in good yields and with high stereoselectivity.[220]

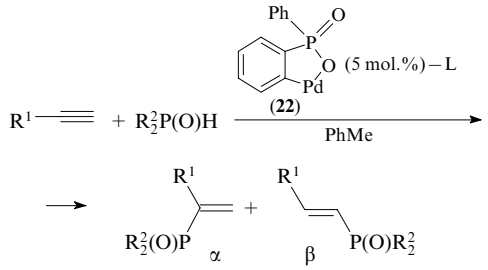
Scheme 65



(R = Ph, 67%; *E*:*Z* = 85:15;
R = Bn, 72%; *E*:*Z* > 99)

In 2011, the first studies were published devoted to the addition of secondary dialkylphosphine oxides to alkynes.[221, 222] Palladium complex **22**, in the presence of bidentate phosphine ligands, catalyzed the addition of the P^V-H substrates (H-phosphonates, H-phosphinates and secondary phosphine oxides) to terminal alkynes.[221] This resulted in the synthesis of a series of α-adducts in quantitative yields with high regioselectivity (Scheme 66).

Scheme 66



R^1	R^2	L	T/°C	Time /h	Yield (%)	α : β
n-C_6H_{13}	Ph	dppp	70	3	99	98 : 2
n-C_6H_{13}	Me	dppp	110	5	99	98 : 2
Bu^t	MeO	dppe	110	25	95	98 : 2
Bu^t	see [a]	dppe	70	19	97	99 : 1

[a] $R^2-R^2 = O(CMe_2)_2O$; dppp = $Ph_2P(CH_2)_3PPh_2$.

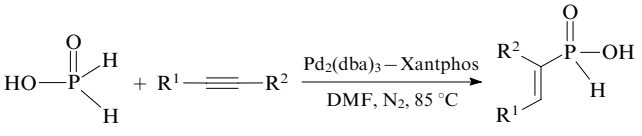
The use of the catalytic system $CpPd(\eta^3\text{-All})$ – dppben – $[3,5\text{-}(CF_3)_2C_6H_3]_2P(O)OH$ [Cp = $Z^5\text{-}C_5H_5$, dppben = 1,2-$(PPh_2)_2C_6H_4$] resulted in the addition of dibutylphosphine oxide to some terminal alkynes and diphenylacetylene.[222]

V.1.c. The addition of hypophosphites $(RO)P(O)H_2$ and H-phosphinates $(RO)(R')P(O)H$ (hydrophosphonylation)

The number of reactions of this class reported in the literature is much less compared to those for hydrophosphorylation and hydrophosphinylation. Effective catalytic systems based on palladium ([Pd] is phosphine ligand) for selective addition of hypophosphites to acetylenic hydrocarbons are known.[223–227] The use of catalytic amounts of $NiCl_2$ provided the addition of alkylphosphinates to terminal and internal alkynes without a phosphine ligand.[228] Unfortunately, in the case of $NiCl_2$, the reaction regioselectivity was lower than in a similar process involving Pd complexes, and hydrophosphonylation of terminal alkynes led to a mixture of α- and β-isomers.

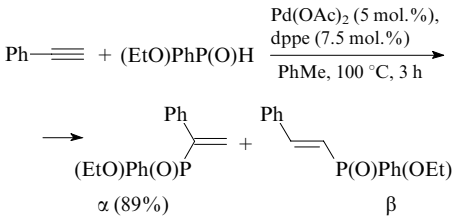
In 2007, a two-step procedure for the synthesis of various phosphonic acids was developed.[229] The first step was the addition of hypophosphorous acid [$HOP(O)H_2$] to the alkyne triple bond to give alkenyl-H-phosphinate (Scheme 67). In the second step, the product was oxidized with air oxygen in dimethylformamide, which gave rise to the corresponding phosphonic acid.

Scheme 67



In the small number of examples of H-phosphinate addition to alkynes, phenyl-H-phosphinates were used in all cases as the P^V-H substrates.[201, 202, 220, 221, 230] It was found that an acceptable selectivity of α-isomer formation in the Pd-catalyzed reaction can be achieved without the addition of acid.[231] Good results were attained by using the $Pd(OAc)_2$ – dppe system as the catalyst (Scheme 68).[231]

Scheme 68



In 2013, Montchamp and co-workers[232] published a study devoted to Pd-catalyzed reactions of phosphorus–carbon bond formation. By using the $Pd(OAc)_2$ – dppf system as the catalyst [dppf is 1,1′-bis(diphenylphosphino)-ferrocene], the addition of various H-phosphinates to internal oct-4-yne was accomplished.

Thus, the addition of P^V-H substrates to the triple carbon–carbon bond is of obvious interest as a tool of hydroheterofunctionalization of organic compounds and opens up broad prospects for the development of effective procedures for the synthesis of valuable $C-P^V$ derivatives. The variation of substituents in one or both reactants (P^V-H-substrate and alkyne) may furnish adducts with a specified structure and properties (polarity, solubility, melting and boiling points). The $C-P^V$ derivatives of various organic compounds find use in important areas of human activity.

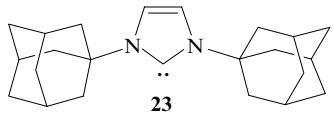
Despite the achievements (see above), many problems in this field of chemistry still remain unsolved. These include: (i) the absence of microwave-assisted synthetic procedures and catalyst recycling methods for catalytic hydrophosphorylations; (ii) rather limited number of substrates for some reactions; (iii) unexpectedly low reactivity of diynes and, as a consequence, few examples of catalytic reactions involving them; (iv) contradictory data obtained for reaction mechanisms; and (v) the absence of procedures for conducting these reactions in 'green' solvents such as polyethylene glycols, ionic liquids or supercritical media.

VI. N-Heterocyclic carbene ligands in homogeneous catalysis

From the previous Sections, it is obvious that appropriate selection of the catalyst plays the key role in the control of the reaction route and for attaining high selectivity. It is the appearance of new ligands that predetermined the success of homogeneous metal complex catalysis in this field of chemistry. This can be exemplified by the use of stable N-heterocyclic carbenes (NHC) as ligands in catalysis.

In the last 20 years, the chemistry of stable carbenes has been an actively developing line of research at the boundary of organic and organometallic chemistry and homogeneous catalysis. In 1991, Arduengo *et al.*[233] demonstrated in relation to compound **23** that free carbenes can be isolated in a pure state. This work aroused considerable interest and attracted new research teams into this area. Effective methods for the synthesis of free carbenes of various types[234, 235] and carbene complexes with transition metals[236–240] were developed. Free carbenes are now widely used as organocatalysts.[241–244] Carbene complexes with transition metals serve as the basis for effective catalytic systems for C–C and C–N cross-coupling reactions, alkene metathesis (see Section III) and some other important catalytic processes.[245–250]

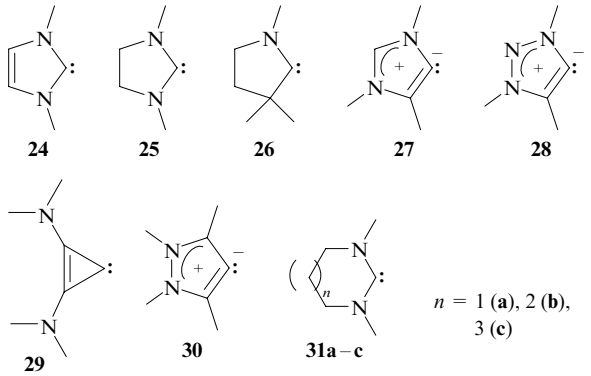
Structure 23



23

Currently, imidazolin- (**24**) and imidazolidin-2-ylidene (**25**) derivatives containing two amine nitrogen atoms in the five-membered ring near the ylidene carbon atom are the best studied stable carbenes that are widely used. However, the series of stable carbenes is not limited to these two structural types. During the last decade, carbenes containing either one nitrogen atom near the ylidene carbon atom (structures **26**–**28**) or no nitrogen atoms in these positions (**29**, **30**) have been synthesized, isolated in a free state and characterized by X-ray diffraction.[251] A simple and efficient modification of stable carbenes is expansion of the diaminocarbene ring to six- (**31a**), seven- (**31b**) and eight-membered (**31c**) rings. These compounds are called expanded ring N-heterocyclic carbenes (expanded ring NHC, er-NHC).[252]

Structures 24–31



24 **25** **26** **27** **28**

29 **30** **31a–c**

n = 1 (**a**), 2 (**b**), 3 (**c**)

As compared with five-membered analogues, expanded ring carbenes have a number of specific features that make them potentially suitable for the design of catalysts:

— higher donor ability;

— the possibility to vary the steric crowding of the ligands over wider limits;

— higher energy of the metal–ligand bond;

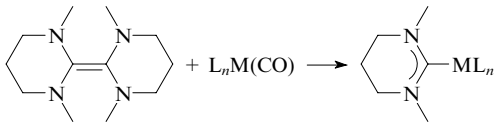
— higher thermal and hydrolytic stability of the complexes and stability against oxidation.

The present Section of the review considers examples of using expanded ring carbene complexes in homogeneous metal complex catalysis.

VI.1. Expanded ring diaminocarbenes and metal complexes

The first complexes of N-heterocyclic carbenes containing a six-membered ring were obtained by Lappert's research team back in 1977[253,254] well before the isolation of free carbenes. The reaction of tetraaminoethylenes with transition metal complexes is accompanied by C=C bond cleavage to give new complexes (Scheme 69). The first free diaminocarbene with a six-membered ring was isolated and characterized by X-ray diffraction in the crystalline state in 2003,[255] while carbenes with seven-[256] and eight-membered[257] rings were prepared and studied in 2008 and 2011, respectively. The methods of synthesis of carbenes and their complexes have been considered in detail in a recent review.[258] This Section briefly presents the structural types of expanded ring diaminocarbenes and principal methods used to prepare their complexes with transition metals.

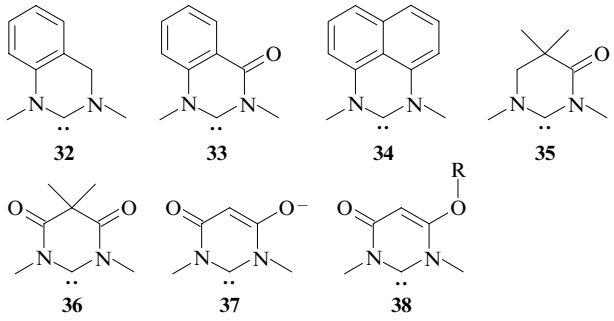
Scheme 69



M = Cr, Mo

Apart from compound **31a**,[256,259] six-membered ring carbenes (or carbene complexes) with one (structures **32** and **33**)[260,261] or two (**34**)[255,262,263] aromatic rings have been prepared. Aminoamido- (**35**)[264] and diamidocarbenes (**36**),[265] carbenes with a malonate anion moiety (**37**) or with a neutral alkyl malonate moiety (**38**) were also reported.[266,267]

Structures 32–38

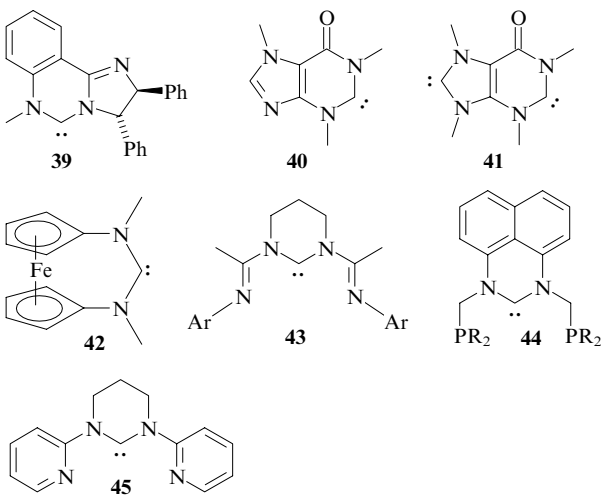


32 **33** **34** **35**

36 **37** **38**

Owing to their heterocyclic nature, carbene ligands can be modified and functionalized in a variety of ways. Indeed, carbenes (or carbene complexes) based on chiral polyheteroaromatic structures (carbene **39**)[268] and natural physiologically active derivatives (**40** and **41**)[269] have been synthesized. Mention should be made of unusual carbene **42** containing a ferrocenyl moiety.[270] A number of tridentate ligands containing imine (**43**),[271,272] phosphine (**44**)[273] or pyridine (**45**)[274] groups as the coordinating moieties have been developed on the basis of six-membered ring diaminocarbenes.

Structures 39–45



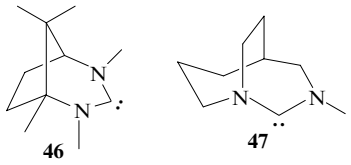
39 **40** **41**

42 **43** **44**

45

In order to modify the steric and electronic properties of carbenes, bicyclic diaminocarbenes have been prepared. The synthesis of carbene **46** based on a camphor derivative was reported.[275–277] Bertrand and co-workers[278] proposed structure **47** in which one nitrogen atom occupies the bridgehead position. This carbene should be regarded as monoamino- rather than a diaminocarbene, because the electron pair of only one nitrogen atom is involved in stabilization of the ylidene moiety.

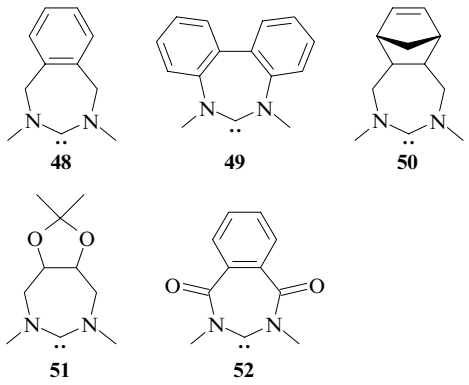
Structures 46, 47



46 **47**

The chemistry of carbenes containing seven- and eight-membered rings has been much less developed than the chemistry of six-membered ring carbenes. Diaminocarbenes comprising an aliphatic moiety (**31a**),[256] one (**48**)[256] or two (**49**)[279, 280] benzene rings, tricyclic (**50**)[281] or heterocyclic (**51**)[282] moieties have been described. The synthesis of complexes of seven-membered ring diamidocarbene **52** has been reported.[283] There is only one example of diaminocarbene **31c** containing an eight-membered aliphatic ring.[257]

Structures 48–52

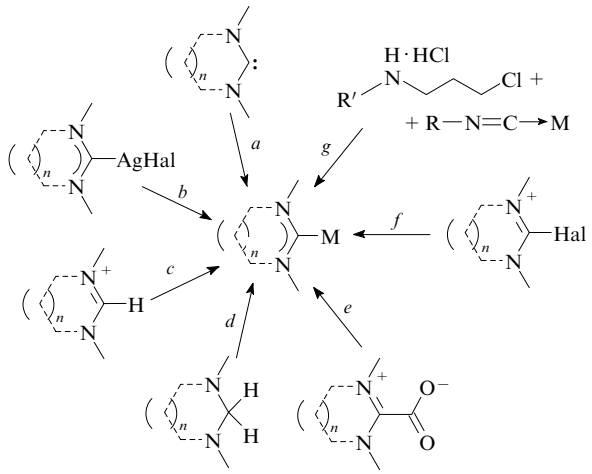


48 **49** **50**

51 **52**

Transition metal complexes of N-heterocyclic expanded ring carbenes can be synthesized in several ways. Historically, the first developed approach — the Lappert method (see Scheme 69) — includes the reaction of tetraaminoethylenes with a metal complex. The most facile and often an effective method for the synthesis of the complexes is the direct reaction of free carbene with a metal salt (Scheme 70, pathway *a*). The free carbene can be either preliminarily isolated (Refs 255, 267, 278, 283–288) or generated *in situ* by treatment with an appropriate strong base (Refs 259–261, 264, 265, 268, 269, 272, 275–277, 279–282). Transmetallation (see Scheme 70, pathway *b*) of silver complexes[288–290] or complexes of other metals (copper,[291] palladium[280]) is often used. A popular method is the reaction of metal complexes containing basic ligands with amidinium salts (see Scheme 70, pathway *c*). The deprotonation of the amidinium salt and the coordination of the resulting carbene to the metal atom occur simultaneously.[256, 257, 274, 277, 292–294] Note also the syntheses by double C–H activation of diaminomethane derivatives (see Scheme 70, pathway *d*)[273] and elimination of CO_2 from zwitter-ionic carboxylates (see Scheme 70, pathway *e*).[295, 296] The complexes can be prepared by the oxidative addition of 2-haloamidines (see Scheme 70, pathway *f*)[297] and by cyclization of metal-coordinated isonitriles with γ-chloro derivatives of secondary amines (Scheme 70, pathway *g*).[298]

Scheme 70



M is transition metal, [M] is the metal compound, B is base, $n = 1–3$; (*a*) [M]; (*b*) [M], −AgHal; (*c*) MB, −HB; (*d*) [M], $-H_2$; (*e*) [M], $-CO_2$; (*f*) [M]; (*g*) −HCl

Despite the considerable diversity of methods, a few transition metal complexes of this type have been synthesized to date. No complexes of titanium, vanadium or zinc group metals have been reported. Only a few examples of chromium group metal complexes are known.[253, 254, 272, 299] Researchers' attention has mainly been attracted by complexes of heavy transition metals. About a dozen of works on the chemistry of iron group metal complexes were published. Most of all, ruthenium complexes and their catalytic properties in alkene metathesis were investigated.[271, 272, 274, 300–305] The greatest number of studies[255, 257, 260, 262–267, 272, 275, 281, 283] are devoted to cobalt group metal complexes. This is largely due to the fact that rhodium and iridium carbonyl complexes serve as convenient models for investigation of the donor properties of carbenes. For these complexes, the Tolman electronic parameter was calculated from the carbonyl vibrational frequencies.[306] On the increase in the donor capacity of the ligands (phosphines, carbenes, *etc.*), the carbonyl vibrational frequency decreases. The decrease in the Tolman parameter corresponds to the increase in the donor properties of the ligand. Considerable attention of researchers was devoted to the chemistry of nickel[270, 275, 279, 280, 284–286] and copper[268, 272, 275, 280, 283, 287] group metal complexes.

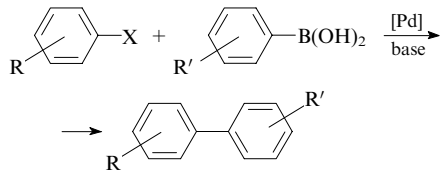
VI.2. Catalysis of cross-coupling, hydrogenation, hydrosilylation, hydroboration, hydroamination, arylation, polymerization and asymmetric reactions

VI.2.a. Suzuki reaction

Suzuki reaction is the cross-coupling of aryl halides with arylboronic acids (Scheme 71). For the discovery of this reaction, A Suzuki, together with E Negishi and R Heck, were awarded the Nobel Prize in chemistry for 2010.[307] This reaction is most efficiently catalyzed by palladium complexes containing highly electron-donating, sterically crowded[239] phosphine[308] or carbene ligands.[309] The use of

expanded ring carbenes as ligands holds good prospects, because they surpass both phosphines and five-membered ring carbenes in the electron donor and steric properties.[252]

Scheme 71



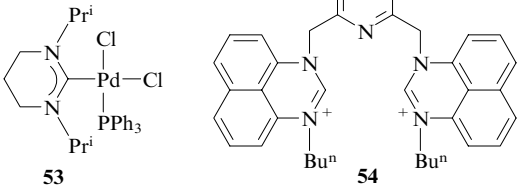
The first example of using palladium complexes with expanded ring carbenes in the Suzuki reaction was published in 2006 by Herrmann ad co-workers.[310] Owing to the high donor capacity of the carbene ligand, complex **53** is very active in this reaction. The authors demonstrated that in the presence of this catalyst, the reaction can involve both deactivated aryl bromides and aryl chlorides. In the case of bromides, the process occurs efficiently in the presence of 0.005 mol.% palladium complex, the turnover number being as high as 1×10^6 in 14 h. For chlorides, these characteristics are 0.01 mol.% and 6×10^3, respectively.

Subsequently, ligand **54** was employed to generate the palladium complex *in situ*.[311] High activity of the complex was demonstrated (turnover number of up to 1.87×10^5, amount of the catalyst 0.005 mol.%) but the results were obtained only for highly active aryl iodides.

It was shown[312] that on treatment with a base, salts **55** and **56** form *in situ* palladium complexes, which catalyze the coupling of *p*-acetylchlorobenzene and phenylboronic acid, giving products in almost quantitative yields within 2 h at 50 °C. However, it is noteworthy that large loads of palladium salts and ligand precursors were used (1.5 mol.% and 3.0 mol.%, respectively).

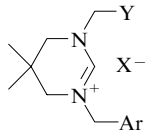
The synthesis of a series of palladium complexes based on ferrocenyl diaminocarbene **57** was reported.[270] The catalytic activity of the complexes was tested in the reactions of *para*-substituted aryl bromides with phenylboronic acid. The complexes were found to give products in high yields with a catalyst amount of down to 1×10^{-4} mol.%.

Structures 53–58



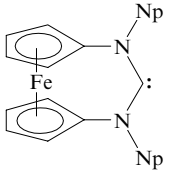
53

54

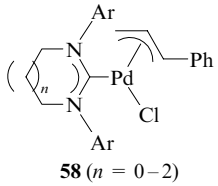


55, **56**

Y = Ar, X = Cl (**55**);
Y = CH_2OAlk,
X = Br (**56**)



57 (Np is neopentyl)



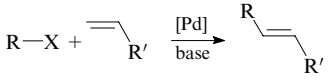
58 (n = 0–2)

A publication of 2013 presents the results of a comparative study of the catalytic activity of palladium complexes **58** in the Suzuki reaction of hetaryl halides in water.[288] Complexes based on carbenes containing five-, six- and seven-membered rings and bulky aromatic substituents [Mes, 2,6-$Pr^i_2C_6H_3$ (Dipp)] were used. The complex comprising a six-membered ring carbene and the Dipp substituent proved to be the most active catalyst. Using this catalyst, hetaryl chlorides of various nature can be coupled with boronic acids containing electron-donating, electron-withdrawing or bulky substituents. The developed procedure complies with the green chemistry principles. The following advantages of this procedure should be noted: (a) the reaction is carried out in water without adding organic solvents; (b) the reaction is carried out in air without solvent degassing; (c) a mild and cheap base, $NaHCO_3$, is used; (d) small amounts of Bu^n_4NBr are needed; (e) a small excess of boronic acid is taken; (f) high yields are obtained after 1 h of refluxing; (g) high purity of the products containing no side homocoupling products is achieved. High activity of the catalyst is due to the appropriate selection of the donor and steric properties of the ligand. This resulted in the complex that exhibited high activity and was stable in the activated state in the reaction medium. It was also shown that these complexes efficiently catalyze the Suzuki reaction without a solvent.[313]

VI.2.b. Heck reaction

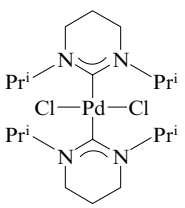
The Heck reaction is the coupling of alkyl and aryl halides with alkenes catalyzed by palladium complexes (Scheme 72).[314]

Scheme 72

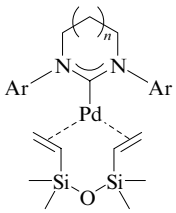


The first example of using expanded ring carbenes in the Heck reaction was published in 2010.[295] The reaction was catalyzed by a palladium complex of a six-membered ring carbene chemically grafted to a polymeric resin. This catalyst showed a high activity in the coupling of styrene or n-butyl acrylate with aromatic bromides (turnover number of up to 1×10^5). Homogeneous catalyst **59** demonstrated a three times higher activity under similar conditions.

Structures 59, 60



59



60

Ar = Mes, 2,6-$Me_2C_6H_3$, 2-MeC_6H_4, 2-$MeOC_6H_4$; n = 1, 2

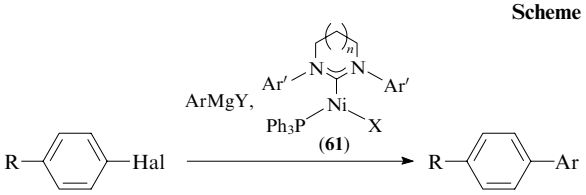
Complexes formed by benzyl-substituted carbenes **55** and **56** catalyze the reactions of styrene with *para*-substituted phenyl bromides containing either electron-withdrawing or electron-donating substituents to give products in >70% yields in 2 h.[312] It was shown in 2011 that Pd^0 complexes with six- and seven-membered ring carbenes (compound **60**) catalyze the reaction of *p*-acetylbromobenzene with n-butyl acrylate.[286] The product yields varied from 50% to 100% for the reaction time of 3 h depending

on the carbene ring size and the nature of aromatic substituents at nitrogen atoms. The amounts of catalysts used were low (0.1 mol.%). The complex containing ferrocenyl ligand **57** demonstrated moderate activity in the coupling of *para*-substituted aryl bromides with n-butyl acrylate.[270]

VI.2.c. Kumada reaction

One example of using complexes of expanded ring diaminocarbenes as catalysts in the Kumada reaction was reported in the literature.[285] A series of Ni^{I} complexes **61** have been prepared and characterized by X-ray diffraction. The coupling reactions with aryl chlorides gave 40%–50% yields (Scheme 73); in the case of aryl fluorides, the product yields did not exceed 30%.

Scheme 73

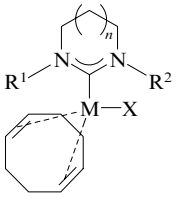


R = H, Me, OMe, CF_3; Hal = Cl, F; Ar = Ph, Mes;
Ar′ = 2,4,6-$Me_3C_6H_2$, 2-$MeOC_6H_4$, 2-MeC_6H_4; X, Y = Cl, Br; n = 1–3

VI.2.d. Hydrogenation with molecular hydrogen

Cavell and co-workers[315,316] reported the synthesis of rhodium (**62**) and iridium (**63**) complexes containing functionalized aromatic and/or aliphatic substituents. These complexes show high activity and stability in alkene hydrogenation with molecular hydrogen. At room temperature, a pressure of 1 atm and 24 h reaction time, hydrogenation products of various cycloalkanes, styrenes and allylic derivatives were obtained in quantitative yields. Similar rhodium complexes were used in hydroformylation of oct-1-ene.[293] It was shown that the catalyst turnover frequency is 1500 h^{-1}; however, the reaction selectivity is low: both linear nonanal and a mixture of isomeric octa-, hepta- and hexanals are formed.

Structures 62, 63



62, 63

M = Rh (**62**), Ir (**63**); $R^1 = R^2 = CH_2Bu^t$, Cy, Mes, Dipp, 2-$MeOC_6H_4$, *etc.*; X = Cl; n = 1, 2

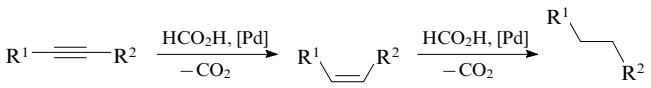
VI.2.e. Hydrogen transfer hydrogenation

In 2010, carbene complexes of rhodium, iridium and palladium chemically grafted to a polymeric support were synthesized.[295] The iridium catalyst was active in the reduction of benzaldehyde with isopropyl alcohol. In the presence of 0.1 mol.% catalyst, the reaction proceeded quantitatively over a period of 4 h; the product contamination by the metal was < 50 ppm.

It was shown[317] that iridium complexes **63** (X = Br; R^1 = 2-$MeOC_6H_4$; R^2 = Mes, Dipp; n = 1, 2) are highly active as catalysts in the reduction of ketones with isopropyl alcohol. The reduction of acetophenones and cyclohexanone occurred quantitatively at 80 °C over a period of 24 h.

Palladium complexes **60** (Ar = Mes, Dipp; n = 1, 2) catalyze the reduction of alkynes with formic acid (Scheme 74).[318] It was found that at short reaction times, *cis*-alkenes are predominantly formed. During 24 h, the reactions give alkanes almost quantitatively.

Scheme 74



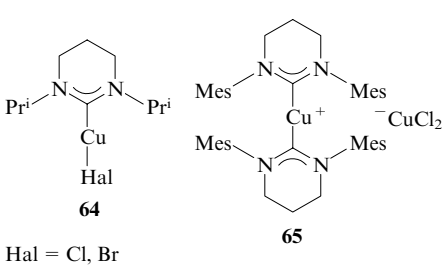
VI.2.f. Hydrosilylation and hydroboration reactions

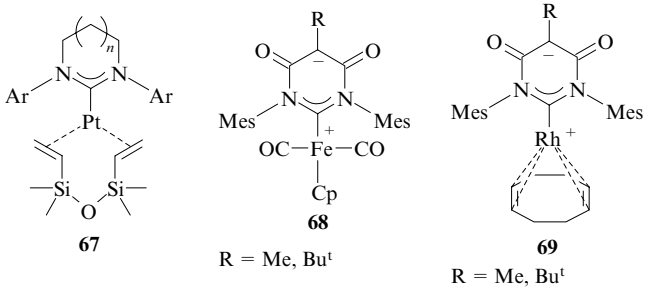
In 2005, copper complexes **64** and **65** were synthesized[319] and found to efficiently catalyze the addition of triethylsilane to carbonyl compounds of various nature. The catalyst amounts were 0.001 mol.%–0.002 mol.%, complete conversion being observed in 1–3 h. Ionic rhodium complex **66a** exhibits high activity in the hydrosilylation of alkynes, styrenes and cyclic ketones.[294] High yields were obtained in the presence of 0.05 mol.% catalyst in 12 h.

Platinum(0) complexes **67** structurally similar to Pd complexes **60** serve as active catalysts for hydrosilylation of ketones, alkenes and alkynes.[320] For a catalyst amount of only 0.005 mol.%, high conversion is achieved. It is noteworthy that the selectivity of reactions is also high in most cases.

It was shown that the zwitter-ionic iron complexes **68** can be successfully used in the catalytic hydrosilylation of aromatic aldehydes.[321] For the catalyst load of 1 mol.%, high conversion is achieved at room temperature in 1–3 h. Analogous zwitter-ionic rhodium complexes **69** are also active in catalytic hydroboration of styrene; however, the reaction rate and selectivity are low.[267]

Structures 64–69



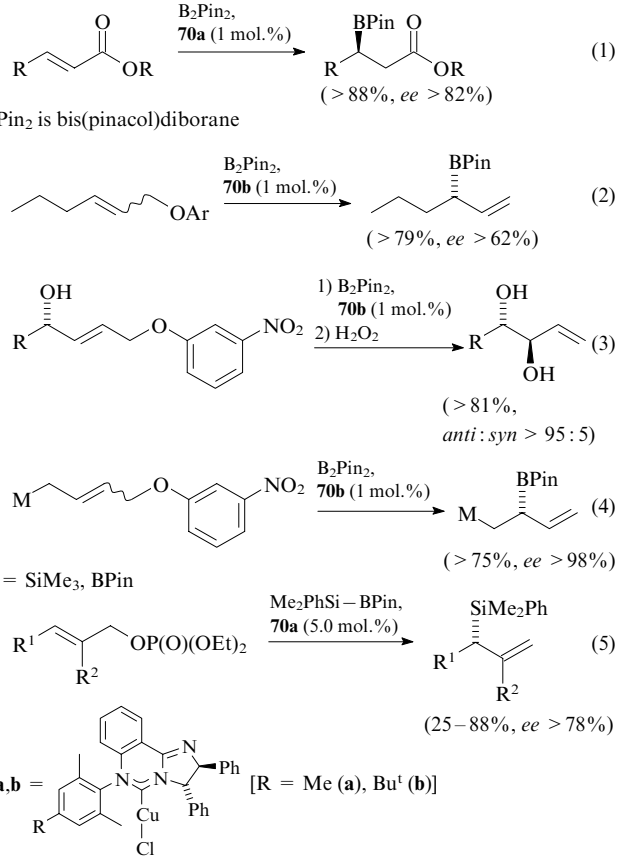


VI.2.g. Asymmetric borylation and silylation reactions

In 2010, complex **70a** was synthesized,[268] and the next year, complex **70b** was reported (Scheme 75).[322] These complexes proved to be very efficient catalysts for asymmetric borylation of unsaturated compounds. The addition products to Michael acceptors were obtained in high yields [see Scheme 75, reaction (1)].[268] The cleavage of allyl ethers to give borylated allyl compounds [reaction (2)][322,323] fol-

lowed by their oxidation to diols [reaction (3)][324] occur in ~80% yields. Noteworthy is the formation of chiral bimetallic boron and silicon derivatives [reaction (4)].[325] In 2013, complex **70a** was used for catalytic silylation of allyl phosphates with silylated pinacolborane $Me_2PhSi-BPin$ [reaction (5)].[326]

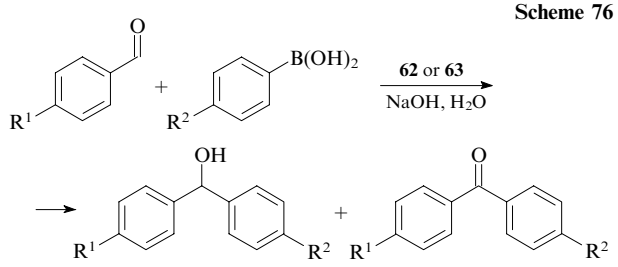
Scheme 75



VI.2.h. Arylation of carbonyl compounds

In 2004, the catalytic activity of rhodium **62** and iridium **63** complexes in the arylation of carbonyl compounds with arylboronic acids was studied (Scheme 76).[327] The complexes were found to be highly active (yields of up to 99%). Also, complexes containing isopropyl substituents are more active than methyl-substituted derivatives. A decrease in the nucleophilicity of the anion X increases the electrophilicity of the metal atom and, hence, increases the catalytic activity. The iridium complexes are less active than rhodium complexes but they increase the reaction selectivity by reducing the trend of oxidation of alcohols to ketones. The same authors showed that a similar ionic rhodium complex containing the BF_4^- anion is more active than neutral complexes. In this case, the selectivity of the catalytic reaction shifts towards the formation of ketones.[294] In a similar reaction, rhodium complexes **62** with benzyl substituents (see Scheme 76) exhibit high activity and selectivity in the formation of alcohols, the yields being 70%–95%.[328]

Scheme 76

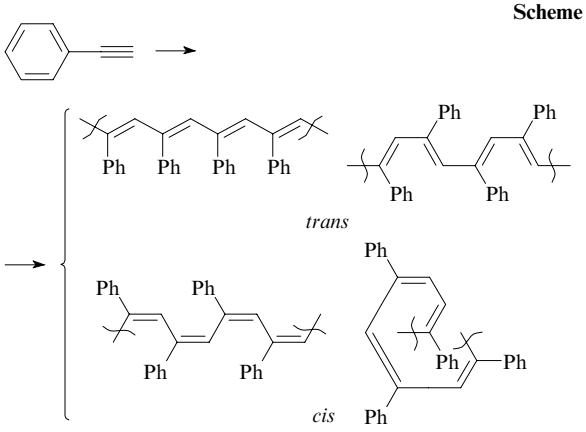


62: X = Cl: $R^1 = R^2 = Pr^i$, Mes, $CH_2C_6H_2(OMe)_3$-3,4,5, $CH_2C_6HMe_4$-2,3,4,5; X = Br: $R^1 = R^2 = Pr^i$, Mes;
63: X = Cl, Br; $R^1 = R^2 = Pr^i$, Mes

VI.2.i. Polymerization of phenylacetylene

A study of the catalytic activity of rhodium complexes **62a–d** [$R^1 = R^2$ = Mes, n = 1, X = Cl (**a**), OTf (**b**), OBu^t (**c**), $OC(O)CF_3$ (**d**)], **66a**,**b** and iridium complexes **63** [$R^1 = R^2$ = Mes, n = 1: X = Cl, $OC(O)CF_3$] in the polymerization of phenylacetylene was reported.[300] The polymer thus formed (polyphenylacetylene, PPA) can have different microstructures depending on the type of the catalyst used (Scheme 77). All rhodium complexes showed a high catalytic activity with predominant formation of the *cis*-isomer of PPA. In the case of catalysts **66a**,**b** having ionic structure, the selectivity towards *cis*-PPA was 100%. The use of iridium complexes **63** resulted in the selective formation of *trans*-PPA.

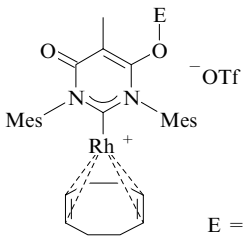
Scheme 77



Rhodium carbene complexes chemically grafted to a polymeric support were also used to prepare PPA.[295] These catalysts performed quantitative polymerization of phenylacetylene (substrate : catalyst = 100 : 1) at room temperature over a period of 2 h to give *cis*-PPA. The metal washing out from the support was only 4.5% per catalytic cycle.

Rhodium complexes containing carbenes with a malonate moiety (complexes **69**) and carbenes modified by an electrophile (complexes **71a–c**) were used for phenylacetylene polymerization.[265] Zwitter-ionic complexes **69** were

Structures 71



E = Me (**a**), Tf (**b**), H (**c**)

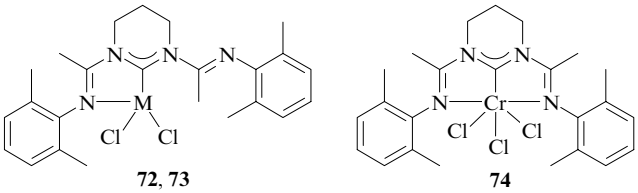
71a–c

found to be more active than cationic complexes **71**. However, complexes of both types show much lower catalytic activity and lower specificity towards *cis*-PPA than complexes **62a–d**, **66a**,**b** containing the tetrahydropyrimidine ligand with more pronounced donor properties.

VI.2.j. Polymerization of ethylene

The cationic metal complex-catalyzed polymerization of ethylene is among the most important processes in the polymer industry. In 2012, Al Thagfi and Lavoie [272] synthesized a series of iron, cobalt and chromium complexes (**72–74**, respectively) containing a potentially tridentate ligand similar to bis(imino)pyridine ligands, which are widely used to design post-metallocene catalysts for the synthesis of polyolefins.[329] An X-ray diffraction study, which confirmed the tridentate coordination of the ligand, was performed only for Cr complex **74**. Upon activation by methylalumoxane, iron (**72**) and cobalt (**73**) complexes do not exhibit catalytic activity. Conversely, chromium complex **74** shows a substantial catalytic activity. However, it should be noted that catalyst **74** is 3–4 orders of magnitude less active than analogous catalysts containing bis(imino)-pyridine ligands.[330]

Structures 72–74



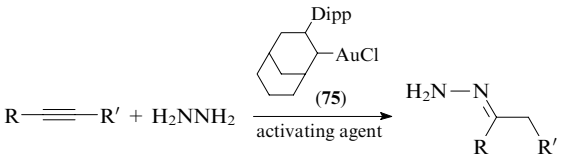
72, **73** **74**

M = Fe (**72**), Co (**73**)

VI.2.k. Hydroamination of alkynes

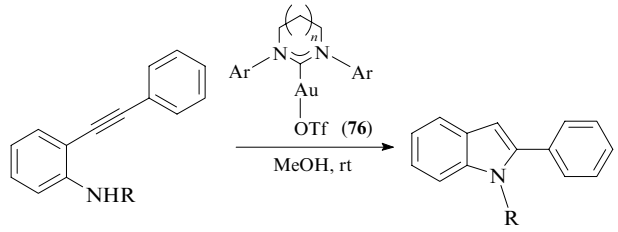
It was demonstrated [331] that complex **75** efficiently catalyzes the addition of hydrazine to alkynes (Scheme 78). Depending on the substrate nature, the product yields of > 80% can be attained over periods of time from 3 to 6 h either at room temperature or on heating.

Scheme 78



Recently, the intramolecular hydroamination reaction to give indoles has been studied in detail (Scheme 79). A comparative study of the catalytic activities of gold complexes with carbenes **76** containing five-, six- and seven-membered rings has been performed. The highest activity was observed in the case of the complex with seven-membered ring carbene containing bulky Dipp substituents at nitrogen atoms. This is due to the fact that the ring expansion and an increase in the substituent bulk results in efficient steric and electronic stabilization of the cationic form of the complex, which is the catalytically active species. Quantitative yields of products are attained with 2 mol.% of the catalyst over a period of 15 min. The developed catalytic system is most active among those described in the literature to date.

Scheme 79



Ar = Mes, Dipp; n = 0–2

Stable expanded ring carbenes have been actively studied in the last decade. These compounds are promising for the design of metal complex catalysts for homogeneous processes. This is due to the large structural diversity, synthetic accessibility and easy functionalization of expanded ring carbenes and the possibility of varying the steric and electronic properties over broad limits. It should be noted, however, that only few catalytic systems able to compete with effective catalysts based on phosphines and other ligands have been developed to date. These systems include catalysts for the cross-coupling of hetaryl halides in water based on palladium complexes, catalysts for asymmetric borylation based on copper complexes, ruthenium catalysts for alkene metathesis, and hydroamination catalysts based on ionic gold complexes. It is evident that the advantages of expanded ring carbenes would be embodied in the near future in new high-performance catalytic processes to run chemical transformations under mild conditions, to activate substrates having low reactivity and to prepare compounds inaccessible by other methods.

VII. Development of methods for the synthesis of heterocyclic compounds. Synthesis of pyrrolidine and piperidine derivatives based on cyclic ketimines

The information presented in the previous Section convincingly demonstrates that by varying the structures of heterocyclic ligands it is possible to design versatile catalysts having high activity and selectivity in a large series of reactions. The enormous significance of methods of variation of heterocycle structure is manifested to even a larger extent in consideration of the modern trends of development of heterocyclic chemistry.

Heterocyclic chemistry is the prior field of organic chemistry. This is due to a diversity of biological activities and some other useful properties of these compounds. This is why primary attention is paid to advanced methods for heterocycle synthesis.[332–335]

Cyclic amines are an important class of heterocyclic compounds; this structural moiety is often encountered in natural products, for example, in the alkaloids nicotine, anabasine and hygrine (Fig. 6). Amino acids containing these structural units (proline, hydroxyproline and pipecolic acid) play an important role in the formation of the secondary protein structure. It is not surprising that in the up-to-date medicinal chemistry, the introduction of a cyclic amine moiety is successfully used to design new drugs. Indeed, among 200 most sold drugs, many drug molecules contain a piperidine or pyrrolidine moiety. Examples of amino acids, alkaloids and drugs containing pyrrolidine and piperidine moieties are presented in Fig. 6.

Cyclic ketimines are valuable reagents for organic synthesis and can be used to introduce an α-substituted cyclic

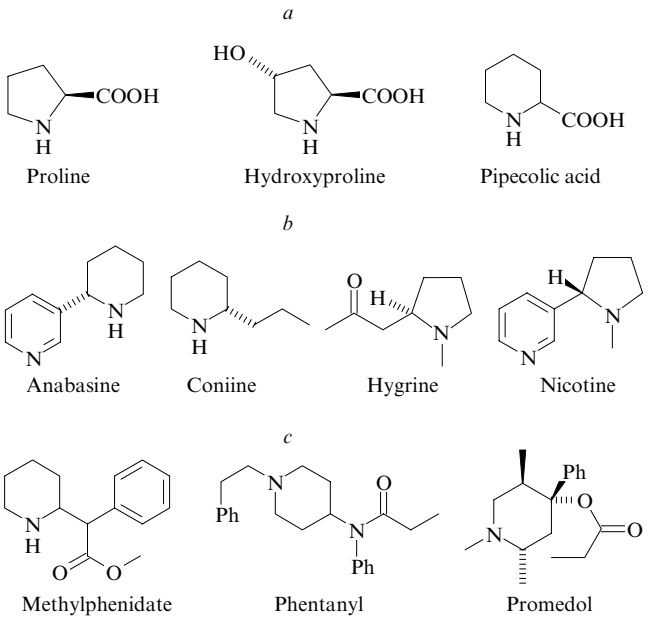


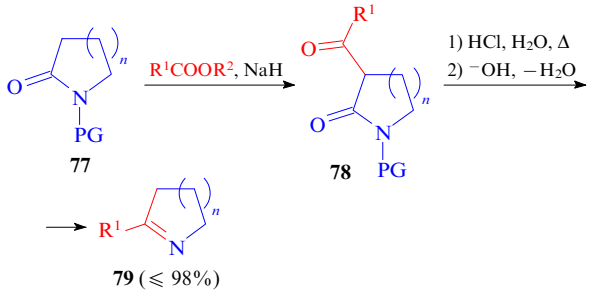
Figure 6. Amino acids (*a*), alkaloids (*b*) and drugs (*c*) containing pyrrolidine and piperidine moieties.

amine moiety into target molecules. As a rule, ketimines have somewhat lower reactivity than the corresponding aldimines; however, they are successfully used in the synthesis. The present review describes the key methods for the synthesis of five- and six-membered cyclic imines and integrates the results of using these compounds to prepare pyrrolidine and piperidine derivatives (except for benzo analogues) during the last 10–15 years.

VII.1. Key methods for the synthesis of cyclic ketimines

A popular and versatile approach to the synthesis of cyclic imines is based on the use of N-protected lactams **77** — commercially available and cheap compounds manufactured by chemical industry on a large scale. The first step is the Claisen condensation of lactams **77** with esters, resulting in acylactams **78**, which are then hydrolyzed and decarboxylated in acid medium on refluxing (Scheme 80). This method is experimentally simple and possesses a broad synthetic potential, being suitable for preparation of imines **79** with alkyl or aryl substituents in up to 98% yield. However, note that this method is not always applicable to preparation of imines containing acidophobic groups.[336–338]

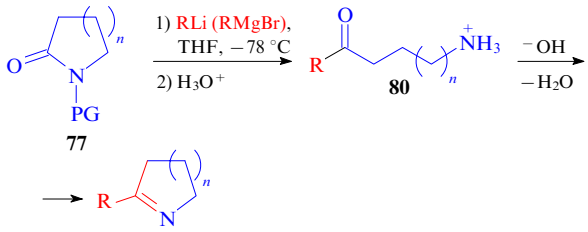
Scheme 80



R^1 = CF_3, C_2F_5, Alk, Ar, Het; PG = CH=CH_2, $CH(OEt)_2$; n = 1, 2

An alternative approach to cyclic ketimines **79** based on N-protected lactams **77** consists in the addition of organometallic reagents to the lactams (Scheme 81). The hemiaminal thus formed is converted upon acidification to cyclic imine **79**. In the case of six-membered imines, acidification of the reaction mixture may give not only cyclic imines **79** but also their open forms **80**, which can be easily converted to desired imines **79** in alkaline medium. It should be emphasized that this method is appropriate for preparing imines **79** containing acidophobic groups; therefore, it successfully complements the above-described method using the Claisen condensation.[339–342]

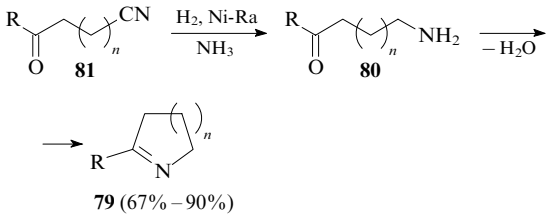
Scheme 81



n = 1, 2

The catalytic reduction of ω-cyanoketones **81** gives rise to aminoketones **80**, which spontaneously cyclize to the corresponding imines **79**. In this reaction, hydrogenation catalyzed by Raney nickel (Ni-Ra) in the presence of ammonia is used most often (Scheme 82).[343, 344]

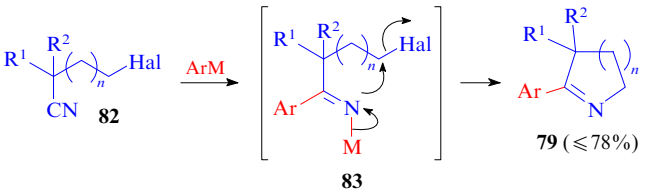
Scheme 82



R = Alk, Ar, Het; n = 1, 2

The addition of organometallic compounds to halonitriles **82** affords metal imidates **83**, which also spontaneously cyclize to give the target imines **79** (Scheme 83).[345–347]

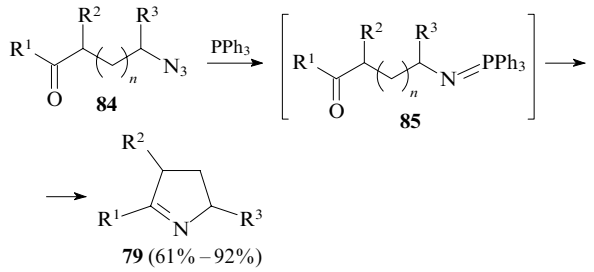
Scheme 83



R^1 = H, Alk; R^2 = H, Ar; n = 1, 2

The widely known Staudinger reaction can be used to prepare various imine derivatives **79**. Treatment of ω-azidoketones **84** with triphenylphosphine affords iminophosphoranes **85**, which cyclize to give imines.[348] This method can serve to prepare trisubstituted imines **79** (Scheme 84).

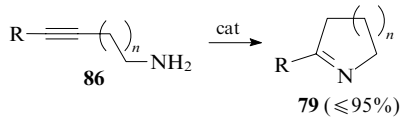
Scheme 84



R^1 = Alk, Ar; R^2, R^3 = H, Alk; n = 1, 2

A number of publications [349–351] describe the intramolecular hydroamination catalyzed by transition metal complexes in which ω-aminoalkynes **86** cyclize to give products in high yields (Scheme 85). The catalysts include palladium(II) chloride complexes, metallocenes, lanthanide derivatives or sodium tetrachloroaurate.

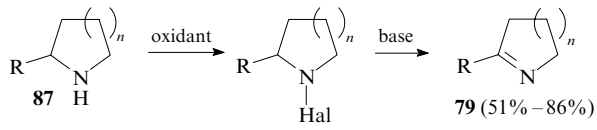
Scheme 85



R = Alk, Ar; n = 1, 2; cat = $PdCl_2$, $CpTiCl_3$, $CpZrCl_3$, $NaAuCl_4$, $CpLaCH(SiMe_3)_2$

Also, cyclic imines **79** can be prepared by oxidation of the corresponding pyrrolidines and piperidines **87** (Scheme 86). In the first step of this process, amine **87** is treated with an oxidant, for example, chlorosuccinimide, and then with a base (Bu^tOK, MeONa, alkali).[352, 353]

Scheme 86



n = 1, 2

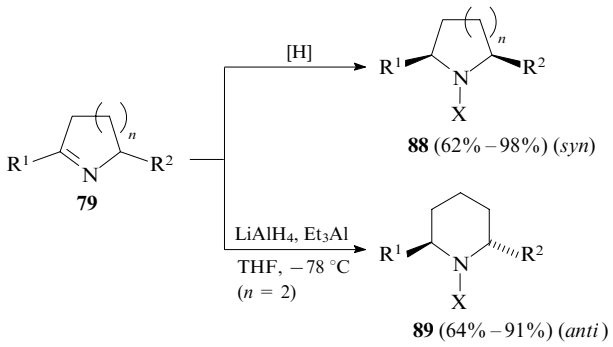
VII.2. Synthetic applications of cyclic ketimines

VII.2.a. Reduction of ketimines

Reduction is among the best studied reactions of cyclic ketimines. Recent investigations have paid considerable attention to diastereo- and enantioselective hydrogenation. For instance, 2,5-disubstituted 1-pyrrolines and 2,6-disubstituted piperideines **79** are reduced, most often, by catalytic hydrogenation in ethanol. The reaction is catalyzed by Adams's catalyst (PtO_2),[354] palladium on carbon,[355–357] platinum on carbon,[358] palladium hydroxide.[359] Under the described conditions, *syn*-addition products **88** were formed, usually in high yields. Complex hydrides (diisobutylaluminium hydride,[360, 361] lithium aluminium hydride [362]) can also be used to prepare *syn*-addition products **88** (Scheme 87).

Trans-2,6-disubstituted piperidines **89** are prepared by lithium aluminium hydride reduction in the presence of triethylaluminium. As a result of Et_3Al coordination to the imine nitrogen atom, this reaction furnishes *anti*-addition products **89** (see Scheme 87).[362, 363]

Scheme 87

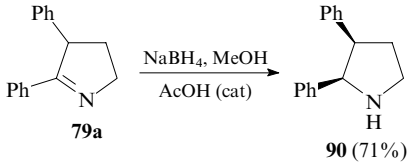


88: R^1 = P(O)(OEt)$_2$, Het, Alk, Ar; R^2 = Alk, Ar, CO_2Me; X = H, Ts; n = 1, 2

89: R^1, R^2 = Alk

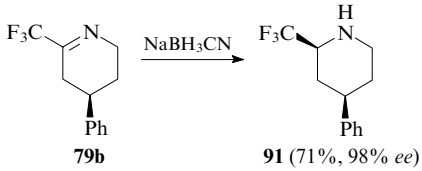
When a substituent is present in position 3 of the cyclic imine, the reduction affords the *cis*-diastereomer. For example, 2,3-diphenylpyrroline **79a** is reduced by sodium borohydride in methanol in the presence of a catalytic amount of acetic acid to give the target product **90** in a yield of 71% (Scheme 88).[364]

Scheme 88



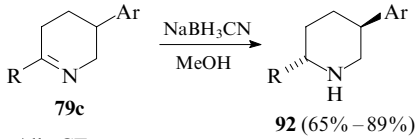
When there are no additional substituents in positions adjacent to the imino group, the same reducing agent can produce both *syn*- and *anti*-addition products. Indeed, the reduction of optically pure piperideine **79b** containing a 4-substituent with sodium cyanoborohydride affords *cis*-diastereomer **91** in a good yield (Scheme 89).[365]

Scheme 89



However, the reduction of 5-aryl-2-substituted piperideines **79c** with sodium cyanoborohydride gives, conversely, *trans*-diastereomers **92** also in good yields (Scheme 90).[366]

Scheme 90

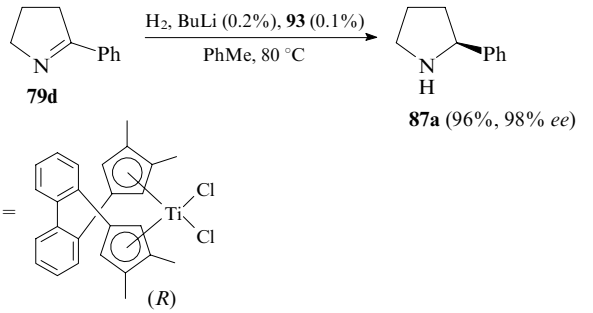


R = Alk, CF_3

Modern medicinal chemistry permanently needs optically active compounds, in particular, amines; therefore, methods for enantioselective reduction of imines are being actively developed.[367] Several recent studies have been devoted to the reduction of cyclic ketimines.

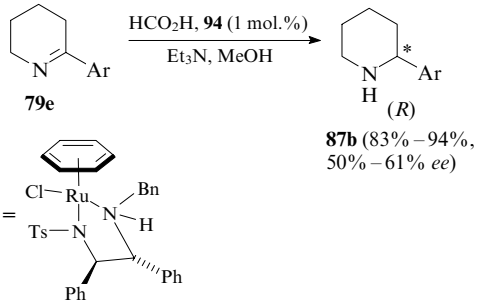
(*R*)-1-Phenylpyrrolidine (**87a**) can be obtained from 2-phenylpyrroline (**79d**) in almost quantitative yield (96%) and with high enantioselectivity (98% *ee*). As the hydrogenation catalyst, the titanium ansa-complex **93** with a biphenyl bridge was used in the presence of 2 equiv. of n-butyllithium (Scheme 91).[368]

Scheme 91



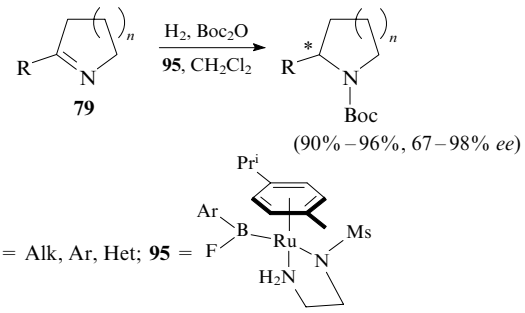
Recently, ruthenium catalyst **94** was developed affording the preparation of α-substituted piperidines **87b** from piperideines **79e** in high yields (83%–94%) with moderate enantioselectivity (50%–61% *ee*) (Scheme 92).[369]

Scheme 92



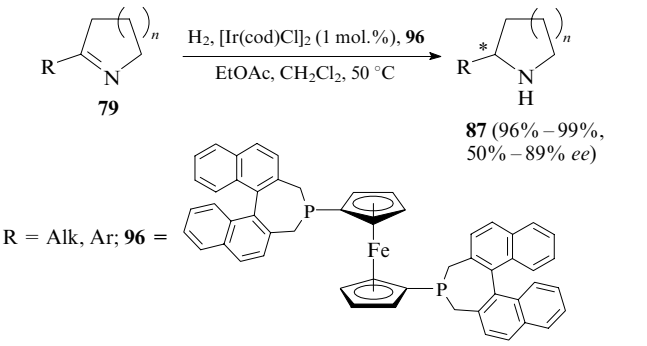
A higher enantioselectivity was achieved by using a similar ruthenium complex **95**. A series of cyclic imines **79** were effectively reduced in the presence of complex **95** giving the products in high yields (up to 98%) and most often with high enantioselectivity (up to 98% *ee*) (Scheme 93).[370]

Scheme 93



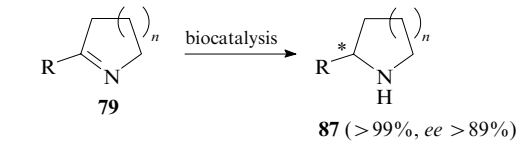
The catalytic complex prepared from di-μ-chlorobis(cycloocta-1,5-diene)diiridium(I) and (*S*,*S*)-f-BINAPHANE (**96**) is an efficient catalyst for enantioselective hydrogenation of cyclic imines **79** suitable for preparing pyrrolidine and piperidine derivatives **87** in high yields and with good enantioselectivity (Scheme 94).[371]

Scheme 94



Further, the method of biocatalyzed reduction of cyclic imines **79** has recently started to be actively developed (Scheme 95). The conversion can be as high as 99%, while the enantiomeric purity of the products is >99%.[372–376]

Scheme 95

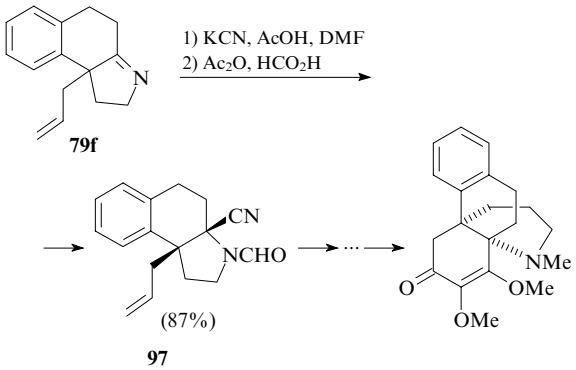


R = Alk, Ar, Het

VII.2.b. Strecker reaction

Of particular interest are reactions of imines with C-nucleophiles because they result in the formation of a new C–C bond. For example, the addition of hydrogen cyanide or its synthetic equivalents to imines results in the synthesis of aminonitriles, which are readily converted to α-amino acids widely used in pharmacology and medicinal chemistry. Recently, the synthesis of the alkaloid hasubanonine belonging to the hasubanan family was performed.[377] The key step in this synthetic route is the Strecker reaction involving imine **79f** (Scheme 96). The target compound **97** was isolated as the only diastereomer in a high yield (87%).

Scheme 96

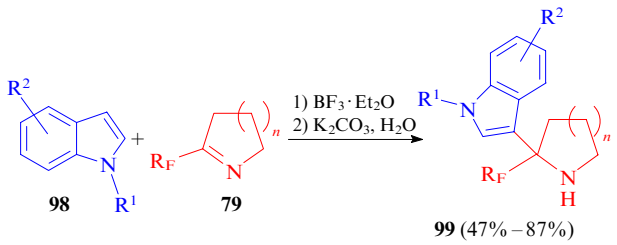


VII.2.c. Friedel–Crafts aminoalkylation (Mannich reaction)

Alkylation of π-donor aromatic systems with imines is classified in different papers as either Mannich reactions or Friedel–Crafts alkylation. The reaction between indoles **98** and cyclic ketimines **79** has recently been studied.[378] It was shown that only perfluoroalkyl-substituted cyclic ket-

imines can participate in this reaction, while non-fluorinated analogues proved to be insufficiently electrophilic. The reaction is catalyzed by Lewis acids, the best results can be achieved by using boron trifluoride etherate. Target compounds **99** were mainly formed in high yields (Scheme 97).

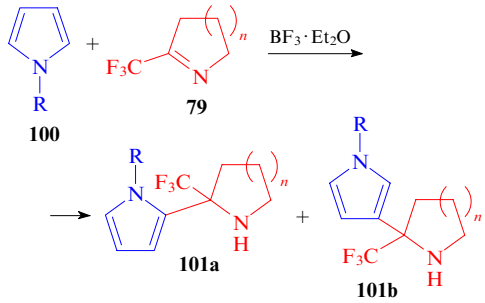
Scheme 97



R^1 = H, Me; R^2 = Me, MeO; R_F = CF_3, C_2F_5; n = 1–3

Perfluoroalkyl-substituted cyclic imines **79** can also alkylate pyrroles **100** in the presence of boron trifluoride etherate (Scheme 98). This reaction is characterized by unusual β-selectivity. Pyrrole reacts with five- and seven-membered ring ketimines to give α- (**101a**) and β-substitution (**101b**) products in ~1 : 1 ratio. CF_3-Piperideine alkylates pyrrole only into the α-position. In the case of N-substituted pyrroles, electrophilic substitution at the β-position unusual for pyrroles is observed, which is due to thermodynamic control of the reaction.[379, 380] It was shown that other π-donor aromatic compounds cannot be alkylated by cyclic ketimines **79**.

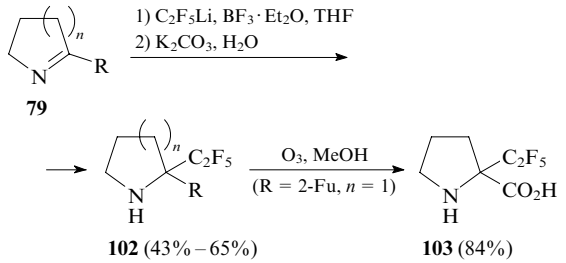
Scheme 98



VII.2.d. Reactions with organometallic compounds

The addition of pentafluoroethyllithium to cyclic imines **79** affords pentafluoroethyl-substituted pyrrolidines and piperidines **102**. The oxidative cleavage of 2-pentafluoroethyl-2-furylpyrrolidine proved to be an effective route to α-pentafluoroethylproline (**103**) (Scheme 99).[381, 382]

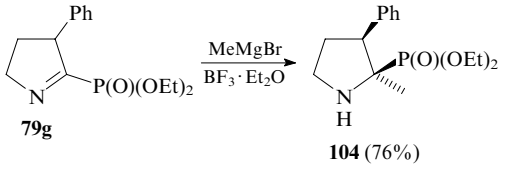
Scheme 99



R = Alk, Ar, Het; n = 1–3; Fu is furyl

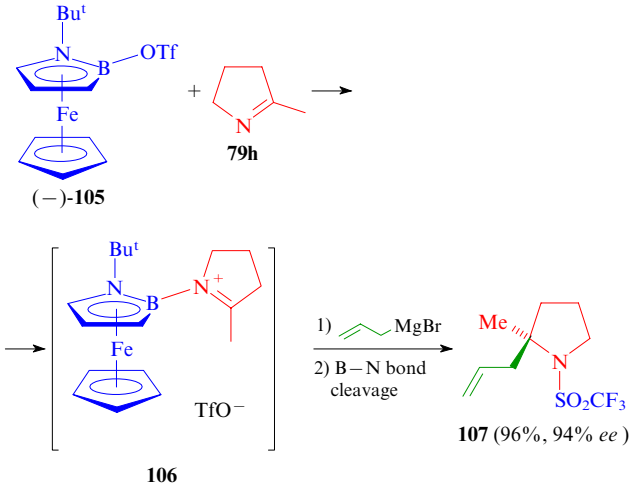
The addition of methylmagnesium bromide to imine **79g** was carried out in the presence of boron trifluoride etherate.[383] The desired compound **104** was isolated as a single diastereomer in high yields (Scheme 100).

Scheme 100



Recently, a method for the synthesis of chiral amines was developed based on the reaction of imines with chiral Lewis acid **105** to give iminium salts, which are then treated with an organometallic reagent (Scheme 101). For example, upon the reaction with allylmagnesium bromide, complex **106** obtained from imine **79h** was converted to optically active pyrrolidine **107** in a high yield and with high enantiomeric excess.[384]

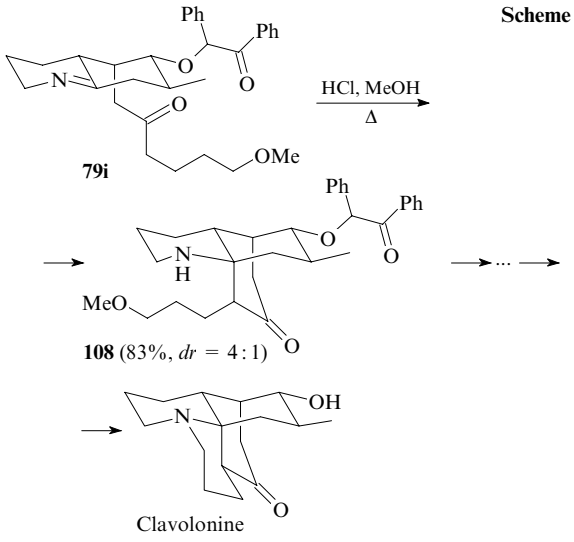
Scheme 101



VII.2.e. Mannich reaction

In various publications, the reactions of imines with any of ketones, π-donor aromatic derivatives, nitroalkanes or other compounds are classified as the Mannich reactions.

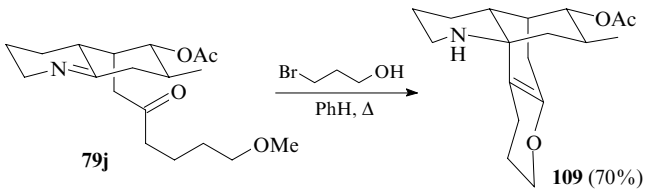
Scheme 102



For example, on treatment with a methanol solution of HCl, bicyclic imine **79i** is converted to tricyclic product **108** in a 83% yield (diastereomer ratio of 4 : 1, the predominant isomer is shown). Then compound **108** is converted to the alkaloid clavolonine (Scheme 102).[385]

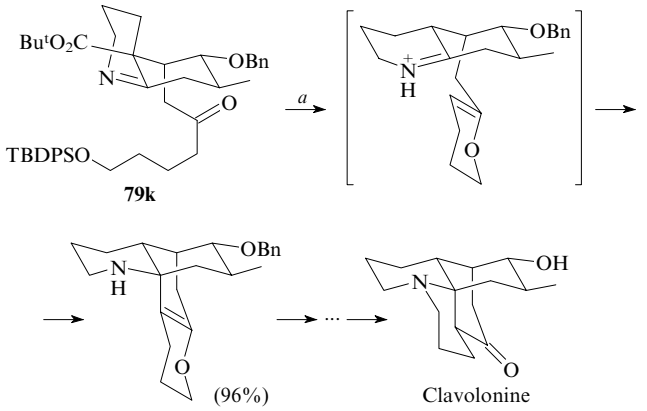
In an alternative synthesis of clavolonine,[386] bicyclic imine **79j** was converted to compound **109** by treatment with HBr generated *in situ*. The Mannich reaction is accompanied by acid-induced cleavage of methyl ether, formation of the enol ether and cyclization (Scheme 103).

Scheme 103



One more similar route to clavolonine has been reported.[387] Imine **79k** used as the precursor was treated with a methanol solution of HCl, which induced decarboxylation accompanied by epimerization of one stereocentre, the subsequent Mannich reaction, acid-induced cleavage of methyl ether, the formation of enol ether and cyclization (Scheme 104).

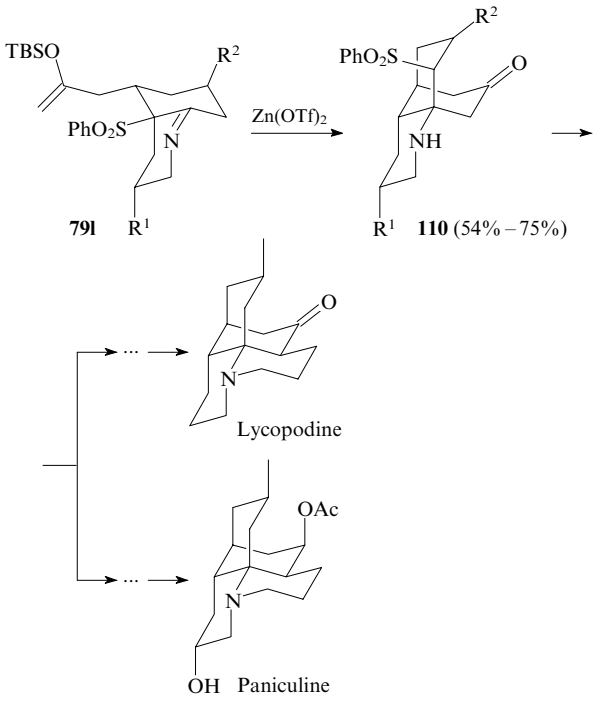
Scheme 104



(*a*) HCl, MeOH, Δ; TBDPS = Bu^tPh_2Si

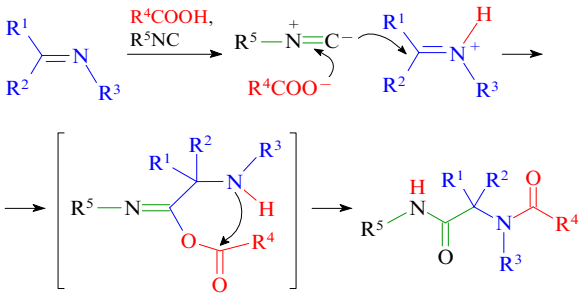
The Mannich reaction was also used in the synthesis of natural alkaloids: lycopodine[388,389] and paniculine[390] (Scheme 105). Instead of ketone, ketone silyl ether was used. Bicyclic imines **79l** were treated with zinc triflate to afford tricyclic amines **110** in moderate or high yields.

Scheme 105



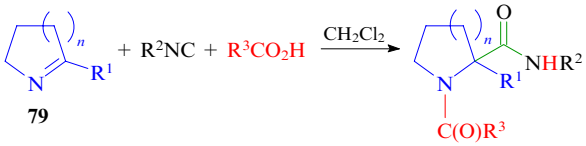
R^1 = H, OTIPS; R^2 = H, Me; TBS = Bu^tMe_2Si, TIPS = Pr^i_3Si

Scheme 106



The three-component Ugi reaction with 2-substituted cyclic imines **79** opened up an effective route to proline and pipecolic acid derivatives with an additional substituent in the α-position.[391,392] By means of the Ugi reaction, semisynthetic dipeptides **111** containing a natural amino acid moiety and α-substituted proline or pipecolic acid have been prepared (Scheme 107).

Scheme 107



R^1 = CF_3, C_2F_5, Alk, Ar; n = 1–3

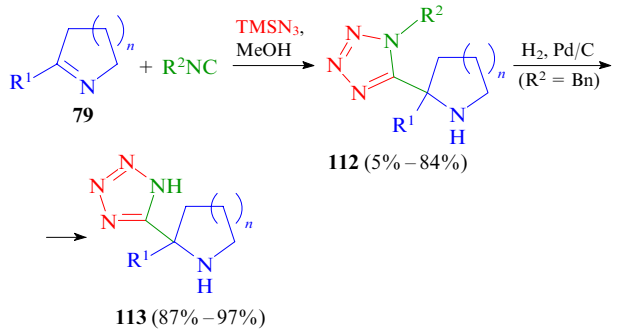
The modified Ugi reaction with cyclic imines **79** and hydrazoic acid (formed from $TMSN_3$ and MeOH) being used in place of carboxylic acid opens up the way to 1,5-disubstituted tetrazoles **112**, which are most often formed in high yields (Scheme 108).[393,394] Using benzylisonitrile as the isocyanide component, upon hydrogenolysis of N-benzyl-substituted Ugi reaction products, it was possible

VII.2.f. Ugi reaction

The Ugi reaction is a multicomponent reaction involving isonitrile, an acid, an amine and a carbonyl compound (imine). The mechanism of this reaction comprises several successive steps: imine formation and protonation, isonitrile and carboxylate addition and intramolecular transfer of the acyl group. Upon this transformation, α-amino acid amides of complex structure can be obtained from simple molecules (Scheme 106).

to obtain 1*H*-5-substituted tetrazoles **113**, which are of considerable interest as organocatalysts (see Scheme 108).

Scheme 108

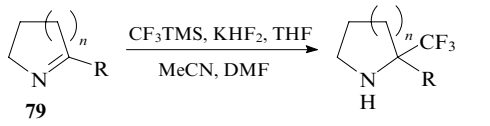


R^1 = CF_3, C_2F_5, Alk, Ar, Het; R^2 = Bu^n, Bu^t, Bn, All, *etc.*; n = 1–3

VII.2.g. Reaction with the Ruppert–Prakash reagent

Cyclic imines **79** react with the Ruppert–Prakash reagent [trimethyl(trifluoromethyl)silane] in the presence of potassium hydrogen fluoride to give the corresponding α-trifluoromethyl pyrrolidine and piperidine derivatives **114** mainly in good yields (Scheme 109). New analogues of nicotine, anabasine and homoanabasine were synthesized in this way.[395]

Scheme 109

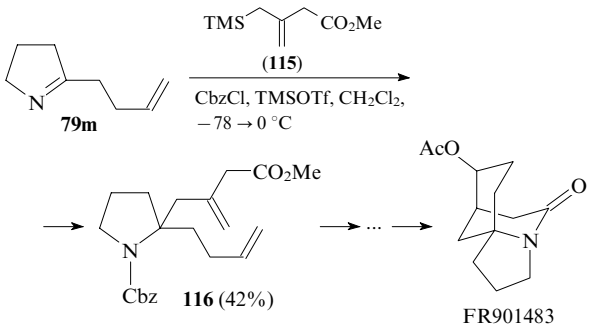


R = Alk, Ar, Het; n = 1–3

VII.2.h. Reactions with miscellaneous C-nucleophiles

Pyrroline **79m** was used in the synthesis of the immunosuppressive agent FR901483[396] (Scheme 110). The key step of this scheme was the reaction of the iminium ion, formed from pyrroline **79m** in the presence of trimethylsilyl triflate (TMSOTf), with allylsilane **115**. This was followed by carbamoylation of the resulting amine and isolation of the Cbz derivative **116**.

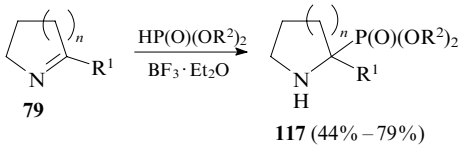
Scheme 110



VII.2.i. Addition of P-nucleophiles

It was demonstrated in a number of papers[397–399] that α-substituted cyclic imines **79** add dialkyl phosphites in the presence of boron trifluoride etherate as the catalyst, thus enabling the synthesis of alkyl aminophosphonates **117** (Scheme 111). Hydrolysis of these products yields potentially biologically active aminophosphonic acids.

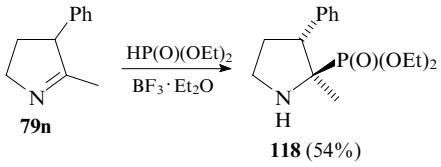
Scheme 111



R^1 = CF_3, C_2F_5, Alk, Ar, Het; R^2 = Et, Pr^i; n = 1–3

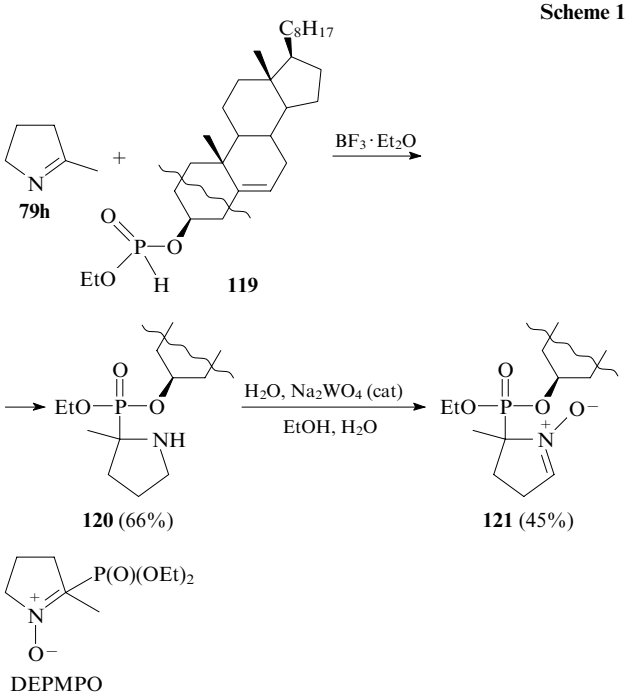
A similar result was obtained upon the addition of diethyl phosphite to 3-substituted cyclic imine **79n** also in the presence of $BF_3 \cdot Et_2O$. The reaction gave the target compound as a single diastereomer **118** in 54% yield (Scheme 112).[383]

Scheme 112



This approach was utilized to synthesize a new DEPMPO analogue widely used in EPR as a trap for detection of short-lived radicals. In this case, too, the key step was the addition of dialkyl phosphite **119** to 2-methylpyrroline **79h** giving rise to amino-phosphonate **120** as a single diastereomer in 66% yield (Scheme 113).[400] This product was converted to DEPMPO analogue **121** containing a cholesterol moiety.

Scheme 113

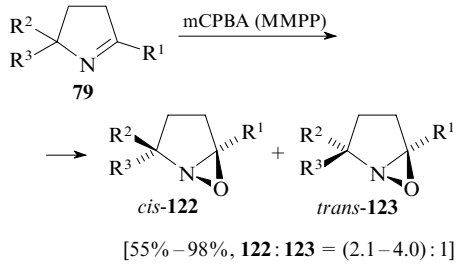


VII.2.j. Oxidation of the C=N bond

Cyclic imines **79** react with peroxy acids [*m*-chloroperoxybenzoic acid (mCPBA) or magnesium monoperoxyphthalate (MMPP)] to give the corresponding diastereomeric oxaziridines **122** and **123** in yields ranging from moderate to nearly quantitative.[401–403] On treatment of trisubstituted pyrrolines **79** (R^2 = Alk, R^3 = CO_2Et) with magnesium monoperoxyphthalate, two diastereomers with predominance of *cis*-diastereomer **122** are formed (Scheme 114).

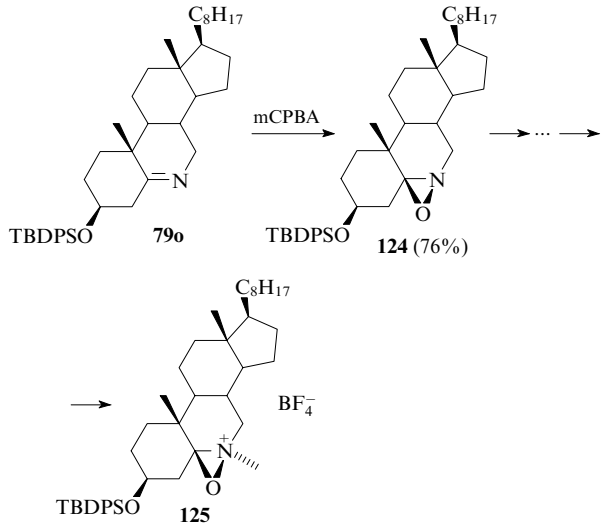
Oxaziridines possess a broad synthetic potential. They tend to react with nucleophiles, undergo radical reactions and some other types of chemical transformations.

Scheme 114



The oxidation of imine **79o** to desired oxaziridine **124** in a good yield (76%) was reported.[404] Product **124** was converted to new efficient reagent **125** for enantioselective oxidation of sulfides to sulfoxides (Scheme 115).

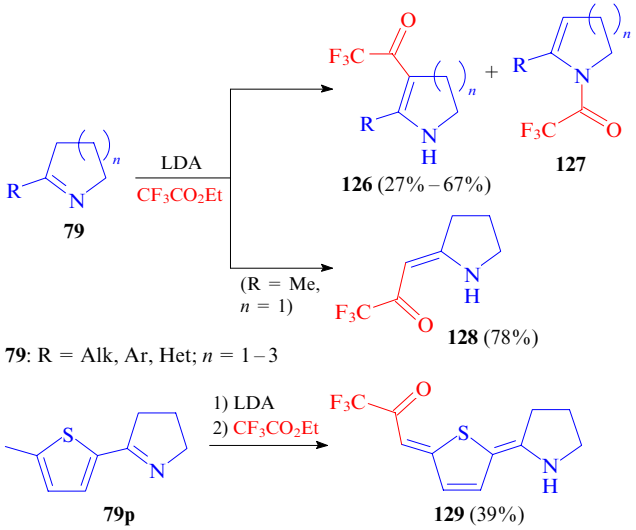
Scheme 115



VII.2.k. Preparation of aza-enolates and reactions based on them

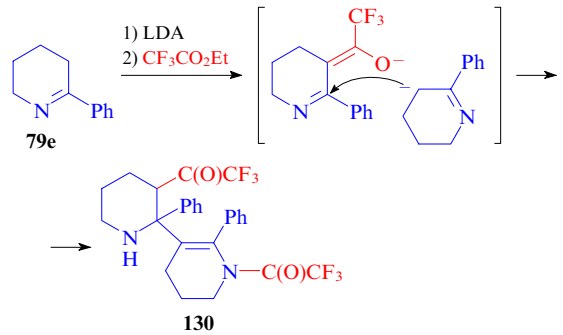
Treatment of imines with lithium diisopropylamide (LDA) affords aza-enolates, which are highly reactive nucleophiles. Treatment of deprotonated ketimines with ethyl trifluoroacetate gave acylation products — enaminoketones **126**. The by-products formed in this reaction, *N*-(trifluoroacetyl)enamines **127**, *i.e.*, aza-enolates, behave as typical ambident nucleophiles. In the case of 2-methylpyrroline (**79h**), deprotonation occurs at the methyl group, and, after acylation, exocyclic aminoenone **128** is formed.[405] It is of interest that trifluoroacetylation of imine **79p** also involved the methyl group of thiophene, resulting in the formation of compound **129** in 39% yield (Scheme 116).

Scheme 116



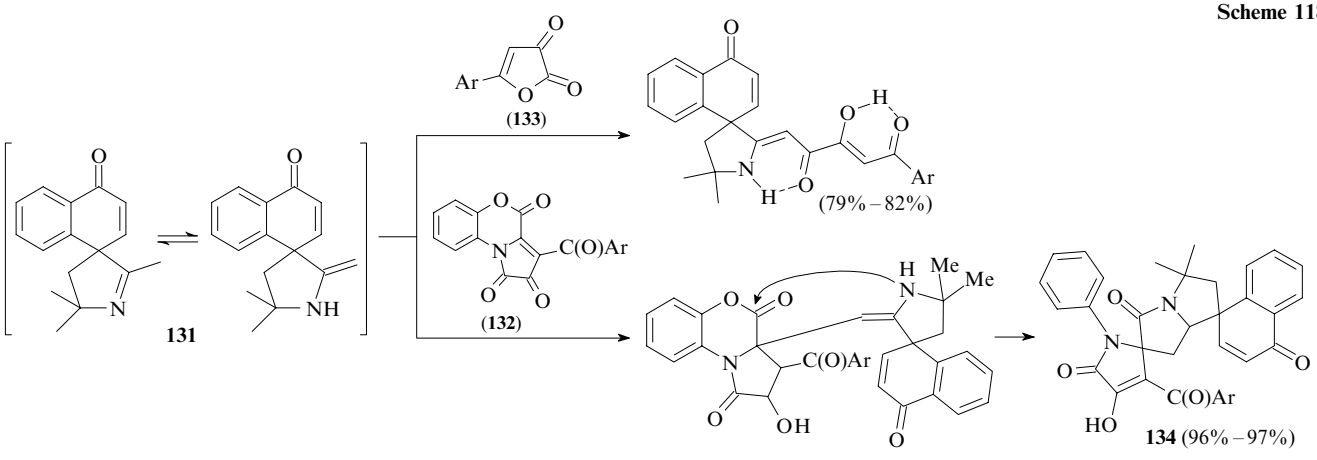
In the case of 2-phenylpiperidine **79e**, the reaction gave a considerable amount of dimeric by-product **130**. This is caused by addition of the anion derived from the starting imine to trifluoroacylated imine (Scheme 117).

Scheme 117



An unusual transformation has been reported.[406, 407] The reaction of spiro compound **131** with 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-thiones **132** or with

Scheme 118

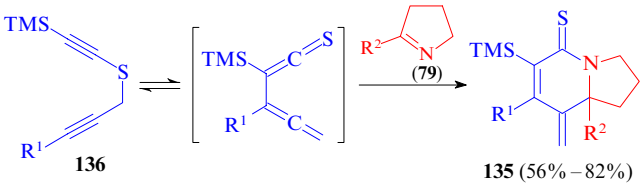


5-arylfuran-2,3-diones **133** occurs on heating. In both cases, imine **131** reacts as the enamine tautomer. In the case of compound **132**, the addition of imine is followed by heterocyclization yielding polycyclic spiro-coupled product **134** (Scheme 118).

VII.2.l. Cycloaddition reaction

Allenyl trimethylsilyl thioketenes undergo [4 + 2]-cycloaddition to imines **79** to give δ-thiolactams **135**.[408] The starting thioketenes are generated *in situ* from propargyl sulfides **136** upon [3,3]-sigmatropic rearrangement (Scheme 119).

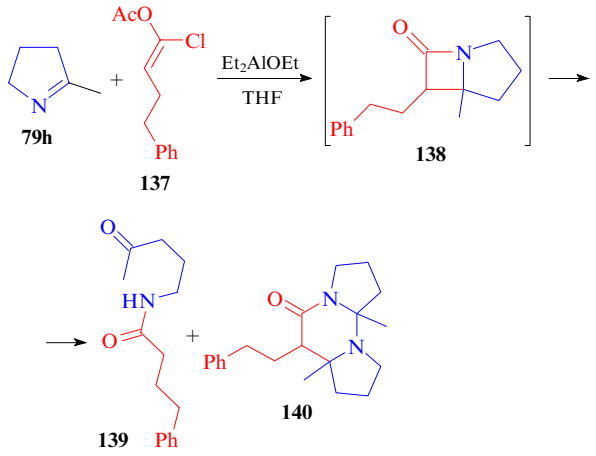
Scheme 119



R^1 = H, Me, Ph; R^2 = Me, Bu^n

New synthetic ketene equivalent **137** (α-halovinyl acetate) was studied as both a nucleophilic and electrophilic reagent in a tandem reaction with imines. Diethylaluminium ethoxide was used as the catalyst (Scheme 120). The reaction between 2-methylpyrroline **79h** and α-halovinyl acetate **137** gives intermediately β-lactam **138**, which was detected by NMR spectroscopy. However, on attempted isolation by passing through silica gel, lactam **138** decomposed to be converted to amide **139**. The other product formed in the reaction was tricyclic compound **140**, which was isolated as a by-product in 25% yield (see Scheme 120).[409]

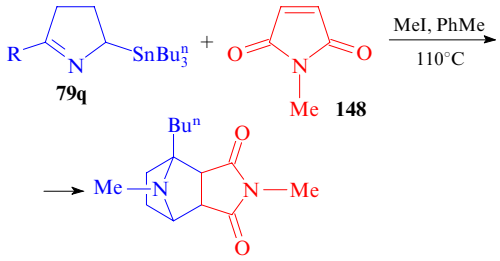
Scheme 120



Yet another type of cycloaddition reaction based on imines is the reaction of cyclic aza-allyllithium derivatives generated *in situ* from stannanes **79q** with alkenes **141** and polyenes **142a**,**b** (Scheme 121). In most cases, [3 + 2]-cycloaddition products **143**–**146** were isolated in acceptable yields and with 1 : 1 ratio of regioisomers in the case of alkenes **141** and 2 : 3 ratio in the case of cyclohexadiene (**142a**). Cycloheptatriene (**142b**) reacts with aza-allyllithium to give cycloaddition product **147** and new cyclic imine **79r** with 1 : 1 product ratio and a total yield of 67% (see Scheme 121).[410]

The same publication describes the reaction of azamethine ylide generated *in situ* from pyrroline derivative **79q** with *N*-methylmaleimide (**148**). The [3 + 2]-cycloaddition products **149** were formed in moderate yields on refluxing in toluene (Scheme 122).

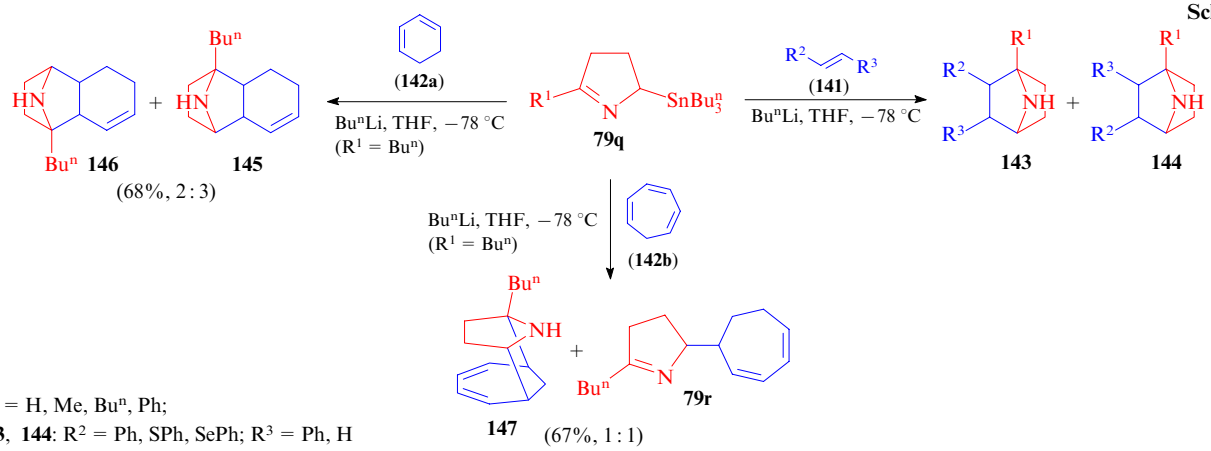
Scheme 122



R = Me, Ph

The presented information clearly demonstrates the great synthetic potential of cyclic imines, which can be easily prepared from commercially available chemicals and used in the synthesis of pyrrolidine and piperidine derivatives. The reactions involving these compounds have already found use in the synthesis of biologically active molecules or precursors of natural products. Certainly, the scope of synthetic applicability of five- and six-membered cyclic imines is not exhausted by reactions covered in this review, which were mainly published in the last 10–15 years. The approach based on the use of the open form of cyclic imines, aminoketones, is also of great interest. These

Scheme 121



R^1 = H, Me, Bu^n, Ph;
143, **144**: R^2 = Ph, SPh, SePh; R^3 = Ph, H

bifunctional reagents can be used in the synthesis of heterocycles having an aminoalkyl moiety, some of the latter compounds, for example, tryptamines, exhibit clear-cut physiological activities.[411–416]

VIII. Photocatalysis in modern organic synthesis: design of hybrid semiconductor nanophotocatalysts

The synthetic methods considered in Sections II–VII were mainly implemented under conditions commonly used in organic chemistry (thermal activation, microwave treatment and other). While analyzing the modern trends in the development of selective organic synthesis, one cannot but pay attention to rapid growth of the interest in photochemical, especially photocatalytic reactions.[417] The advent of available and convenient equipment for practical implementation of photocatalytic reactions (light-emitting diode matrices, microreactor technology, reactors for effective use of sunlight) has become an additional stimulating factor.

In recent years, works dealing with selective transformations of organic compounds on inorganic photocatalysts have been published.[418–420] Although the number of these publications is still modest, selective transformations of organic compounds in the presence of photocatalysts activated by visible sunlight at ambient temperature are of prime significance for preservation of the human health, increase in the quality of life and for environmental protection.[421–424] Indeed, the oxidation of organic pollutants of water and air photocatalyzed by inorganic semiconductors proceeds on exposure to sunlight and air oxygen,[425,426] *i.e.*, no oxidant needs to be added and no temperature change is required. The final products of this oxidation are harmless water and carbon dioxide. Conduction of the selective synthesis under direct action of sunlight or visible artificial light provides direct conversion of the electromagnetic wave energy to the chemical energy of the synthesized compounds. Owing to the direct energy conversion on the inorganic photocatalyst, *i.e.*, the absence of intermediate stages of conversion, the energy expenditures for the organic synthesis substantially diminish. Furthermore, the use of sunlight for selective oxidation is consistent with the green chemistry concept, because it saves the energy-intensive natural raw materials and rules out the discharge of hazardous wastes to the atmosphere.[427,428]

The scope of applicability of selective oxidation of organic compounds includes cleaning of water areas, industrial wastes or air including indoor air, from hazardous organic pollutants.[421–423] In addition, visible light-activated photocatalysts can be used to perform water photolysis.[424] Selective organic synthesis making use of inorganic photocatalysts is important not only for solving environmental and energy problems, in particular, for the development of so-called hydrogen power engineering, but also for targeted synthesis of new functional materials, in particular, for pharmaceutical industry.[428]

Despite the fact that the first works on the selective oxidation on metal oxide semiconductors were published more than 30 years ago,[428,429] only in the last decade, did substantial progress in this area take place.[418–420,430–439] Currently, methods for selective oxidation of various organic compounds, *e.g.*, cyclohexane,[418] ethanol,[419,420] glycerol[435] and so on are being actively developed. In parallel with the oxidation processes actually catalyzed by the same photocatalysts, development of selective reduction methods is in progress, for example, carbon dioxide reduction in cyclohexanol.[440] In addition, the influence of various factors on the selective oxidation is investigated, for example, the influence of water impurity,[418] modification of semiconductors by doping with metals[441,442] and nonmetals[442] and so on.

Photocatalysis of the selective organic synthesis is performed using inorganic semiconductors with a particular band gap. As a rule, these are semiconductors based on nanostructured oxides and sulfides or their combinations. The selectivity of photocatalyst operation is determined by the band gap width and the defectiveness of the crystal structure. The size of the band gap dictates the wavelength range in which electromagnetic radiation is absorbed and the photocatalyst is activated. For example, for operation on exposure to visible light, the band gap (E_g) of the photocatalyst should be not more than 2.5–3 eV. The operation intensity, *i.e.*, the catalytic activity, is caused by a large free surface area of the photocatalyst, which is achieved most efficiently by nanostructuring. As a rule, the smaller the particle size and the larger the surface area, the higher the catalytic activity per unit weight and unit volume of the catalyst. The intensity of photocatalyst operation also considerably depends on the concentration of active sites and on the lifetime of the electronically excited state. Note that for increasing the photocatalyst activity and the quantum yield of the reaction, it is necessary to take measures for suppressing radiative transitions in the electronic subsystem of the photocatalyst. It follows from the above that synthesis of semiconductor photocatalysts with a specified band gap, small nanoparticle and nanopore size, high concentration of the active sites, long lifetime of the electronically excited state and minimized probability of radiative transitions is a topical challenge of inorganic and physical chemistry and solid-state chemistry.

VIII.1. Selective oxidation of organic compounds by photocatalysts activated by visible sunlight

The previously developed methods for the synthesis of heavy metal chalcogenide nanoparticles (quantum dots)[443–446] imply the use of a toxic organic dispersion medium, which considerably complicates the application of these procedures in environmentally friendly processes. One of the ways for elimination of this drawback is to prepare an aqueous colloidal solution of cadmium sulfide nanoparticles.[447] Aqueous solutions of cadmium chloride and sodium sulfate are used as cadmium and sulfur ion sources, respectively, and a non-toxic aqueous solution of the disodium salt of ethylenediaminetetraacetic acid (EDTA) is used as a stabilizing agent to prevent coagulation of colloidal particles. At room temperature, this solution remains stable for a year, while at reduced temperature (4 °C), it is stable for 5 years. The dispersion medium is non-toxic true aqueous solution of sodium chloride and EDTA disodium salt.

The obtained catalysts were studied by a set of physicochemical methods.[448,449] A study of the size distribution of scattering sites found by the dynamic light scattering technique demonstrated that most of the particles have the size of 15 nm. This size includes the 1 nm thick layer of the stabilizing agent (small-angle neutron scattering data) and the 5 nm thick solvation shell. Thus, CdS nanoparticles in aqueous solutions occur in micelles, which also contain stabilizing agent molecules and polarized solvent mole-

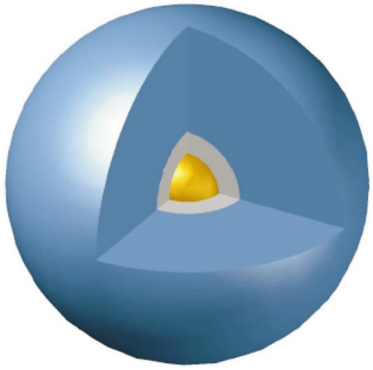


Figure 7. CdS nanoparticle (yellow) of 3 nm diameter encapsulated into a micelle.[439]
Shown are the stabilizing organic shell about 1 nm thick based on EDTA molecules (grey) and the 5 nm-thick aqueous solvation shell (blue).

cule.[447] These entities consisting of CdS nanoparticles, a stabilizing layer and a solvation shell of the dispersion medium molecules act as the scattering sites. The model of the micelle with CdS nanoparticles inside is shown in Fig. 7.

Detailed studies of the structure of cadmium sulfide nanoparticles by high-resolution transmission electron microscopy (HR TEM) and X-ray diffraction (XRD) demonstrated that particles of <5 nm size have a disordered closely packed structure with space group *P*6 and exhibit different colours of photoluminescence ranging from green to orange depending on the solution type.[450, 451]

Using optical absorption data for 1 week-, 1 month- and 1 year-aged solutions, the band gap widths were calculated to be 2.69, 2.66 and 2.66 eV, respectively. The E_g values for CdS particles from a solution that grew turbid and that exhibited the highest absorbance was 2.56 eV. Evidently, the longer the time of solution ageing, the smaller the band gap. For CdS single crystal this value is known to be $E_g = 2.36$ eV.

The observed time variations of the fluorescence wavelength and the band gap width are probably attributable to coagulation of nanoparticles in solution. Controlled coagulation of nanoparticles can be used to adjust the band gap width of cadmium sulfide, which is very important for photocatalysts working under visible light.

Due to high stability, low cost and the absence of toxicity, titanium dioxide and its various modifications are considered most often as promising photocatalysts. The above described method used to obtain a stable aqueous solution of cadmium sulfide is not used to prepare the hybrid sulfide/oxide photocatalysts, because it is necessary to ensure a high degree of adhesion of the sulfide to oxide phase. Therefore, deposition of sulfide nanoparticles on oxide nanoparticles was accomplished by using a slowly operating sulfiding agent, namely, thiourea.[437]

It is known that the key drawback of TiO_2, as regards practical use, is the insufficiently narrow band gap and, as a consequence, low photoactivity on exposure to sunlight of which only several percent fall in the range of < 365 nm.[452, 453] Therefore, to increase the efficiency of the catalytic process, it is necessary to displace the absorption band of the TiO_2 photocatalyst to longer wavelengths of the optical spectrum. Kozhevnikova *et al.*[437] reported the fabrication of a complex catalyst using semiconducting CdS. Another study [453] describes the chemical design of the composite catalyst in which spatial separation of the photogenerated electrons and holes takes place, resulting in the increased rate of photocatalytic processes. By depositing CdS particles having a narrower band gap on the wide band gap semiconductor TiO_2, the light sensitivity range of the photocatalyst extends from 365 to 515 nm; therefore, the photocatalyst can be used in the sunlight-induced photocatalyzed decomposition of water to give hydrogen.[454–456] Visible light-activated catalysts based on cadmium sulfide and titanium dioxide composite ($CdS@TiO_2$) were prepared in the aqueous medium by chemical deposition of cadmium sulfide nanoparticles on the pre-formed titanium dioxide powder nanoparticles.

Photocatalysts are prepared using two types of sulfiding agents: sodium sulfide and thiourea. The CdS nucleation and particle growth rates in solution depend appreciably on the type of sulfiding agent used, and for Na_2S, these values are fairly high and the particle size of the solid phase is very small. Therefore, to deposit CdS onto the nanocrystalline TiO_2 powder with highly extended surface [TiO_2 Hombifine N (100% anatase)], aqueous solutions of Na_2S are used. It is known that the size of CdS particles thus formed does not exceed 5 nm.[447] To deposit CdS on TiO_2 with a smaller specific surface area [TiO_2 Degussa P25 (25% rutile, 75% anatase)], the sulfide was deposited as a thin polycrystalline discrete film [457] using $(NH_2)_2CS$ as the sulfiding agent.

The overall process of CdS formation from aqueous solutions of cadmium salts and a stoichiometric amount of the sulfiding agent can be represented by the following equations:

$$CdL_n^{2+} + (NH_2)_2CS + 2\,HO^- = \\ = CdS + n\,L + H_2NCN + 2\,H_2O$$

$$CdL_n^{2+} + S^{2-} = CdS + n\,L$$

where CdL_n^{2+} is a water-soluble complex ion. As the ligands L (complexing agents), the researchers used EDTA, sodium thiosulfate, citric acid, ammonia and NaOH. The choice of the complexing agents is governed by the formation constants of the corresponding complex ions, which should be high enough to suppress the hydrolysis involving the Cd^{2+} ions, *i.e.*, to prevent the formation of oxygen-containing cadmium compounds poorly soluble in water. However, at the same time, the concentration of free Cd^{2+} ions in the solution should be sufficient for the solubility product of CdS to be achieved.

The second stage of the preparation of catalyst samples based on hybrid $CdS@TiO_2$ nanoparticles was deposition of CdS nanoparticles on TiO_2. A TiO_2 nanopowder was placed into a reaction vessel during preparation of the reaction mixture for CdS synthesis. The powder X-ray diffraction analysis and structural characterization of the $CdS@TiO_2$ systems showed that the structure of cadmium sulfide nanoparticles corresponds to a disordered closely packed cadmium sulfide structure with space group *P*6 studied by Rempel and co-workers.[450, 451] The disordered closely packed CdS structure has the same short-range order as coarsely crystalline CdS modifications of *B*3 type (sphalerite structure) and *B*4 type (wurtzite structure) and differs only by the lack of periodicity in the arrangement of closely packed cadmium and sulfur layers. For all of the

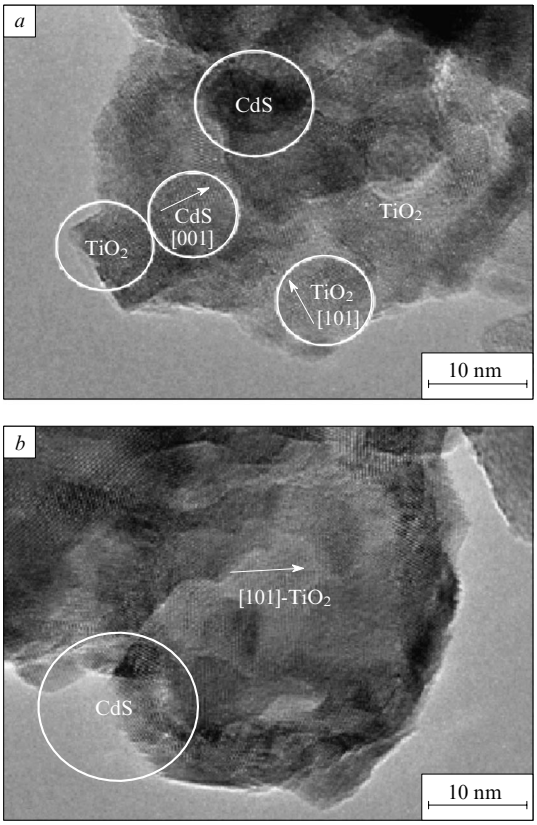


Figure 8. High-resolution TEM images of the CdS@TiO_2 powders [TiO_2 Degussa P25 (*a*) and TiO_2 Hombifine N (*b*)] prepared from aqueous solutions at 25 °C.[420]

synthesized photocatalysts, the size of titanium dioxide nanoparticles was ~5 nm.

High-resolution TEM examination was used to confirm the two-phase nature of the CdS@TiO_2 samples obtained by cadmium sulfide deposition on titanium dioxide.[420] Figure 8 *a*,*b* shows photomicrographs of the CdS@TiO_2 (Degussa P25) and CdS@TiO_2 (Hombifine N) samples. Detailed analysis of the images shows that cadmium sulfide nanoparticles isolated from one another tightly adjoin the larger titanium dioxide nanoparticles, thus forming nanoheterostructures or hybrid nanoparticles. It is the heterojunction between nanoparticles that is often responsible for high photocatalytic activity. It can be seen from these Figures that adhesion of cadmium sulfide nanoparticle on the Degussa titanium dioxide nanoparticles is higher than in the case of the Hombifine sample. In the sample containing Degussa titanium dioxide, CdS nanoparticles cover the oxide by a discrete film, while in the Hombifine sample, cadmium sulfide nanoparticles form agglomerates (10–15 nm) on the oxide surface, which have few heterojunctions with oxides.

The activity of the CdS@TiO_2 catalysts was studied in the oxidation of ethanol to acetaldehyde in a flow type system. For ethanol oxidation, the catalyst was deposited onto a glass substrate. The oxidation proceeded at the wavelength $\lambda > 400$ nm. Under these conditions, the catalytic activity of pure (*i.e.*, not modified by cadmium sulfide) TiO_2 is negligibly low.

The catalytic activity of the CdS@TiO_2 system (Degussa P25) proved to be close to the values for the CdS@TiO_2 system (Hombifine N) being 0.34 μmol of acetaldehyde per hour. The activity of CdS@TiO_2 (Hombifine N) without the addition of any complexing agent was 0.1 μmol of acetaldehyde per hour.

Thus, the design of hybrid CdS@TiO_2 nanoparticles using complexing agents gives rise to a highly active oxidation catalyst under the action of sunlight. Subsequently, it is necessary to elucidate the causes for such high activity of this two-phase photocatalyst, in particular, to elucidate the ratio of the electric potentials of the different-type sulfide and dioxide nanoparticles and the mechanism of spatial charge separation between the phases. In addition, further research should be aimed at replacing CdS by silver and tin sulfides, which are also semiconductors having narrower band gap than titanium dioxide. In this case, the photocatalyst can comply to even a higher extent with the green chemistry criteria.

From the kinetic curves presented in Fig. 9, it can be seen that the activity of the hybrid photocatalyst is very high in the first two hours, being equal to 1.49 μmol h^{-1}; after 4 h, it decreases threefold and then remains unchanged during a long period. This high stability substantially differs from the stability of pure CdS: the activity of the latter decreases sixfold in 6 h and then continues to decrease down to zero.

Since preliminary investigations have shown that CdS is unstable under conditions of catalytic transformations, *i.e.*, it is deactivated with time, it was decided to synthesize the hybrid CdS7TiO_2 photocatalysts according to a new chart. Presumably, the destruction of cadmium sulfide would be considerably retarded if CdS nanoparticles were enclosed into the TiO_2 matrix (Fig. 10 *a*) or coated by a titanium dioxide film (Fig. 10 *b*), *i.e.*, the purpose of the study[458] was to desire the TiO_2@CdS composite material. It was necessary to obtain a microstructure that would eliminate the contact of CdS with the reactants involved in the photocatalytic reaction, which induce its degradation, on the one hand, and ensure high light absorption by cadmium sulfide, on the other hand. Kozhevnikova *et al.*[458] inserted isolated CdS nanoparticles into a TiO_2 matrix by the sol–gel method. In the first stage, non-agglomerated nanocrystalline CdS particles were obtained as a colloidal solution, while in the second stage, the sol–gel method was applied:

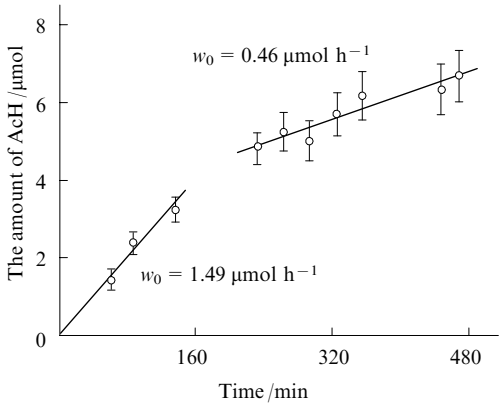


Figure 9. Kinetic curves for selective oxidation of ethanol to acetaldehyde on the hybrid CdS@TiO_2 photocatalyst.[420]

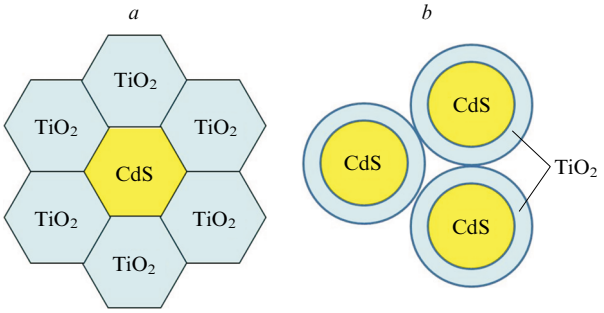


Figure 10. Models of hybrid TiO_2@CdS nanoparticles catalytically active on exposure to visible solar light.
(*a*) The CdS nanoparticle with a characteristic size of ~3 nm is tightly surrounded by titanium dioxide nanoparticles of the same size; (*b*) the CdS nanoparticle with a diameter of 3 to 5 nm is coated by a ~3 nm-thick titanium dioxide film.

hydrolysis and condensation of titanium alkoxide[459,460] were conducted in the presence of the prepared colloidal solution of CdS. Titanium tetrabutoxide $Ti(OBu^n)_4$ and a stable colloidal solution of CdS served as the initial reactants. The average size of nanoparticle agglomerates in the disperse phase of the sol (xerosol) was ~8 μm. Then the whole slurry was evaporated in air at 130 °C for 3 h. According to the laser diffraction method, the white powder obtained after drying consisted of agglomerates with an average size of ~10 μm. A scanning electron microscopic (SEM) study of the microstructure of the agglomerates formed by the hybrid TiO_2@CdS nanoparticles showed at a 500-fold magnification the average particle size of ~10 μm, which is consistent with the laser diffraction data. However, 10 000-fold magnification clearly demonstrated that these particles are dense agglomerates of smaller coagulates with a size of 200–300 nm.

An X-ray diffraction study (Fig. 11) demonstrated that xerosol particles of the CdS–TiO_2 composite contain two crystalline phases: TiO_2 (92 mass %) and CdS (8 mass %). The TiO_2 matrix both with and without the inserted CdS is a mixture of two phases: tetragonal (anatase, space group $I4_1/amd$) and orthorhombic (brookite, space group *Pbca*) phases in 1 : 3 ratio by weight.

Optical microscopy study of the sample fluorescence showed that all of them possessed photoluminescence. Stoichiometric coarsely crystalline CdS tends to emit green luminescence at ~510 nm. Green colour was observed by sight for TiO_2@CdS composite particles. Luminescence in the indicated wavelength range, *i.e.*, near the CdS fundamental absorption edge, implies the formation of bound electron–hole pairs (excitons) in CdS nanoparticles. In the case of proper contact between the CdS nanoparticle and the TiO_2 matrix, owing to the lower potential of the TiO_2 conduction band compared to the potential of the CdS conduction band in the sulfide–oxide pair, an electron excited in the sulfide can migrate to the TiO_2 conduction band (Fig. 12) and, being on the TiO_2 surface, participate in the catalytic reaction. The indicated electron transitions lead to substantial stabilization of sulfide particles in the photocatalyst because they only function as suppliers of excited electrons to the oxide matrix. Hence, the degree of deactivation of the composite photocatalyst considerably decreases.

Thus, it has been proven[458] that a sol–gel process using $Ti(OBu^n)_4$ and a stable aqueous colloidal solution of CdS nanoparticles affords the TiO_2@CdS composite material, while the gelation stage is bypassed. The experimentally found fluorescence of the composite near the CdS fundamental absorption edge attests to a high probability of exciton formation in CdS particles on exposure to light. In turn, this implies the presence of a heterojunction between the CdS particles and the TiO_2 matrix and, hence, hitting the goal set forth in the study — embedding isolated CdS nanoparticles into a wide band gap crystalline TiO_2 matrix. Thus, the microstructure of the obtained TiO_2@CdS composite provides high photocatalytic activity, while the transfer of energy as excited electrons from sulfide to oxide particles makes the photocatalytic activity substantially more durable.

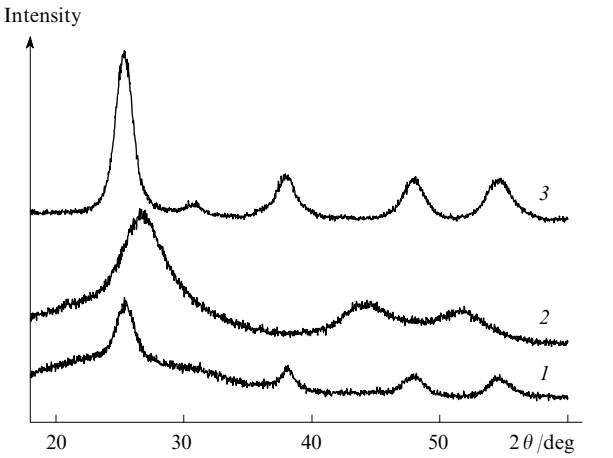


Figure 11. X-Ray diffraction patterns of the TiO_2@CdS composite xerosol (*1*), disperse phase of the aqueous colloidal solution of CdS (*2*) and xerosol of the matrix TiO_2 (*3*) recorded using Cu$K\alpha_{1,2}$ radiation.[458]
The nanoparticles of the CdS disperse phase have a disordered closely packed structure (space group *P*6) and have a ~3 nm size.

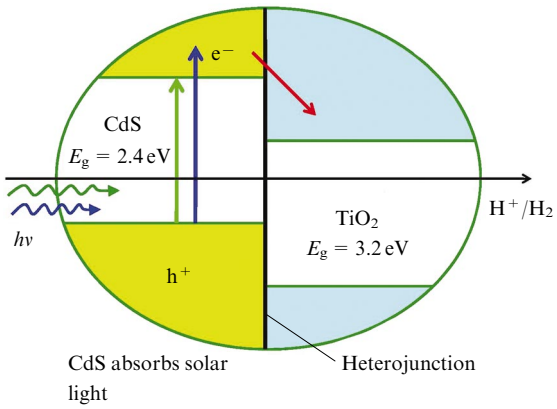


Figure 12. Diagram of excitation of the active sites in the hybrid semiconductor TiO_2@CdS nanoparticle.
The vertical line in the centre shows the nanoheterojunction between the CdS nanoparticle and TiO_2. The electron transfer from the CdS valence band is done by light quanta *hv* with > 2.4 eV energy.

The key problems that have not yet been solved in the selective synthesis of organic compounds on inorganic semiconductor photocatalysts on exposure to visible light can be divided into two groups. The first group refers to selection of the optimal chemical and phase composition of the photocatalyst, while the second group concerns the tailored synthesis (design) of particular photocatalysts.

While selecting the optimal composition, it is necessary to solve problems related to adjustment of the photocatalyst band gap, combining the catalytic activity and photoluminescence, degradation of the photocatalyst with time, development of methods for purification and regeneration of the photocatalyst. The problem of adjusting the band gap can be solved by nanostructuring, namely, by changing the size of nanoparticles or nanopores that form the active surface of the photocatalyst. In this regard, an important role is played by the quantum confinement of excitons in the photocatalyst and by the optimal combination of phases of hybrid photocatalysts. The suppression of photoluminescence for increasing the catalytic activity can be achieved by reducing the probability of radiative transitions as a result of affecting the electron and photon subsystems of the photocatalysts. The problem of activity decrease and regeneration of the photocatalysts should be solved considering the construction of the correct spatial distribution model for active sites performing the oxidative and reductive reactions. Furthermore, it is necessary to find methods for catalyst treatment to remove the reaction products and other derivatives that are often deposited on the surface. In some cases, these deposits are very strongly attached to the photocatalyst.

The implementation of the tailored syntheses or, in essence, the design of the photocatalyst is related to selection and combination of synthetic procedures and to the search for new, in principle, synthetic methods. The traditional high-temperature methods (gas phase synthesis, chemical and physical vapour deposition, plasmochemical synthesis, self-propagating high-temperature synthesis) and low-temperature methods (chemical deposition, sol–gel procedures, solvothermal and sonochemical synthesis) are used for this purpose. Development of new methods of synthesis is based on the latest achievements of the physics, chemistry and biology.

When the photocatalyst has been manufactured, the question inevitably arises of what is the real mechanism of the photocatalytic reaction. Here it is necessary to use both *ex situ* and *in situ* methods, the latter becoming more and more available.

The prospects for development of *in situ* methods with excitation of the electron and phonon subsystems of the photocatalyst directly during the photocatalytic reaction are very high owing to the advent of powerful sources of X-ray (synchrotron) and neutron radiations both all over the world and in Russia. Intense X-ray and neutron beams can penetrate directly into the chemical reactor where the photocatalytic reaction occurs and provide the experimentalist with information about the photocatalyst behaviour.

Owing to the development of targeted methods for the synthetic design of complex nanostructures, it would become possible to overcome the key difficulties of the selective synthesis. By using these nanostructures and substantiated combination of inorganic semiconductor phases, it is possible to increase the yield of the product of organic photocatalytic synthesis and increase the process selectivity.

IX. Approaches of the surface science to the development of new catalytic systems for organic synthesis

Currently, most of selective organic reactions are based on homogeneous catalytic systems, which have demonstrated outstanding synthetic potential in a considerable number of important reactions (see Sections II–VIII). Nevertheless, for scaling up the processes and decreasing the production cost, heterogeneous catalytic systems are still of prime importance. A number of heterogeneous catalytic processes with selectivity compared with or even surpassing that of homogeneous processes can be regarded as very interesting findings. However, for active introduction of heterogeneous catalytic systems into the everyday practice of fine organic synthesis, it is necessary to bear in mind a number of important specific features of the design of catalytic systems described below. Subsequent Sections X–XII consider particular examples of implementation of in-demand synthetic methods.

In recent years, a fundamental approach to the development of new catalytic systems, including those for organic synthesis, has become popular in the science of catalysis. A distinctive feature of this approach, as opposed to the more traditional empirical approach, is that the molecular design (controlled assembly) of the active component is preceded by detailed investigations of the mechanisms of catalytic reactions and structures of active sites. In the case of homogeneous catalytic processes where the catalytic reaction is a sequence of stoichiometric steps of transformation of usual, although often intricate, chemical compounds, this approach can be efficiently implemented by means of physical methods sensitive to the molecular structure (*e.g.*, NMR, EPR or IR spectroscopy). These methods are used not only to measure the concentrations of reactants and reaction products but also to determine the structures of intermediates. Thus, a detailed mechanism of the catalytic reaction can be determined.

The situation becomes much more complicated if we are dealing with a heterogeneous catalytic process of organic synthesis that is catalyzed by particles of noble metals (Pd, Ag, Au, Pt) deposited on oxide or carbon supports with large specific areas (from ten to several hundreds of $m^2\ g^{-1}$). In this case, the low concentration of the active component (for noble metals, it usually does not exceed 1 mass %–2 mass %) is at the limit or even below the limit of sensitivity of many physical methods. This circumstance, together with the nonuniform size distribution of metal particles, complicates the measurements and isolation of spectral characteristics of surface active sites responsible for the catalytic reaction.

Solution to this problem became possible owing to the vigorous development of a field of knowledge adjacent to heterogeneous catalysis, namely, the surface science, which is based on the use of surface-sensitive physical methods to study the structure and composition of a solid surface. Unlike standard methods, physical methods for surface investigation collect information only on several surface layers (up to 10 nm), which also makes it possible to study the surface structures of the adsorbed particles formed upon reactant activation.

The second foundation stone of the surface science approach is investigation of the model catalysts in which the surface concentration of the active component can be increased. Analysis of publications demonstrates that the applied model catalysts can be subdivided into three large groups:

(i) atomically smooth (low-index) and stepped single crystal surfaces (their definite surface structure is suitable for studying structural effects);

(ii) supported monometallic particles on flat massive or film supports (a change in the amount of sputtered metal results in variation of the resulting particle size and, as a consequence, in the possibility to study size effects);

(iii) supported bimetallic particles on flat supports (a change in the coverage of the surface of metallic particles by a particular metal achieved by varying the annealing temperature and the ratio of metals taken provides the possibility to study the synergistic effects).

Among modern trends of application of surface science approaches to catalysis, mention should be made of the development of physical methods of surface investigation for *in situ* experiments, *i.e.*, reactions in the presence of the gas phase above the sample. Indeed, the pressure during catalytic measurements ($P \geqslant 1$ bar) can be several orders of magnitude higher than that used in surface science experiments ($P \leqslant 10^{-6}$ mbar) and, as a consequence, the chemical potential of the gas phase, which is ignored under ultrahigh-vacuum (UHV) conditions, starts to make a significant contribution to the free surface energy. This means that structures identified under unrealistic UHV conditions could hardly play any role in catalytic reactions. The changes in the structure and composition of the surface and near-surface catalyst layers taking place in this case can be of paramount importance not only for catalyst activity but also for the whole reaction mechanism.

This Section is an attempt to demonstrate the potential of surface science approaches as applied to investigation of two comparatively simple catalytic organic reactions — oxidative conversions of ethylene to ethylene oxide and to vinyl acetate. The ethylene oxide synthesis by direct oxidation of ethylene with oxygen

$$C_2H_4 + 0.5\,O_2 \longrightarrow C_2H_4O$$

discovered by Lefort[461] in 1935 is currently the best known large-scale industrial process of organic synthesis using modified $Ag/\alpha\text{-}Al_2O_3$ catalysts. The world consumption of ethylene oxide amounts to millions tonnes per year and continues to increase.[462]

The synthesis of vinyl acetate from ethylene and acetic acid in the presence of oxygen

$$C_2H_4 + 0.5\,O_2 + CH_3CO_2H \longrightarrow CH_3CO_2CH{=}CH_2$$

can be accomplished as either a liquid-phase or vapour-phase process. In the former case, the process is carried out in acetic acid with AcONa or LiCl additives in the presence of a homogeneous $PdCl_2$ catalyst and $CuCl_2$ at 110–130 °C and 1–3 MPa.[463] The vapour-phase synthesis of vinyl acetate is conducted by passing a mixture of ethylene, oxygen and acetic acid vapour through a solid catalyst bed at 100–250 °C and 0.5–1.0 MPa.[464] Platinum metals, most often, palladium supported on various porous materials serve as catalysts. The content of platinum metals is 0.1 mass %–10 mass %. Quite a few known patents propose introducing gold into the palladium catalyst to increase its productivity.[465]

IX.1. Catalyst design and experiment setting up procedure

Before proceeding to the results of investigations of the mechanisms of above-indicated catalytic reactions, it is necessary to discuss characteristic features of sample preparation for model investigations.

IX.1.a. Single crystals

The interest of researchers in single crystals as model metal catalysts, which predominated in the 1970–1990s, was due to the quest for elucidating the effect of the surface structure on the nature of species formed upon adsorption of small molecules and transformation steps of these species into the intermediates and products of the catalytic reaction. The preparation of single crystals with a definite surface structure for experiments starts with growing perfect single crystalline rods of diameter $\sim$1 cm, which are then cut along one of the crystallographic directions to form a 1–2 mm-thick parallel-plate pellet, which thus restricts the contribution of the side surfaces with uncertain structure ($< 10\%$). The disorder of the principal faces of the pellet should not exceed 1 deg (better, fraction of a degree) from the chosen orientation. Cutting at a large angle provides allows for the formation of stepped single crystal surfaces with a strictly definite terrace size and monoatomic step structure. The subsequent treatment of the single crystal surface is performed in high vacuum chambers of spectrometers and, as a rule, involves the standard cleaning cycle repeated many times, comprising surface etching by argon ions, heating in an oxygen atmosphere under specified temperature conditions and the final UHV annealing at premelting temperatures.

IX.1.b. Supported metal particles on planar substrates

The most popular method for the reproducible preparation of model supported catalysts is the ultrahigh-vacuum deposition of disperse metal particles on a planar support.[466–468] When this preparation of metal nanoparticles is carried out inside spectral equipment, it is possible, first, to pretreat and prepare of the support and the sputtering system and, second, to transfer the prepared sample into the analysis zone without contact with air. Thus, one can avoid surface contamination and quickly prepare a series of samples with variable size of metal clusters. This circumstance accounts for the large number of studies that used this technique to model real catalysts in order to study the electronic properties and morphology of metal nanoparticles depending on their size. Attempts were also made to study adsorption on disperse metal particles.[469, 470]

Despite the obvious advantages, for effective use of this preparation technique in the catalytic studies, special precautions in the support preparation should be taken. On the one hand, the support should provide heating of the sample up to the reaction temperature (as a rule, several hundred degrees) in the presence of the reaction medium, while the chemical composition of the support should remain invariable, and ensure the stability of metal particles against sintering, on the other hand, the substrate should have a good conductivity, which is required for investigations by scanning tunnelling microscopy (STM, measures the tunnel current between the tip and the conducting sample), X-ray

photoelectron spectroscopy (XPS, removing the electron photoemission-induced charge leading to spectral line broadening) and so on. These problems can be solved without deterioration of the atomic smoothness of the support (which is necessary for STM determination of the size of nanoscale metal particles) by using thin oxide films [*e.g.*, Al_2O_3 films grown on the surface of NiAl(110) metallic single crystals[466]] and highly oriented pyrolytic graphite (HOPG) the surface of which is modified either chemically or by formation of induced defects.[468]

The procedural details of using physical methods for *in situ* investigations of the surface and adsorbed species during the catalytic reactions also deserve special discussion, which is beyond the scope of this Section (see, for example, Ref. 471).

IX.2. Catalytic epoxidation and acetoxylation

IX.2.a. Ethylene epoxidation

Despite the immense interest in the study of silver-catalyzed ethylene epoxidation using physical techniques of surface science,[472–477] the nature of oxygen species active in ethylene epoxidation has long remained a debated issue.[472–475] This situation was related to impossibility of simultaneous investigation of adsorption layers and testing of catalytic properties, while only in this case, it would be possible to elucidate the correlations between the concentration of various adsorbed oxygen species and the yield of the reaction products — ethylene oxide and CO_2 (resulting from total oxidation of ethylene). The situation changed only in the last decade owing to the advent of the *in situ* XPS method, which can be used to measure the spectra in the millibar pressure range[471] in which ethylene oxide starts to be detected in the reaction products by, for example, mass spectrometry.[478] Figure 13 presents the mass spectra of ethylene oxide measured by the proton transfer reaction mass spectrometry (PTR-MS) for two different pressures; the presented data confirm the existence of the pressure gap problem for this reaction. Indeed, no ethylene oxide signal is present in the PTR-MS spectra at $P(C_2H_4)$ = 0.0715 mbar, and only a pressure increase to 1 mbar results in the appearance of this signal starting from the temperature of 420 K.

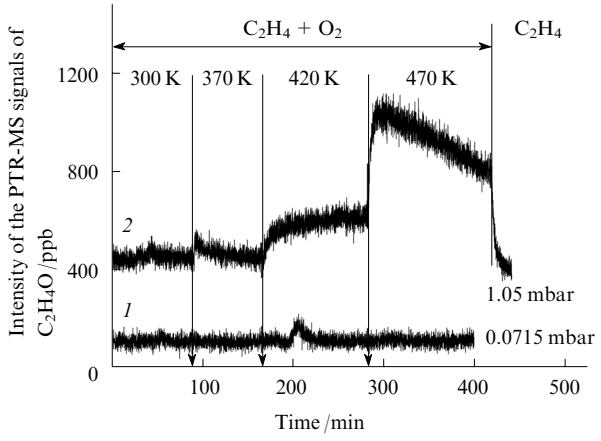


Figure 13. Change in the PTR-MS signals of ethylene oxide in the reaction mixture *vs.* the sample temperature: $P(C_2H_4)$ = 0.0065 mbar, $P(O_2)$ = 0.065 mbar (*1*); $P(C_2H_4)$ = 0.1 mbar, $P(O_2)$ = 0.95 mbar (*2*).[478]
The last part of the high-pressure curve is measured in the absence of O_2.

The O1s core level spectra recorded under similar conditions indicate that only nucleophilic oxygen (O_{nucl}) characterized by the O1s binding energy of 528.2 eV occurs on the surface at low pressure. This state was observed in most studies that used post-reaction analysis; it was shown that this oxygen is active only towards the total oxidation of ethylene to CO_2 and H_2O. The pressure increase to 1 mbar results in a second component with a higher binding energy appearing in the spectrum. Results of numerous experiments of this sort at different reactant ratios, temperatures and pressures made it possible to plot linear correlations between the concentration of this oxygen species and the ethylene oxide yield (Fig. 14). This substantiated the involvement of this oxygen, which was called electrophilic (O_{el}), in the ethylene epoxidation step.[478]

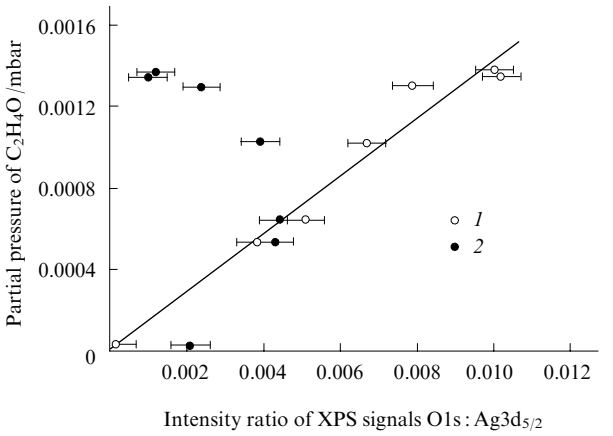
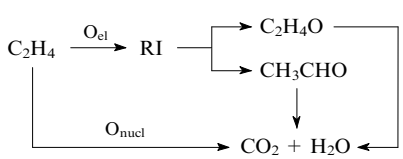


Figure 14. Correlation of the concentrations of electrophilic (*1*) and nucleophilic (*2*) oxygen species with the ethylene oxide yield.[478]

An attempt to plot a similar correlation for nucleophilic oxygen showed, as expected, the opposite trend: the yield of ethylene oxide decreased upon the increase in the O_{nucl} concentration (see Fig. 14). On the basis of the obtained data, a reaction mechanism was proposed (Scheme 123).

Scheme 123



RI is the reaction intermediate

More recently, it was shown that the formation of electrophilic oxygen is related to considerable restructuring of the initial silver surface, which is also caused by interactions with components of the reaction medium at high pressure.[479]

IX.2.b. Size effect in ethylene epoxidation

Yet another issue that would have not been resolved without the use of model silver catalysts is interpretation of the

size effect in the epoxidation, which is manifested as an increase in the reaction rate by more than an order of magnitude upon the increase in the silver particle size to > 50 nm.[480] Indeed, the intense O1s signal from alumina in 'real' Ag/α-Al_2O_3 catalysts overlaps the signal from the surface oxygen species, which made the XPS method non-informative for identification of ethylene epoxidating oxygen (O_{el}, see the previous Section). It was proposed to replace alumina by a carbon substrate, namely by HOPG. Owing to the atomically smooth surface of HOPG, this would enable using STM and SEM methods to determine the silver particle size. This brings about two problems that are to be solved for successful *in situ* studies. The first problem is related to the weak interaction of silver particles with the defect-free surface of the annealed pyrolytic graphite and, as a consequence, high mobility of silver particles on the atomically smooth HOPG surface with the diffusion coefficient reaching 10^{-8} cm^2 s^{-1} (Ref. 481), which may result in fast agglomeration of the silver particles. The second problem is possible degradation of HOPG due to burning of the carbon support under the oxidative atmosphere of the reaction.

For the solution of the first problem, a procedure for forming a defective HOPG surface by soft ion etching was proposed. It was assumed that these defects would serve as sites for crystallization and stabilization of silver particle.[468] Figure 15 shows the STM and SEM images of two model Ag/HOPG samples with equal atomic ratio $Ag:C \approx 0.5$ prepared by UHV thermal sputtering of silver onto atomically smooth (sm) (see Fig. 15 *a*) and defective (see Fig. 15 *b*) graphite surfaces followed by annealing of samples at 250 °C. It can be seen that silver particles deposited on a smooth HOPG surface sinter at high temperatures to form agglomerates located near steps, that is, borders of atomically smooth surface terraces. In the case of the Ag/HOPG(Ar) sample with the initially defective surface, the situation is quite different: silver nanoparticles are uniformly distributed over the surface and have a rather narrow size distribution. Analogous conclusions can be drawn from the high-resolution SEM data (see Fig. 15 *c*,*d*). These results served for the development of a preparation procedure for model Ag/HOPG catalysts having high stability of Ag particles against sintering at elevated temperature, comprising the following stages: (i) etching of the HOPG surface with argon ions in order to create stabilization sites for the silver particles being sputtered; (ii) silver sputtering (it was shown that the amount of introduced metal determines the average particle size); 3) heating of the pretreated surface at $T \geqslant 250$ °C in a vacuum in order to anneal defects and stabilize the surface of the model catalyst.

The stability of pyrolytic graphite against the oxidative atmosphere was also verified by SEM. Figure 16 presents the SEM images of the Ag/HOPG(Ar) sample after being used in ethylene epoxidation experiments ($O_2:C_2H_4 = 5:1$, $P = 0.25$ mbar) at various temperatures for several hours. It can be seen that below 230 °C, the sample surface is stable (see Fig. 16 *a*), whereas the temperature rise to 250 °C results in burning-out of graphite layers under diffusing and agglomerating silver particles (see Fig. 16 *b*). The detected temperature limit of stability of pyrolytic graphite in the reaction medium in the presence of silver particles restricts the application of model Ag/HOPG catalysts for *in situ* investigation of ethylene epoxidation to a temperature of 230 °C, which, however, is high enough for ethylene oxide to be detected among the reaction products.[478]

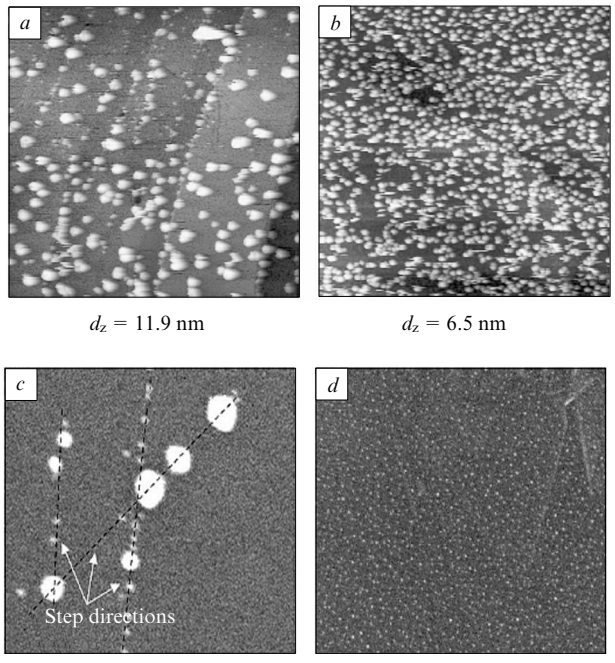


Figure 15. Images obtained by STM (100×100 nm) (*a*, *b*) and SEM (500×500 nm) (*c*, *d*) for the Ag/HOPG (sm) (*a*, *c*) and Ag/HOPG(Ar) (*b*, *d*) samples after heating in vacuum at 250 °C for 1 h (d_z is the particle height).[468]

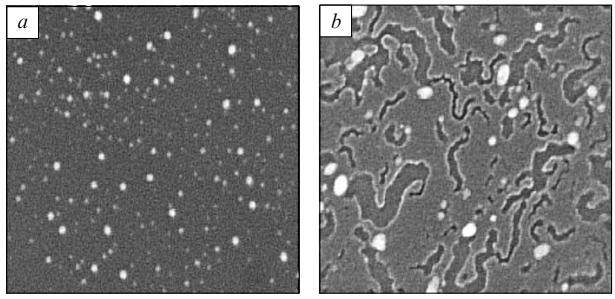


Figure 16. SEM images (250×250 nm) of the Ag/HOPG(Ar) surface recorded after the sample has been used for many hours in ethylene epoxidation experiments ($P = 0.25$ mbar) at 230 (*a*) and 250 °C (*b*).[468]

To study the nature of the size effect in ethylene oxidation, two Ag/HOPG(Ar) samples with an average metal particle size of 8 and 40 nm, were prepared by the developed procedure. Figure 17 presents the changes in the PTR-MS signals of ethylene oxide and XPS spectra for the Ag/HOPG (8 nm) and Ag/HOPG (40 nm) samples recorded in the 170–210 °C temperature range.[482] It can be easily seen that, in full conformity with published data,[480] ethylene oxide cannot be detected among the reaction products when a sample with fine silver particles is used, whereas the Ag/HOPG sample with coarse particles exhibits catalytic activity in ethylene epoxidation (see Fig. 17 *c*,*d*). This

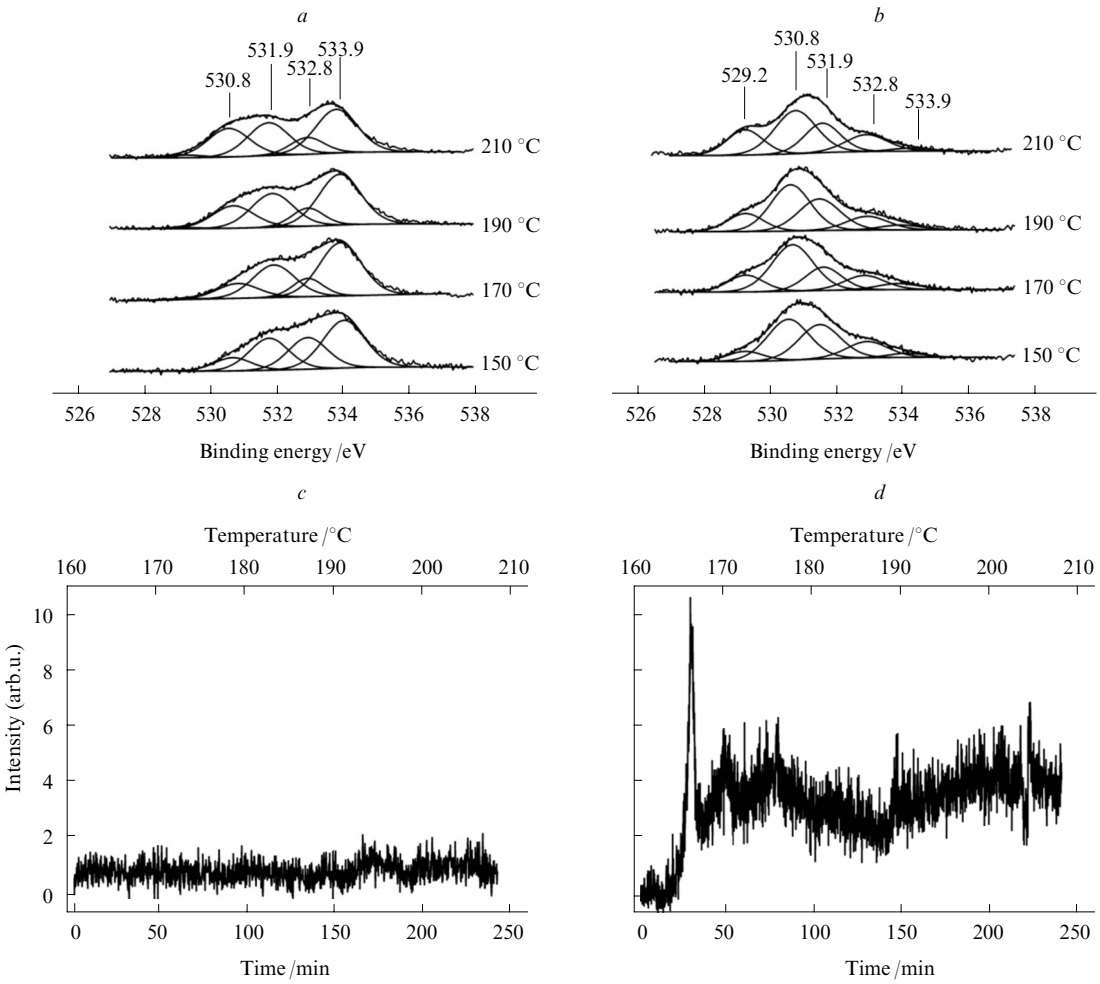


Figure 17. Photoelectron O1s spectra (*a*, *b*) and change in the mass spectrometric signal for ethylene oxide (*c*, *d*) *vs.* temperature and time for the Ag/HOPG samples with an average silver particle size of 8 (*a*, *c*) and 40 nm (*b*, *d*).[482]
Experimental conditions: $C_2H_4 : O_2 = 2 : 1$, $P = 0.5$ mbar.

behaviour can be interpreted based on analysis of the XPS spectra. The key distinctive feature of the O1s spectrum of the coarse-particle sample is the presence of a peak with the binding energy of 529.2 eV due to nucleophilic oxygen on supported silver particles.[482] The peak with $E_b(O1s) =$ 530.8 eV is a superposition of two oxygen species — oxygen dissolved in the surface layers of silver particles and O_{el} providing the formation of ethylene oxide (see Fig. 17 *a*,*b*). Peaks at higher binding energies correspond to oxygen-containing functional groups on the support surface.[482] Thus, it is the appearance of nucleophilic oxygen that triggers the activity of silver in the ethylene epoxidation, which accounts for the size effect.[480]

The question of why the presence of nucleophilic oxygen, which is active in the total oxidation of ethylene, increases the activity in the epoxidation, can be answered by taking into account the transfer of electron density from silver to oxygen and formation of Ag^+ ions.[479] These silver ions serve as sites of ethylene adsorption as π-complexes without activation of the C–H bond. Only after that, is the adsorbed ethylene able to react with electrophilic oxygen to give ethylene oxide either *via* the formation of oxymetallacycle[477] or directly.[480] The reaction mechanism proposed relying on model investigations can not only account for specific features of the process such as the need to promote the silver catalyst used in industry by chlorine and caesium compounds and the higher selectivity of bimetallic Ag–Cu catalysts in this reaction but can also help to develop approaches to the design of the optimal silver catalyst for propylene epoxidation.[483]

IX.2.c. Oxidative acetoxylation of ethylene

The ethylene adsorption as a π-complex is also the key factor ensuring the high selectivity of oxidative acetoxylation of ethylene. Along with this desired reaction, other side reactions can occur in the system and thus decrease the selectivity towards vinyl acetate (Scheme 124).

Scheme 124

$$C_2H_4 + 3\,O_2 \longrightarrow 2\,CO_2 + 2\,H_2O$$

$$CH_3CO_2H + 2\,O_2 \longrightarrow 2\,CO_2 + 2\,H_2O$$

$$CH_3CO_2CH{=}CH_2 + 2.5\,O_2 \longrightarrow 2\,CO_2 + 3\,H_2O$$

The contribution of these reactions has been estimated.[484] It was shown that at the temperature of vinyl acetate synthesis (413 K),[485] the rate of palladium-catalyzed oxidation of acetic acid is relatively low, and acetic acid addition does not affect the kinetics of ethylene oxidation.

Similar experiments dealing with the effect of vinyl acetate on the CO_2 formation rate demonstrated that introduction of 3.5 kPa $CH_3CO_2CH{=}CH_2$ into the reaction mixture comprising ethylene, acetic acid and oxygen resulted in an increase in the total oxidation rate by only 5%.[484] Thus, it was concluded that the major contribution to the decrease in the selectivity towards vinyl acetate is made by the total oxidation of ethylene, which, in turn, depends on the type of ethylene adsorption.

The ethylene adsorption and decomposition have been studied in detail by temperature-programmed desorption (TPD) on model Pd/SiO_2 and $Au-Pd/SiO_2$ catalysts.[486] Uniform heating of the sample, without which TPD experiments are impossible, has been provided by a special design of the model catalyst based on a refractory molybdenum single crystal. A SiO_2 film grown epitaxially on the Mo(110) surface is complementary to the metal structure.[487] One monolayer (ML) of palladium and then gold in different amounts (from 0.1 to 1 ML) were sputtered on the prepared SiO_2 film and then the samples were annealed in a vacuum at 800 K. A study of adsorption of deuterated ethylene on the samples prepared in this way showed that in the case of a monometallic palladium sample, adsorption at 90 K gives rise to a broad desorption peak with T_{max} = 250 K. Upon introduction and increase in the content of gold, this peak narrows down and the desorption maximum shifts towards lower temperatures (down to 215 K) (Fig. 18 *a*). In view of the fact that in the case of bimetallic samples, D_2 formed upon C_2D_4 decomposition disappears from the TPD spectra (see Fig. 18 *b*), the low-temperature peak in the TPD spectrum of C_2D_4 was assigned to ethylene desorption from the π-complex. Considering the intense D_2 desorption peaks recorded after adsorption on the monometallic palladium sample or on the samples with low gold contents (see Fig. 18 *b*), the high-temperature shoulder in the TPD spectrum of ethylene was identified as desorption from the di-σ-state, which is the intermediate for the total ethylene oxidation pathway.[486] These data demonstrate that the introduction of gold changes the surface composition of particles.

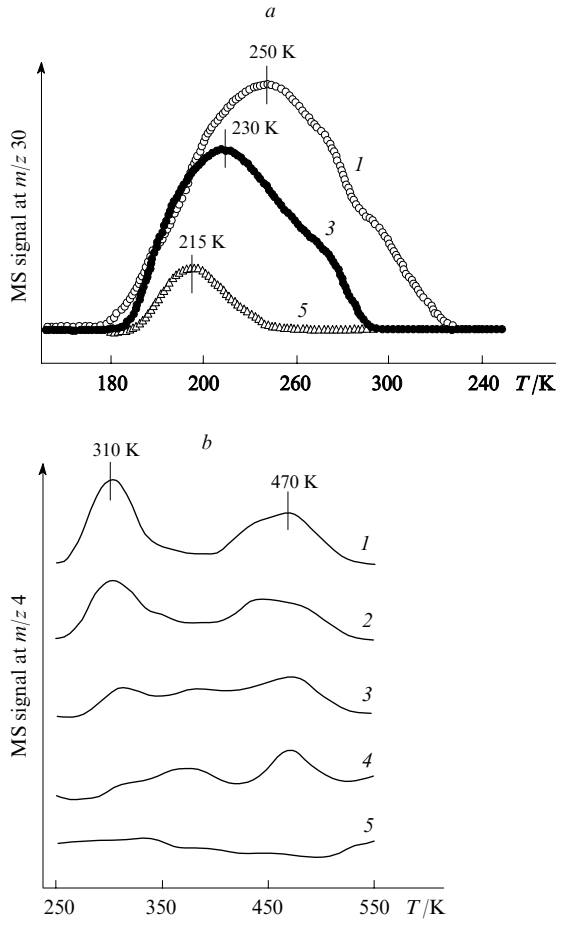


Figure 18. TPD spectra of C_2D_4 (*a*) and D_2 (*b*) recorded after adsorption of C_2D_4 (exposure of 2.0 L) at 90 K on model catalyst samples [the gas exposure unit is Langmuir (L): 1 L = 10^{-6} Torr s).[486]
(*1*) Pd(1 ML)/SiO_2, (*2*) Au(0.1 ML)/Pd(1 ML)/SiO_2, (*3*) Au(0.2 ML)/Pd(1 ML)/SiO_2, (*4*) Au(0.4 ML)/Pd(1 ML)/SiO_2, (*5*) Au(1 ML)/Pd(1 ML)/SiO_2.

The surface composition of the prepared bimetallic catalysts was studied by the ion scattering spectroscopy (ISS),[488] while the atomic structure of the surface sites was investigated by IR spectroscopy.[489] These experiments were carried out using model samples of a different type in which gold and palladium were successively sputtered onto a cleaned surface of the Mo(110) face. Owing to the high melting point of molybdenum, the samples could be heated up to the gold (1400 K) and palladium (1420 K) desorption temperatures,[486] which was used for calibration and for estimation of the amount of introduced metal depending on the sputtering time. During the deposition of metal onto metal, layer-by-layer coverage by the Frank–van der Merwe mechanism[490] takes place to give a continuous film, which is necessary for efficient use of ISS and IR spectroscopy. If the metal is deposited on silica, as in the previous example, the stronger metal–metal interaction (cohesion) compared with the metal–oxide interaction (adhesion) provides the formation of 3D particles by the Volmer–Weber mechanism.[486, 490]

Two samples with different metal sputtering sequences, (i) Pd/Au/Mo(110) and (ii) Au/Pd/Mo(110), were prepared for these experiments. Figure 19 *a* presents the initial ion scattering spectra, which represent the dependence of the number of elastically reflected low-energy He^+ ions on the ion energy, while Fig. 19 *b* shows the temperature dependence of the palladium and gold concentration in the surface layer. The He^+ ions monochromatic in energy are formed in a special source and reflected from palladium and gold atoms and, hence, they are manifested in the ion scattering spectra at different energies (see Fig. 19 *a*), which enables chemical analysis of the surface. It can be seen that successive deposition of gold and palladium gives rise to the corresponding peaks in the ion scattering spectra; the introduction of palladium hides almost completely the gold signal, which proves that the films grow by the Frank–van der Merwe mechanism. An increase in the temperature leads to blending of the gold and palladium films to give an alloy, which is manifested as a gradual decrease in the palladium signal and an increase in the gold signal. Quantitative data (see Fig. 19 *b*) demonstrate that the system achieves at equilibrium at 700 K, and then up to the annealing temperature of 900 K, the surface composition does not change. The same state of the surface is also achieved for the second sample in which gold was deposited after palladium (see

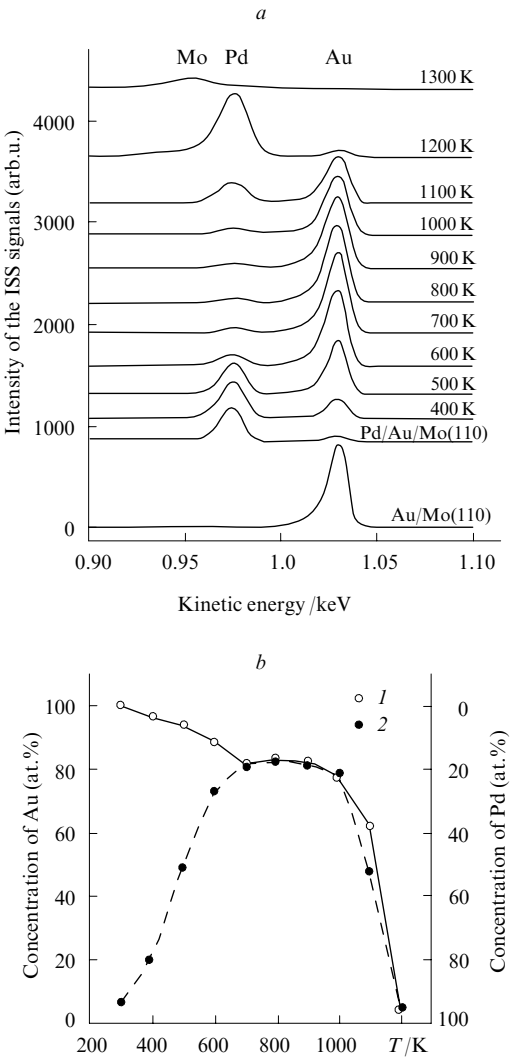


Figure 19. Ion scattering spectra of the Pd(5 ML)/Au(5 ML)/Mo(110) sample depending on the annealing temperature (the spectra were recorded at room temperature after annealing at the specified temperature for 20 min) (*a*); surface concentrations of Au and Pd in the samples: Pd(5 ML)/Au(5 ML)/Mo(110) (*1*) and Au(5 ML)/Pd(5 ML)/Mo(110) (*2*) depending on the annealing temperature (*b*).[488]

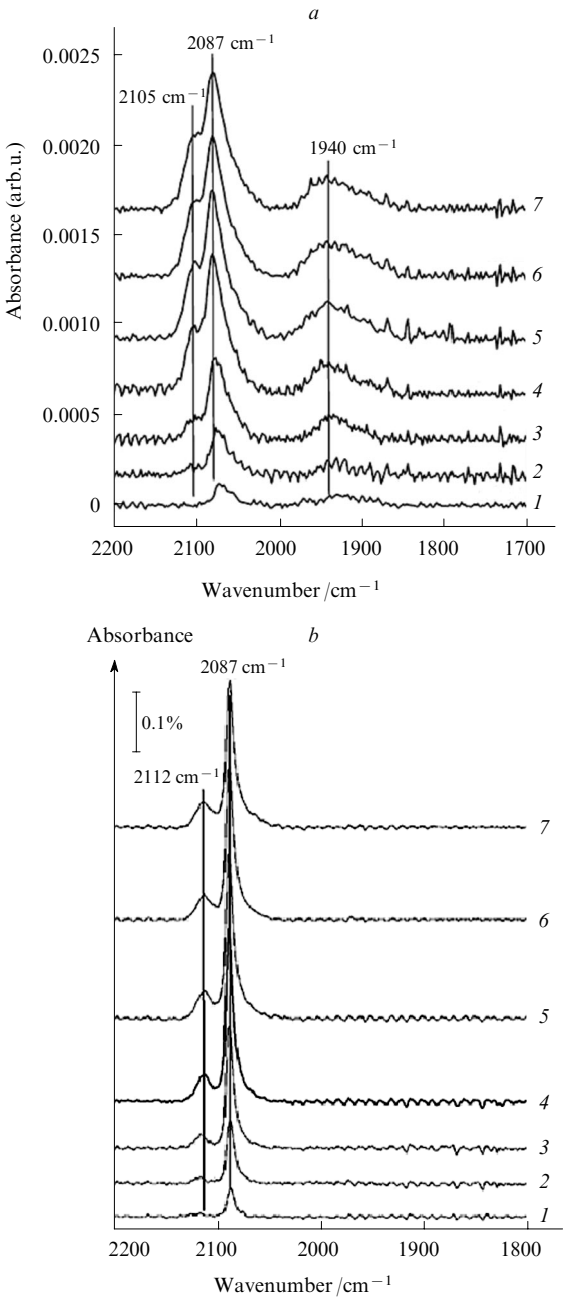


Figure 20. Infrared spectra of CO adsorbed on the Pd(5 ML)/Au(5 ML)/Mo(110) samples, which were annealed at 600 (*a*) and 800 K (*b*) for 20 min depending on the exposure to CO (in L): 0.02 (*1*), 0.05 (*2*), 0.10 (*3*), 0.20 (*4*), 0.50 (*5*), 1.0 (*6*) and 2.0 (*7*).[489]

Fig. 19 *b*). Further heating of the samples results in the desorpion of gold and then palladium (see Fig. 19 *a*). In full conformity with surface tension data for gold and palladium, the equilibrium surface of the alloy is enriched in gold (~80% Au and ~20% Pd). The surface segregation of gold was detected previously for massive Pd–Au alloys.[491,492]

The data shown in Fig. 19 also indicate that by varying the annealing temperature, it is possible to control the composition of the alloy surface. Meanwhile, it is of interest to study the structure of the palladium surface sites as it is diluted with gold. This was done using the IR spectroscopy for adsorbed CO the molecular vibration frequency of which depends on the surface site geometry.[489] Three types of CO adsorption are distinguished in the literature: (i) three-point adsorption where the CO molecule is located above a triangle of palladium atoms, (ii) bridging adsorption where the CO molecule is bonded to two neighbouring palladium atoms, (iii) terminal adsorption where the CO molecule is located above one palladium atom.[493–496] Figure 20 shows the IR spectra of adsorbed CO for samples prepared by successive sputtering of gold and then palladium onto the surface of the Mo(110) single crystal followed by annealing at 600 and 800 K. These temperatures were selected in view of the data presented in Fig. 19; in the first case, the alloy surface contains 1.5 times more palladium than in the second case. From comparison of the IR spectra, it can be seen that the major difference between there two model catalysts is the appearance of the bridging CO form

adsorbed on palladium sites in the sample annealed at lower temperature. This is indicated by the signal at ~2030 cm^{-1} (Ref. 495), which appears in the spectrum in addition to the intense signal at 2050–2080 cm^{-1} due to the terminal species CO_{ads}/Pd.[494] Because of weak interaction of CO with gold (8–10 kcal mol^{-1}) (Ref. 497), the contribution of CO_{ads}/Au to the IR spectra recorded at room temperature (see Fig. 20) should be excluded. This result indicates that in the equilibrium state, the surface of the Pd–Au alloy contains only single palladium atoms surrounded by only gold atoms. As a consequence, ethylene can be adsorbed on this surface only as π-complexes. Annealing at lower temperature retains some neighbouring palladium atoms. The possible formation of di-σ-complexes by adsorbed C_2H_4 would increase the probability of the total oxidation pathway for ethylene, thus decreasing the process selectivity with respect to vinyl acetate. A practically important recommendation that follows from the performed fundamental research of the oxidative acetoxylation of ethylene on model Pd–Au catalysts is to use high annealing temperatures.

Taking into account these recommendations, the Pd(1%)–Au(0.5%)/SiO_2 catalyst was prepared by incipient wetness method and annealed at 500 °C.[498] Comparison of its catalytic properties with those of the monometallic Pd(1%)/SiO_2 catalyst prepared in a similar way showed[499] that the addition of gold increases by more than an order of magnitude the catalyst activity expressed as the number of vinyl acetate molecules formed in 1 s on one surface palladium atom; the selectivity in this case reaches 96% (for comparison, the best monometallic catalyst provides only 90% selectivity).[498] High annealing temperatures (500–600 °C) are also indicated in modern patents devoted to improvement of palladium–gold supported catalysts for vinyl acetate synthesis.[500]

Thus, the understanding of the mechanisms of catalytic reactions and determination of the active site structure may serve for pronounced improvement of the reaction selectivity towards the target product. The use of this approach will be extended in the near future; however, there are some obvious limitations to applying it to complex organic reactions in the liquid phase. The first step in solving this problem may be the post-reaction analysis of heterogeneous catalysts by surface-sensitive physical methods for detection of changes in the structure and chemical state of the surface upon the catalytic reaction. The atmosphere-free loading technique (dry chamber) becomes especially significant for transfer of samples from the reaction medium inside spectrometers or microscopes. Yet another direction for the development of this area is to choose simple compounds that model some organic reaction (hydrogenation, oxidation, functionalization, *etc*.).

X. Bimetallic catalysts in organic synthesis

Although bimetallic catalysts have been used for rather long time, there has been a boom in the research in this area in recent years, which is reflected in the enormous number of publications. This trend is due to both the advances in the elaboration of synthetic routes to nanostructured materials and the development of the physicochemical methods for their research including the appearance of *in situ* procedures.

The aspects of synthesis of bimetallic nanoparticles are considered in detail in a number of reviews. A review by Chandler and Gilbertson[501] is devoted to the synthesis, investigation and application of dendrimer-encapsulated bimetallic particles. Liquid-phase synthesis and catalytic applications of bimetallic nanocrystallites have been analyzed in a considerable detail in a review.[502] Techniques for the preparation of bimetallic particles of a specified geometry by up-to-date methods of colloidal chemistry are comprehensively described in reviews.[503–505]

A considerable contribution to understanding of the relationship between structural features of small metal particles, including bimetallic particles, is made by advanced physicochemical investigations, especially performed *in situ*, *i.e*., directly during the catalytic reaction.[506, 507]

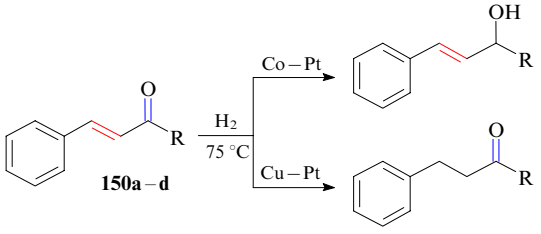
Unfortunately, very few reviews are devoted to the application of bimetallic catalysts and bimetallic nanoparticles in organic synthesis. These issues are covered most comprehensively in reviews by Cai *et al.* [508] and by Yu *et al.* (devoted to platinum-based catalysts).[509] The use of heterogeneous bimetallic and nanocomposite catalysts in organic synthesis is considered in a review by Shi.[510] This Section deals with synergistic effects observed in the reactions conducted on heterogeneous nanocomposite catalysts. It was stated[511] that the causes of synergistic effects for various catalytic systems significantly differ and cannot always be generalized, because they depend on the specific character of a particular catalytic system (catalyst + the reaction it catalyzes). Within the framework of this Section, we made an attempt to analyze the available published data on the use of bimetallic catalysts in some important reactions of fine organic synthesis including selective hydrogenation and cross-coupling.

X.1. Hydrogenation of alkenes, alkynes, carbonyl compounds and nitro compounds

The selective hydrogenation of compounds containing C=C and C=O bonds is a fairly topical task, because the unsaturated products thus formed are used to prepare fragrance alcohols and biologically active compounds and are also widely employed in pharmaceutics. The key obstacle interfering with the selective process is that hydrogenation of the C=C bond is ~35 kJ mol^{-1} more thermodynamically favourable[512] than hydrogenation of the C=O bond. Nevertheless, analysis of the modern literature indicates that the use of bimetallic catalysts is an effective method for increasing both the activity and selectivity of the reaction.

The efficiency of the monometallic Pt/SiO_2 catalyst and supported bimetallic (Co–Pt/SiO_2, Cu–Pt/SiO_2) catalysts has been studied in detail in the hydrogenation of cinna-

Scheme 125

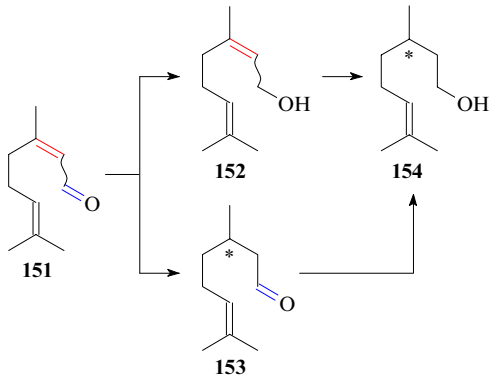


R = H (**a**), Me (**b**), Ph (**c**), OEt (**d**)

maldehyde (**150a**).[513] Platinum catalyst promotion by cobalt or copper markedly increases its activity (the conversion over a period of 2 h increases from 4.8% to 10%–28%). Apart from the increase in the activity, the introduction of the second metal provides the possibility for controlling the process selectivity. Indeed, the catalyst promotion by cobalt enables selective hydrogenation of the C=O bond, while the introduction of Cu results mainly in C=C bond hydrogenation (Scheme 125).

Similar results were obtained by Bertero *et al.*[514] It was found that modification of a Pt catalyst by cobalt makes it possible to suppress undesirable hydrogenolysis and decarbonylation processes in the liquid-phase hydrogenation of citral (**151**) and thus increase the catalyst activity and to control the selectivity towards the formation of either geraniol (**152**) or citronellal (**153**) and citronellol (**154**) (Scheme 126).

Scheme 126

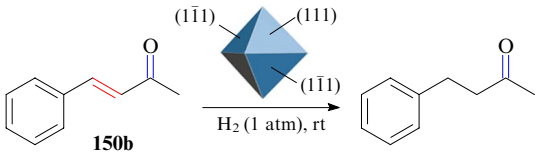


In another work,[515] a highly selective catalyst based on Pt–Co nanoalloy particles was prepared by decoration of Pt nanocrystals with Co atoms under controlled conditions using a colloidal solution. By using cobalt-decorated platinum nanoparticles, the researchers were able to perform highly selective hydrogenation of the terminal C=O group of cinnamaldehyde, while completely suppressing the undesirable hydrogenation of the C=C bond as a result of blocking of low-coordinate Pt sites and optimization of the electronic properties of Pt nanoparticles by means of Co addition.

The reason of an increase in the selectivity of hydrogenation when catalyzed by bimetallic catalysts, including Pt–Co, was studied theoretically by Murillo *et al.*[516] using surface science approaches and density functional theory (DFT) calculations. It was found that the increase in the selectivity of C=O bond hydrogenation in the acrolein molecule conducted on the Pt–Co–Pt(111) surface is related to the increase in the energy of the di-σ-C–O bond between the intermediate and the catalyst surface; the more electropositive metal (Co) acts as the electron-donating ligand and increases the electron density on the surface Pt atoms. As a result, the C=O bond hydrogenation accelerates, whereas the C=C bond hydrogenation slows down.

Interesting results have been obtained by Wu *et al.*,[517] who showed that the activity of bimetallic catalysts in the benzylideneacetone (**150b**) hydrogenation is determined by not only the composition but also the shape of bimetallic alloy nanoparticles (Scheme 127). The highest reaction rate is achieved with octahedral particles, while on going to cubic nanocrystals, the activity decreases almost twofold. The introduction of Ni results in the turnover frequency increasing from 23 to 139 h^{-1} and in a substantial increase in the C=C bond hydrogenation selectivity, the carbonyl group remaining almost intact.

Scheme 127



It was shown[518] that the activity and selectivity of Pt catalysts in the cinnamaldehyde hydrogenation can be increased upon the catalyst modification with tin. The selectivity of formation of cinnamic alcohol grows following an increase in the Sn : Pt ratio to 0.8. It is noteworthy that the process rate also grows reaching a maximum at Sn : Pt = (0.2–0.4). The beneficial effect of Sn on the selectivity of cinnamaldehyde hydrogenation was confirmed in another work.[519] Also, the researchers demonstrated that a similar effect can be induced by modifying the Pt catalyst with gallium. It should be noted that the crucial factor is the presence of clear-cut interaction between Pt and the modifying component, which was achieved by means of the reductive deposition–precipitation technique developed by the authors.

In conclusion, mention should be made of the catalytic systems able to perform C=O bond hydrogenation using such hydrogen sources as hydrazine or $NaBH_4$, which is of much interest for laboratory practice. The use of bimetallic Rh–Co particles was shown[520] to provide effective hydrogenation of the C=C double bond in unsaturated ketones and esters, the C=O bond remaining unaffected.

X.1.a. Selective hydrogenation of alkynes

The catalytic hydrogenation of alkynes has a fundamental value both for laboratory practice and for chemical industry,[521] because it can create *trans*- and *cis*-alkene moieties serving as building blocks in fine organic synthesis. The hydrogenation is typically catalyzed by supported metallic catalysts. Therefore, numerous research teams all over the world are engaged in the research of the main regularities of the catalytic action of these materials.[522, 523] The key goals are, first, to minimize the conversion of alkenes formed in the reaction to alkanes and, second, to select process conditions that would result in the desired stereoselectivity.

For *cis*-alkene synthesis from alkynes, the heterogeneous Lindlar catalyst (Pd–Pb) is often used. A considerable drawback of this catalyst is the toxicity of lead compounds, which are needed for partial catalyst deactivation for preventing the reduction of the target products (alkenes) to alkanes. In addition, this catalyst is inapplicable to some substrates. For example, terminal alkynes cannot be selectively converted to alkenes as they are rapidly hydrogenated to alkanes. In some cases, the use of the Lindlar catalysts is accompanied by instability and irreproducibility of the results under experimental conditions.[524]

A promising way for attaining selective hydrogenation of the C≡C bond is the use of bimetallic catalysts. The studies along this line carried out to date demonstrated that the highest selectivity results from the use of bimetallic catalysts containing a Group 8 metal (usually Pd) as one

of the active components.[525, 526] The key role is then played by two factors: the nature of the second metal and the degree of homogeneity of the bimetallic nanoparticles that are formed during the catalyst preparation.

For example, the introduction of Zn or Ag into a Pd catalyst considerably increases the selectivity in alkyne hydrogenation to alkenes, although the activity somewhat decreases.[527] The observed increase in the selectivity to alkenes is usually attributed to electronic and/or ligand effects and to the disappearance of the palladium hydride β-PdH phase. The two first-mentioned factors are tightly interrelated. The presence of the second metal on the surface and in the bulk of a bimetallic alloy particle changes the electronic properties, resulting in a decrease in the desorption energy of the alkene being formed, which thus becomes lower than the activation energy of the second (alkene → alkane) hydrogenation step. Hence, alkene desorption rather than further hydrogenation becomes the predominant reaction pathway.[528] The second, geometric effect of the introduction of the second metal is 'dilution' of the Pd surface layer by inactive metal atoms, which reduces the probability of formation of multiatomic sites in which strong multicentre adsorption of alkylidene intermediates is possible. These intermediates are believed to be responsible for the direct hydrogenation of alkynes to alkanes.[529]

A considerable role is also played by the degree of homogeneity of the prepared bimetallic nanoparticles. In the ideal case, the composition of every nanoparticle should correspond to the component ratio of the whole catalyst; however, obtaining this high degree of homogeneity is a challenging task. An effective process for the preparation of highly homogeneous bimetallic catalysts is the use of heterobimetallic palladium acetate complexes with the second metal $PdM(OAc)_4(OH_2)$ (M = Zn, Ce, Co, Ni).[527, 530] These catalysts are more active in the hydrogenation of alkynes to alkenes than the catalyst samples prepared by the traditional deposition of the metal precursors from solutions of individual salts.[527]

An ingenious method for increasing the selectivity of bimetallic catalysts for hydrogenation of alkynes to alkenes is the use of intermetallic compounds in which the electronic effect of the second component on the adsorption and catalytic properties of the active metal is much more pronounced than in disordered alloys. Indeed, it was ascertained [531] that the Ni_3Ge/MCM-41 catalyst performs highly selective hydrogenation of acetylene in an excess of ethylene up to almost complete conversion of the alkyne. Similar results have been obtained [532, 533] for the intermetallic compounds PdGa and Pd_3Ga_7.

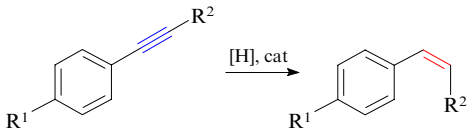
It should be noted, however, that the results of reactions of fine organic synthesis in the liquid phase catalyzed by supported bimetallic catalysts are not always consistent with the results obtained for the gas-phase heterogeneous catalysis. For example, liquid-phase hydrogenation of phenylacetylene on the above-mentioned PdGa intermetallic [532, 533] showed only a minor increase in the selectivity with respect to that on monometallic Pd catalyst.[534] Furthermore, it was found that the same is true for the Lindlar catalyst. The authors attributed these significant discrepancies of the results obtained for the gas-phase hydrogenation of acetylene and liquid-phase hydrogenation of phenylacetylene to specific effect of the liquid phase on the surface chemistry of the PdGa intermetallic compound, resulting in partial oxidation and pronounced surface segregation of gallium.

Nevertheless, in some cases, the results of the gas-phase and liquid-phase hydrogenation are well correlated with each other. Thus for catalysts based on the bimetallic complexes $PdM(OAc)_4(OH_2)$ (M = Zn, Ce, Co, Ni), it was found that introduction of the second metal leads to higher selectivity of diphenylacetylene hydrogenation, as in the case of gas-phase hydrogenation, and results in higher percentage of the target *cis*-isomer in the reaction products. It was shown that the activity of catalysts deposited from bimetallic complexes considerably depends on the nature of the second metal and increases in the order PdZn < PdCo < PdNi.[535] Therefore, the results confirm good perspectives for the catalysts based on bimetallic palladium acetate complexes in the selective hydrogenation of C≡C bonds.

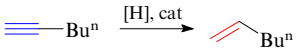
Homogeneous bimetallic particles can also be prepared in solution. Spee *et al.*[536] reported a detailed investigation of the catalytic properties of the Pd–Cu/SiO_2 bimetallic systems in the selective hydrogenation of substituted alkenes and propargyl alcohols. The Pd–Cu nanoparticles were obtained by the reaction of lithium di(4-tolyl)cuprate with palladium acetate, resulting in deposition of Pd–Cu particles on the silica gel surface. The formation of the Pd–Cu alloy was verified by high-resolution electron microscopy and EXAFS. The Pd–Cu/SiO_2 catalysts demonstrated much higher selectivity than the Lindlar catalyst towards the formation of *cis*-alkenes in the hydrogenation of mono- and disubstituted alkynes.

Interesting results of selective hydrogenation of terminal alkynes were obtained in the already mentioned study by Lin *et al.*[520] It was found that bimetallic Rh–Co nanoparticles provide high yields of terminal alkenes and diphenylethylene (Scheme 128). Hydrazine hydrate served as the hydrogenating agent and, hence, the reaction could be easily conducted using common laboratory ware for organic synthesis.

Scheme 128



R^2 = H: R^1 = H, Me, Bu^t, F, Br; R^1 = H, R^2 = Ph

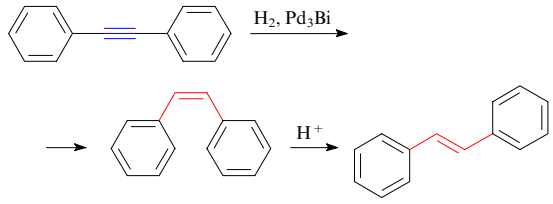


A new method for the preparation of bimetallic Rh–Ag nanoparticles has been proposed,[537] namely, entrapment of the catalytically active Rh within a silver metal matrix. This was done using an original procedure based on reduction of $AgNO_3$ with Zn metal to give finely dispersed Ag in solution. This is accompanied by entrapment of the Rh complex, giving rise to a bimetallic particle. This Rh–Ag complex showed high selectivity towards the formation of *cis*-stilbene. This result is even more notable because monometallic Rh nanoparticles provide the formation of only exhaustive hydrogenation products.

The synthesis of *trans*-alkenes from alkynes is a more complicated task than the synthesis of *cis*-alkenes by the hydrogenation reaction. An ingenious method for the synthesis of *trans*-isomers upon diphenylacetylene hydrogena-

tion was proposed by Komatsu *et al.*[538] Using the Pd_3Bi/SiO_2 catalyst containing a palladium intermetallic compound as the active component, the authors were able to achieve high selectivity in the transformation of diphenylacetylene to *cis*-stilbene up to a >90% conversion. The catalyst shows much higher selectivity than the classical Lindlar catalyst. By using Pd_3Bi/SiO_2 as the hydrogenating component and by mechanically mixing it with the H-USY zeolite, the authors achieved a ~74% yield of *trans*-stilbene. The Pd_3Bi/SiO_2 catalyst performs the selective hydrogenation of diphenylacetylene to *cis*-stilbene, whereas on the zeolite component, the resulting *cis*-stilbene isomerizes to the thermodynamically more stable *trans*-product (Scheme 129).

Scheme 129



X.1.b. Reduction of the nitro group

The reduction of the nitro group of substituted aromatic compounds is of considerable interest both for laboratory organic synthesis and for the industrial production of various pharmaceuticals, polymers, dyes, *etc*. Unfortunately, many currently existing catalysts do not meet the high activity and selectivity requirements simultaneously.[539, 540] On the one hand, the classical systems such as Pd/C are highly active but they do not provide the sufficient process selectivity because of undesirable by-products formation, and an additional step for the target product purification is required. On the other hand, catalysts that show high selectivity require conducting the reactions at high temperature and high hydrogen pressure due to their low activity. Bimetallic catalysts help to overcome this problem and carry out the process under relatively mild conditions with the required selectivity.

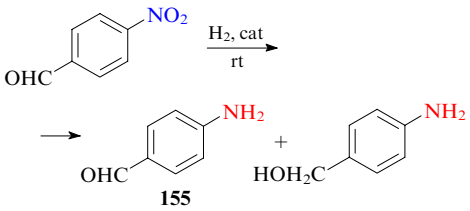
In a detailed study of the bimetallic Pd–Au/Al_2O_3 catalysts,[541] the catalysts were prepared by the deposition–precipitation technique and by the conventional impregnation technique; the atomic Au : Pd ratio varied from 8 to 88. It was found that the introduction of Pd in the ratio Au : Pd = 20 results in a threefold increase in the activity, while maintaining exceptionally high selectivity towards the formation of 4-chloroaniline from 4-chloronitrobenzene.

It was also found [542] that the bimetallic Pd–Au catalyst shows an exceptionally high activity in the selective hydrogenation of 2-chloronitrobenzene to the corresponding amine. The Pd–Au catalyst proved to be substantially more active than the monometallic Pd sample. In this study, the bimetallic nanocatalyst stabilized by polyvinylpyrrolidone (PVP) was prepared by dropwise addition of solutions of the precursors ($PdCl_2$ and $HAuCl_4$) to a colloidal solution of the support (activated carbon) and PVP. The high activity of the obtained sample made it possible to carry out hydrogenation under relatively mild conditions (50 °C, 3 atm of H_2).

Liu *et al.*[543] found that the bimetallic Pt–Ru catalyst prepared by deposition of the Pt–Ru nanoparticles onto SnO_2 has a much higher activity and selectivity in the hydrogenation of 2-chloronitrobenzene compared with Pt–Ru/SnO_2 prepared by the classical impregnation method. Physicochemical measurements demonstrated that the higher activity of the catalyst based on nanoparticles is due to a smaller particle size and a narrower particle size distribution of the bimetallic alloy.

The highly active bimetallic catalysts based on fine nanoalloy particles are able to perform the selective hydrogenation of the nitro group under relatively mild conditions and, therefore, they are of considerable value for laboratory practice. It was shown, for example,[544] that unsupported Rh_3Ni nanoparticles catalyze the reduction of the NO_2 group of 4-nitrobenzaldehyde with molecular H_2 at room temperature (Scheme 130). Product **155** is formed with a selectivity of > 99% at virtually complete conversion of the initial compound. It was found that the Rh_3Ni catalyst ensures effective reduction of the NO_2 group in nitroaromatic compounds containing diverse functional groups and can be reused many times without substantial activity loss.

Scheme 130



155

Yet another notable result that presents considerable interest for laboratory practice was reported by Jiang *et al.*[545] A catalyst containing Au–Ag nanoalloy as the active component was prepared by depositing pre-synthesized bimetallic Au–Ag nanoparticles onto a metal-organic framework (MOF). This catalyst is suitable for nitrophenol reduction with $NaBH_4$ in an aqueous solution. The authors showed that the crucial role is played by the structure of Au–Ag nanoparticles. The best results were found for particles with the core–shell structure (Ag core and Au shell; $Au_{shell}Ag_{core}$), while the monometallic Au catalyst and a catalyst based on disordered Au–Ag alloy were substantially less active.

X.2. Cross-coupling reaction

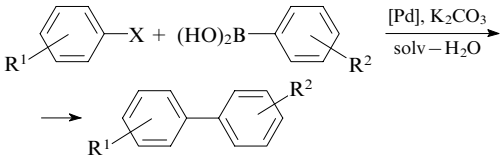
X.2.a. Suzuki cross coupling

A typical example of the Suzuki reaction is the coupling of arylboronic acid and aryl halide to give substituted biphenyl (Scheme 131). The most efficient catalyst for this reaction is Pd (both as complex compounds and as the metal); therefore, Pd-based catalysts are vigorously studied (see Section VI.2). Catalysts containing bimetallic Pd–M particles can efficiently solve problems of increasing the catalyst activity, selectivity and stability and help to elucidate details of reaction mechanisms.

The bimetallic Pd–Au catalysts find rather wide use in the Suzuki cross-coupling reaction owing to higher activity and stability of the catalytic action. For increasing the activity and stability of Pd catalysts, Tan *et al.*[546] used bimetallic Au–Pd nanoparticles enclosed in SiO_2 nanospheres. Both the Au : Pd ratio and the nanoparticle structure were varied over broad limits. It was found that the catalytic activity increases in the series Au < Pd < $Pd_{shell}Au_{core}$ < $AuPd_3$ < AuPd < Au_3Pd. It is

of interest that alloyed Au–Pd@SiO_2 particles with the lowest Pd content had the highest catalytic activity and selectivity. The use of the SiO_2 shell for Pd stabilization prevented the particles from agglomeration during the process. In addition, the effect of Pd leaching from the catalyst is markedly suppressed for these nanoparticles. It was found that the Pd content in the reaction solution after the AuPd@SiO_2-catalyzed process is ~51 ppb, whereas for commercial Pd/C catalyst, this value can be as high as 650 ppb.

Scheme 131



R^1 = 4-Me, 4-OMe, 4-NH_2, 4-Ac, 2-NH_2, H; R^2 = H, F, 4-NH_2; X = Br, I; solv is organic solvent.
Conditions: 0.0235 mmol of Pd, 0.25 μmol of Au, 1.1 mmol of boronic acid, 3 mmol of K_2CO_3, 1 mmol of aryl halide, EtOH : H_2O = 2 : 1 (25 ml), 70 °C, 24 h

R^1	R^2	Conversion (%)	
		Pd	Pd–Au
4-Ph	H	0	88
4-Me	H	4	100
H	4-F	58	100
2-NH_2	H	0	6
H	2-NH_2	98	36

A comparison of the catalytic activities of Pd–Au and monometallic Pd catalysts has been reported.[547] It was shown that on introduction of electron-donating groups into aryl halides, the bimetallic catalyst shows a much higher activity; a similar effect is induced by introduction of electron-withdrawing substituents (*e.g.*, F atom) into arylboronic acid (see Scheme 131).

It is noteworthy that in the series of aryl halides, the activity varies as I > Br ≫ Cl and that bimetallic Pd–Au catalysts show much higher activity when 'inert' substrates such as bromobenzene are used. Presumably, the introduction of Au leads to acceleration of the rate-limiting oxidative addition step and, hence, Pd–Au catalysts provide much higher conversion for a broad range of substrates than the monometallic Pd catalyst. These results are in good agreement with the results of another publication [548] in which the highest catalytic activity was achieved for catalysts with the $Pd_{shell}Au_{core}$ structure. The key role of the oxidative addition giving rise to the $ArPd^{II}X$ species has been confirmed by Shi.[510] It was shown that the Pd/$NiFe_2O_4$ composite catalyst has a high catalytic activity owing to the electron density donation from $NiFe_2O_4$ to Pd nanoparticles. Note that, generally, this fact is in good agreement with experimental data, indicating enhanced catalytic activity of the Pd catalysts supported on basic supports.[549–551] This conclusion was confirmed [552] for both the monometallic Pd/C catalyst and bimetallic Pd–Au/C and Pd–Au/SBA-15 samples (SBA-15 is a silica brand).

A somewhat different conclusion was drawn by Fang *et al.*,[553] who used nanoparticles with the $Pd_{shell}Au_{core}$ structure to elucidate the mechanism of the Suzuki reaction and the effect of Pd leaching on the overall reaction mechanism. Cyclic voltammetry and inductively coupled plasma mass spectrometry measurements showed that Pd leaching may be caused by joint action of the base and arylboronic acid rather than by oxidative addition of aryl halide.

The introduction of a non-noble 3d metal having ferromagnetic properties into the Pd–M nanoparticle (M = Ni, Co, Fe) facilitates the separation of the catalyst from the reaction medium and increases the stability of catalyst operation. Wu *et al.*[554] carried out the cross-coupling reaction using Pd–Ni nanoparticles of a definite size (~10–15 nm) and shape. The introduction of Ni into Pd nanoparticles resulted in a considerable increase in the catalytic activity as compared with the monometallic Pd nanocatalyst: the yield of the target product reached ~90% at 80 °C. Moreover, even at room temperature, the reaction occurred with a yield of up to 40%. Note that the catalytic activity of the Pd–Ni nanoalloy increases with increase in the Ni content up to $Pd_{50}Ni_{50}$, and, hence, the consumption of the expensive noble metal can be decreased. The Pd–Ni catalyst is fairly stable and can be used for up to 5 times without loss of activity. Owing to the presence of Ni in the alloy structure, the nanoalloy particles can be magnetically separated from the reaction products.

Magnetic separation of the catalyst from reaction products is also possible for Pd–Co nanoparticles. Alonso *et al.*[555] prepared catalytic $Pd_{shell}Co_{core}$ particles supported on a polymer and distributed in the polymer surface layer. In the presence of this catalyst, the yield of the target product in the Suzuki cross-coupling reached 95%–100% after 18 h at 70 °C. The reaction was carried out in a DMF–H_2O mixture (4 : 1); upon the increase in the H_2O content from 10% to 20%–40%, the yield of the reaction product increased from 20%–40% to 80%–90%.

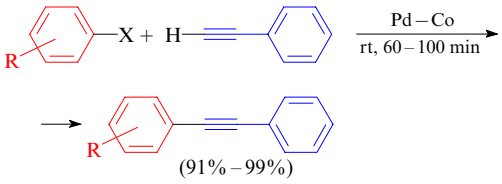
An example of application of bimetallic catalysts for cross-coupling has been reported by Kim *et al.*[556] The authors prepared mono- and bimetallic nanoparticles stabilized by PVP and supported on the Vulcan XC-72™ carbon support. The reduction to the metal was accomplished without chemical reducing agents on exposure to γ-radiation. The alloy formation was confirmed by powder X-ray diffraction based on the characteristic shift of reflections corresponding to Pd(111). The catalytic activities of the obtained catalysts were studied in the Suzuki cross-coupling performed for 3 h at 78 °C. The highest activity was found for the Pd–Cu/C samples where the yield reached 96%–97%. The catalyst activity varied in the sequence Pd–Cu/C > Pd/C > Pd–Ag/C > Pd–Ni/C. The most valuable characteristics of the bimetallic catalyst is high stability: for five successive catalytic cycles, the product yield was found to somewhat decrease in the first cycle and then the catalyst activity was found to remain almost invariable.

X.2.b. Sonogashira cross-coupling

Yet another reaction widely used in organic synthesis for the formation of the C–C bond is the Sonogashira reaction, which is the cross-coupling of vinyl and aryl halides with terminal alkynes to give arylacetylenes and conjugated enynes.[557] This reaction requires elevated temperatures and occurs in the presence of Pd catalysts.

The application of bimetallic catalysts makes it possible to carry out the reaction under substantially milder conditions. An example is the Pd–Co nanocatalyst with the active component represented by Pd–Co alloy nanoparticles supported on polypropyleneimine dendrimers attached to the surface of graphene nanolayers.[558] With this catalyst, the reaction proceeded at room temperature (25 8C) without a solvent (Scheme 132).

Scheme 132



R = Me, OMe, NO_2; X = I, Br, Cl

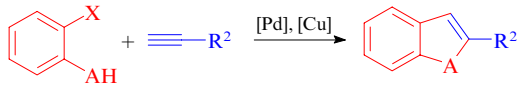
The authors compared the bimetallic and monometallic catalysts in reactions of various substrates. The monometallic Co catalyst is virtually inactive, the monometallic Pd particles supported on graphene also show low activity (18 h is required to achieve a 85%–90% product yield). Meanwhile, the bimetallic Pd–Co catalyst produced a 90%–96% yield in 1.5 h at room temperature. A comparison with various types of Pd catalysts was also carried out: the Pd–Co/graphene catalyst was much more active than monometallic samples. Another important characteristics of the Pd–Co catalyst is the high stability of catalytic action: for six successive catalytic cycles, the yield of the reaction products decreased from 99% (the first cycle) to 93% and then stabilized. The results indicate high stability of Pd–Co nanoparticles.

The high activity of the Pd–Co catalyst was confirmed in another study [559] where spherical particles of the Pd–Co nanoalloy were prepared and used to perform the Sonogashira cross-coupling in an aqueous medium at 80 °C. The high product yields were achieved when the process was conducted for 4–9 h.

It is noteworthy that for high efficiency of bimetallic catalysts, an alloy with tight contact of metal atoms with one another is required. To confirm this 'bimetallic' effect, bimetallic Pd–Cu catalysts and monometallic nanoparticles supported on montmorillonite (MMT) were prepared.[560] The catalyst structure was investigated by SEM, TEM and powder X-ray diffraction. The Pd–Cu catalyst showed high efficiency in the cross-coupling of a series of substrates; a diphenylacetylene yield of 97% was attained in 3 h at 65 °C. For the MMT@Pd + MMT@Cu mechanical mixture, the yield did not exceed 25%. The authors suggest that the role of Cu is to activate the alkyne, which facilitates the transmetallation step to give the reaction product; it is necessary that both metals be parts of the same nanoparticle because a mechanical mixture of monometallic catalysts demonstrates low activity.

An interesting example of using the bimetallic Pd–Cu/C catalyst in a cascade process including the Sonogashira cross-coupling followed by cyclization to give indoles, azaindoles and benzofurans in water has been reported.[561] In this case, Cu plays a dual role, being the catalyst for the alkylation step and the Lewis acid in the cyclization step (Scheme 133).

Scheme 133



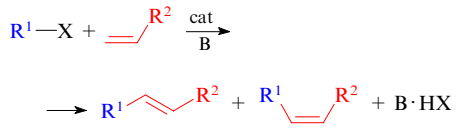
X = I, Br; A = O, NR^1

High efficiency of heterogeneous bimetallic Pd–Cu catalysts in similar cascade processes was shown in a number of works.[562, 563]

X.2.c. Heck reaction

The typical Heck reaction is coupling of aryl halide and alkene in the presence of a base and catalytic amounts of Pd. The reaction gives a C–C bond and an HHal molecule as a by-product (Scheme 134).

Scheme 134

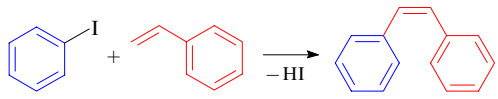


R^1 = Ar, CH=CH_2; R^2 = Ar, CN, Ac; X = Cl, Br, I

According to the modern views, the catalytic cycle involves intermediate anionic Pd^0 complexes. An important condition for the reaction to occur is stabilization of Pd^0 compound in solution; otherwise, palladium black may be rapidly formed and the catalytic activity will decrease. The anionic Pd^0 complex is stabilized in solution upon coordination of some ligands such as phosphines, amines, carbenes, thiols and so on. However, stabilization by these ligands brings about some complications for the synthesis. Ligands, especially phosphines, usually cannot be isolated and reused, they are highly sensitive to air and toxic and also decompose at elevated temperatures required for the synthesis. Therefore, vigorous search is in progress for catalytic systems that would enable the synthesis without these ligands. A possible solution to this problem is the use of bimetallic catalysts.

For example, a bimetallic nanocatalyst was used to perform the Heck reaction without phosphine ligands (Scheme 135).[564] The Pd, Ag, Pd–Ag, Pd–Ni and Pd–Cu nanoparticles were prepared using a 'water-in-oil' microemulsion. The average nanoparticle size was ~15 nm and the formation of a bimetallic nanoalloy was confirmed by powder X-ray diffraction and UV spectroscopy. The catalytic properties of the prepared samples were studied in the cross-coupling of iodobenzene with styrene (MeOH solvent, 100 °C, 18 h). The catalyst activity was found to vary in the following sequence: Pd–Cu (4 : 1) > Pd ≫ Pd–Ni (1 : 1) > Pd–Ag (1 : 1) > Ag. The highest activity was manifested by the catalyst with the atomic ratio Pd : Cu = 4 : 1; this resulted in the product yield of 91%, whereas for monometallic catalysts, the yield did not exceed 74%.

Scheme 135



Although the bimetallic Pd–Cu nanocatalyst has a higher activity than monometallic catalysts, its major advantage is still the much higher stability of the catalytic action in repeated reactions. Whereas the activity of the monometallic catalyst rapidly decreases and as soon as in the second cycle the product yield does not exceed 22%, in the case of the bimetallic catalyst, the yield remains almost constant for 5–6 cycles, a noticeable decrease being observed only in the seventh cycle. The bimetallic Pd–Cu catalyst was studied in the cross-coupling of various alkenes (with Ac and CN functional groups) with substituted aryl halides (with OMe, CHO, Ac, NH_2, OH, CO_2H substituents). The yields of the cross-coupling products varied from 66% to 100%, indicating a high activity of the bimetallic catalyst.

Similar results have been obtained in an above-mentioned work by Kim *et al.*,[556] who used Pd–M nanoparticles (where M = Ag, Ni, Cu) deposited on the carbon support (Vulcan XC-72^{TM}). The catalysts were used in the cross-coupling of various types of compounds. In all cases, the Pd–Cu/C catalyst was most active. However, as in the previous work, the major advantage of the bimetallic catalyst is the higher stability of the catalytic action.

X.2.d. Ullman reaction

An interesting example of the use of bimetallic nanocatalysts for the condensation of aryl halides (Ullman reaction) has been reported.[565] The reaction is usually carried out at 100–360 °C in an inert solvent in the presence of a stoichiometric amount of Cu needed for binding the halides formed in the reaction (Scheme 136).

Scheme 136

$$Ar^1\text{—Hal} + \text{Hal—}Ar^2 \xrightarrow[-CuHal_2]{Cu} Ar^1\text{—}Ar^2$$

To carry out this reaction under milder conditions, a bimetallic nanoalloy-based Au–Pd-catalyst with PVP-stabilized metal particles has been developed and tested in the reaction carried out in DMF–H_2O (1 : 2) at 35 °C under Ar for 12–24 h.[565] In this reaction, DMF served as both the solvent and the reducing agent. The authors detected a clear-cut effect of the use of the bimetallic catalyst: $Au_{0.5}Pd_{0.5}$ nanoparticles gave the reaction products in a yield of up to 96%, the yield being markedly affected by the Au : Pd ratio. Monometallic particles or their mixtures were inactive in this process. It is noteworthy that a similar effect in the presence of a bimetallic catalyst was observed [566] in the Suzuki cross-coupling of chlorobenzoic and phenylboronic acids in water at room temperature.

Dhital *et al.*[565] have used the developed catalyst to carry out the Ullman reaction with various substituted chloro- and bromopyridines and 2-chloropyrazine and chloroquinolines. Unlike the classical process, in the presence of the bimetallic Au–Pd catalyst, chloro derivatives were considerably more active than bromo derivatives. It was found that in the reactions with bromoarenes, Pd was intensively leached to the solution, while the reaction rate was very low. Conversely, in the case of chloro derivatives, leaching virtually did not occur. All this suggested that leaching of Pd atoms is, in this case, unfavourable and retards the process, unlike Suzuki and Heck cross-coupling reactions.

XI. Carbon materials in catalysis

As shows in Sections III–VI, the selection of ligand plays the key role in the control of the catalytic activity and selectivity of homogeneous catalysts. For heterogeneous catalytic systems, a very important factor is selection of the support, which substantially affects not only the activity and selectivity but also stability of the catalyst. In fine organic synthesis, highly demanded substrates are carbon materials (CMs), which are the subject of the present Section. It is noteworthy that graphene systems are currently of most interest.

The applications of carbon materials are extremely diverse, covering all spheres of human activity. This is due to the unique properties of carbon allotropes and great diversity of CMs and carbon-based composites.

Active research into development and investigation of CMs resulted in the targeted synthesis of previously known diamond and graphite as well as the design of new carbon allotropes (carbynes, fullerenes, nanotubes, circulenes and so on) and a broad range of porous materials mixed (transition) forms of carbon (activated carbons, carbon black, pyrolytic graphite, glass carbon, fibres, clothes, felts and so on). Note that in 2010, A Geim and K Novoselov were awarded the Nobel Prize in physics for the study of graphene — a two-dimensional carbon allotrope formed by a monolayer of carbon atoms.

Carbon materials can be considered as spatially-cross-linked polymers. They are classified most conveniently in terms of chemical bond types with allowance for hybridization of the electron orbitals of carbon (Fig. 21). The structural and textural characteristics and methods of preparation of these materials are covered in detail in a review.[568] Note also that parameters of their porous structure (pore size, size distribution, pore volume and specific surface area) are varied over broad limits. The specific surface area is a specific characteristics for each type of CM, and although ranges of the specific surface areas overlap (Fig. 22), the type of CM can be suggested if this value is known.

Non-porous or low-porous CMs are mainly used to produce goods or structural parts or are used as components of various materials, whereas porous CMs with developed surface (PCMs) are used, first of all, in the processes related to adsorption and catalysis.

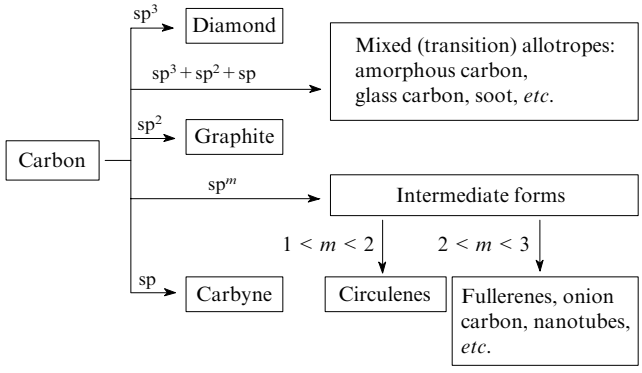


Figure 21. Classification diagram of carbon allotropes.[567]

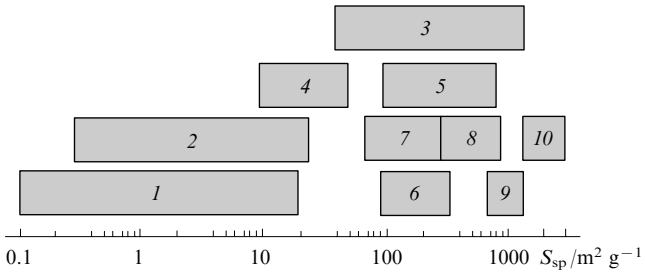


Figure 22. Typical ranges of specific surface area for carbon materials.[568]
(*1*) Natural graphite, (*2*) synthetic graphite, (*3*) furnace carbon black, (*4*) thermal black, (*5*) channel black, (*6*) carbon–carbon composite materials, (*7*) catalytic fibrous carbon, (*8*) charcoal, (*9*) nutshell carbon, (*10*) petroleum coke carbon.

In the development of catalytic processes, of most practical value are the transition forms of carbon; therefore, in this Section, most attention is devoted to the properties of such forms. In addition, so-called carbon–carbon composite materials (CCCMs) comprising several carbon forms are considered. Well-known representatives of this class are CMs of the Sibunit family. The Section also covers data on the use of PCMs as catalysts and catalyst supports for selective organic synthesis and on the application of platinum group metals supported on CMs as electrocatalysts for low-temperature fuel cells (FC).

XI.1. Carbon materials as catalysts

Systematic research of the catalytic properties of activated carbons started back in the early 20th century. Currently, PCMs occupy a special place among known bulk catalysts, being characterized by a broad spectrum of processes they catalyze and by high stability in corrosive reaction media. It was shown that PCMs accelerate isotope exchange reactions, ligand exchange in metal complexes, redox transformations of inorganic compounds, halogenation and oxidation (involving O_2 and H_2O_2) of organic compounds of various classes, oxidative dehydrogenation and coupling reactions, condensation, poly- and oligomerization, isomerization, esterification and transesterification, dehydration, decomposition and other.[569–573] The reason for this diversity of their catalytic behaviour is variability of the following characteristics: (i) chemical functional composition of the surface, (ii) microstructure of the carbon framework, (iii) porous space morphology, (iv) nanotexture (crystal chemistry) of the pore surface and (v) electrophysical properties of the carbon matrix. The problems of control of these properties of carbon materials have traditionally received much attention of numerous research teams and substantial progress in this field has now been made.

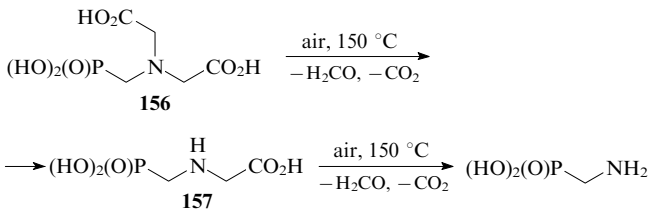
In carbon catalysis, chemical impurities, either natural or introduced artificially in the initial stages of formation of the carbon body, may play a pronounced role (although it is often just suggested or poorly studied); a more fruitful approach is apparently deliberate functionalization of the surface by heteroatomic groups using traditional organic chemistry techniques. By imparting particular properties to the PCMs being synthesized, it is in principle possible to create active sites with any geometric and chemical characteristics and to control the transport properties of PCMs (with respect to reactant molecules and protons in the pores and electrons and holes in the carbon matrix).

The optimal combination of steric (morphology of the pore space, surface nanotexture), acid–base, redox, hydrophobic–hydrophilic and transport properties of carbon-based catalysts is necessary for effective reactant activation and interaction under mild conditions, coordination of the steps of complex transformations in time and space to achieve high selectivity to target products. In this respect, PCMs can approach enzyme systems with similar action (parallels with enzymatic catalysis were first drawn by O Warburg in 1921–1923 and S Zylbertal in 1931 back at the early stage of investigations of the catalytic properties of active carbons in the total oxidation of simple organic substrates with oxygen).[570] This forms the unique character and high potential of PCMs as highly selective catalysts.

In addition, a topical task aimed, first of all, at the solution of environmental and energy problems is to create PCMs having photo- and electrocatalytic activities. This is achieved either in the traditional way (by attachment of semiconductor and metallic nanoparticles or organic metal complexes, by doping the carbon matrix with heteroatoms) or by searching for new carbon allotropes (fullerenes and graphenes) and synthesis of their derivatives.[573, 574] It is worth noting that electrochemical aspects of redox transformations of organic compounds on the PCM surface still remain undisclosed. In ion-conducting solutions, a PCM particle can function as a short-circuited galvanic cell in which the transformations of the oxidant and reductant molecules occur on different surface active sites (nanoanodes and nanocathodes) with appropriate exchange of charge carriers (electrons, holes) between them through the carbon body and dissolved ions through the system of interconnected pores filled with the electrolyte. This spatial separation of the anodic and cathodic processes can obviously significantly affect the kinetics of redox transformations on the PCM surface in ion-conducting media. Hence, in the study of the mechanisms of reactions of this type, the primary task is to estimate the contribution of each of the pathways — catalytic and electrocatalytic ones — to the overall process.

The first pronounced success in the use of PCMs on an industrial scale as catalysts to prepare complex organic compounds and intermediates for organic synthesis was reached at the end of the 20th century. In this connection, noteworthy is the oxidative decarboxylation of *N*-phosphonomethyliminodiacetic acid (**156**) in water with air on carbon catalysts to give *N*-phosphonomethylglycine (**157**) — a herbicide manufactured by Monsanto and known under the Round-up trade name (Scheme 137).[571]

Scheme 137



This reaction is efficiently catalyzed by microporous activated carbons with S_{sp} = 400–1000 m^2 g^{-1}; functional groups on their surface should mainly be of the basic

nature. More basic nitrogen-containing groups arising upon carbon calcination at 900 °C in the presence of NH_3 give rise to a higher catalyst efficiency than weakly basic oxygen-containing groups, which are similar to γ-pyrone groups and are formed as carbon pre-calcined under inert atmosphere comes in contact with air at room temperature. Although the reaction mechanism is still unknown, it has been demonstrated to date that nitrogen-containing carbons are fairly efficient in O_2 activation.

Yet another vivid example of successful use of PCMs in industry is the synthesis of phosgene (intermediate for the preparation of polyamides, polycarbonates, pharmaceuticals, *etc.*) from CO and Cl_2. Although this process has been known for more than 130 years, in 2000, DuPont published unexpected and exceptionally interesting information on the use of the mesoporous graphite-like material Sibunit as the catalyst.[575] As compared with the conventional coking coal, which is highly structurally disordered, all other factors being the same, the use of Sibunit resulted in a much lower amount of CCl_4 by-product (only 50 ppm) and a 10 times longer service life. Even after two years of operation in an industrial reactor (80 °C, 4.83 bar), the performance of this catalyst remained at an acceptable level.

In the last decade, the general requirements to the physicochemical state of carbon catalysts for various transformations of organic compounds have been outlined (Table 1). There is the trend towards deliberate extension of the ranges of acid–base, redox and electrophysical

Table 1. Typical catalytic transformations of organic compounds and catalysts used.

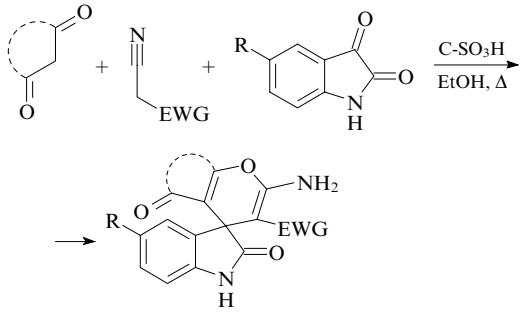
Type of catalyzed reaction	Carbon catalyst	
	PCM origin [a]	nature of functional groups in the active site
Oxidative dehydrogenation of alkylarenes (ethylbenzene to styrene) with oxygen	AC, CMS, MWCNT, filament carbon, onion carbon, graphenes	micropores 0.5–0.7 nm (plugged by coke deposits); conjugated diketones or quinone–hydroquinone pair; graphene edges
Oxidative dehydrogenation of alcohols to ketones or aldehydes with oxygen	AC, graphite oxide	weakly acidic (phenolic)
Oxidation of methylbenzenes to aldehydes with oxygen	graphite oxide	oxygen-containing redox groups
Oxidation of benzyl alcohol to benzaldehyde with $O_2 + HNO_3$	MWCNT	π-electron system as the electron donor–acceptor
Oxidation of cyclic ketones (with ring opening) to dicarboxylic acids	AC	quinone–hydroquinone pair
Oxidation of benzene to phenol with H_2O_2	OC	conjugated diketones
Total oxidation of organic impurities in H_2O with H_2O_2, O_3 or O_2 (mineralization)	AC	π-electron system as the electron donor–acceptor, O- and N-containing basic sites
Dehydrogenation of alcohols	AC	Lewis acid and base sites
Dehydrogenation of propane	AC	basic sites
Hydrodechlorination	nitrogen-doped PCM	N-containing basic sites
Reduction of nitrobenzenes with sulfides or ethylbenzene	AC	quinone–hydroquinone pair
Hydrogenation of cyclohexene	nitrogen-doped PCM based on carbon black	quinoline groups
Knoevenagel condensation, aldol condensation	AC from nitrogen-containing polymers, N-containing filament carbon	N-containing basic sites (pyridine)
Hydration of alkynes	graphite oxide	acidic
Alcoholysis and aminolysis of epoxides, hydrolysis of esters, cellulose, alkylation at $=N-H$ groups, dimerization of $PhC(CH_3)=CH_2$	sulfonated coal	strongly acidic groups (carboxy, sulfo groups)
Dehydration of alcohols, transesterification, esterification	OC, sulfonated coal	strongly acidic groups (carboxy, sulfo groups)

[a] AC is activated carbon (neutral or alkaline), OC is oxidized carbon (acidic), CMS is carbon molecular sieve, MWCNT are multiwalled carbon nanotubes.

properties of PCMs by means of structure and surface modification with heteroatoms (B, N, Si, S, P, *etc.*), which are usually present in traditional carbons in low concentrations.[576, 577] In addition, methods for the formation of chemical groups that are nearly absent in traditional analogues (*e.g.*, amino or sulfo groups) on the surface of novel carbon catalysts are being developed. Generally, this period was marked by high intensity of works on the use of PCMs as catalysts to solve applied problems covering various areas: environmental protection (detoxification and mineralization of organic and inorganic compounds in industrial effluents and waste waters), alternative energy (production of biofuels by vegetable oil transesterification), green chemistry (hydrolysis of biopolymers like cellulose and further processing of hydrolysis products into valuable chemical feedstock), polymer chemistry (monomer synthesis), fine organic synthesis (manufacture of medical drugs, highly selective catalysis in oxidation and condensation reactions, coupling of steps in multistep processes, *i.e.*, one-pot synthesis).

The greatest number of publications are devoted to the use of sulfonated coals (C-SO_3H) (prepared by sulfonation of activated carbons or their precursors by concentrated sulfuric acid) as heterogeneous acid catalysts, which often surpass in efficiency the known catalysts such as Nafion.[578] Cases in point are multistep processes involving more than two molecules, which can proceed on the sulfonated coal surface. An example is the synthesis of spirooxindole derivatives — intermediates for the preparation of alkaloid-like drugs — by the Knoevenagel condensation of isatin, malononitrile and 1,3-dicarbonyl compounds, the yields of target products being 80%–94% (Scheme 138).[579]

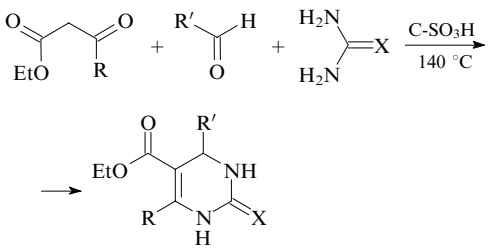
Scheme 138



EWG = CN, CO_2Et

One more example is the preparation of dihydropyrimidin-2(1*H*)-one (or -thione) derivatives by the Biginelli condensation of β-ketocarboxylic acid esters, aldehydes and urea (or thiourea) (Scheme 139).[580] The catalysts withstand 5–6 cycles without loss of activity.

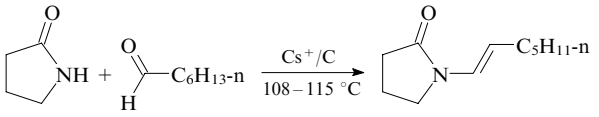
Scheme 139



X = O, S

The ability of carbon to absorb microwave radiation opens up an alternative way of maintaining the temperature of the reaction mixture. In addition, direct microwave heating of the catalyst can substantially increase the degree of conversion, while the contact time of the reaction mixture and the catalyst decreases. For example, in the synthesis of N-substituted γ-lactams in an excess of aldehyde on the Norit RX-1.5 Extra activated carbon doped with alkali metal ions (in particular, caesium ions, 0.08 mass %), short-term microwave irradiation (2450 MHz, 600 W, 5 min) of the reaction mixture at 115 °C resulted in a 70% conversion at 100% selectivity, whereas with the reaction temperature being maintained by conventional heating, only 50% conversion at 100% selectivity was reached over a period of 1 h (Scheme 140).

Scheme 140



Thus, the above examples provide new, rather convincing evidence for the fact that carbon materials with the adequately adjusted physicochemical state of the surface can catalyze complex organic reactions under fairly mild conditions giving final products in nearly quantitative yields, as it is inherent in biological catalysts — enzymes.

XI.2. Carbon materials as supports for the catalyst active component

Processes catalyzed by metals and metal compounds supported on carbon materials cover almost the whole spectrum of known catalytic reactions. Of course, it is impossible to consider them all. As examples, Table 2 lists some organic reactions catalyzed by Group 8 metals or their compounds supported on PCMs (M/C), while Table 3 presents examples of processes catalyzed by efficient Pd/Sibunit catalysts.

In the discussion of modern organic synthesis problems, the attention is focused on the activation of unsaturated C=C and C≡C bonds, the formation of new C–C bonds and oxidation reactions catalyzed by Group 8 metals supported on carbon nanotubes.

XI.2.a. Supported M/C metallic catalysts

In M/C type catalysts used in organic synthesis, the content of the active component is, most often, not higher than 5 mass %. During the last decades, a vast number of procedures have been proposed for targeted preparation of supported catalysts with a desired degree of dispersion and pre-specified distribution of the active component over the PCM grain. Characteristic features and properties of these catalysts are described in a number of reviews.[569, 581]

Apart from the development of methods for deposition of the active component, approaches to catalyst preparation by simultaneous formation of the support and the active component have been developed. For example, nanoglobular carbon (the primary particles of this material are spherical items 2 to 200 nm in diameter) is studied as a catalyst or catalyst support in liquid-phase reactions, especially when they occur in microchannel reactors, as the absence of porosity and a great specific surface area promote increase in the activity by a large factor and

Table 2. Organic synthesis on M/C type catalysts.

Reactions	Metals					
	Pd	Pt	Ni	Ru	Rh	Os
Isomerization	+	+	+	+	+	+
Reactions involving hydrogen						
Dehydrogenation, dehydrocyclization and dehydroisomerization	+	+	+	+	+	+
Hydrogen addition at the C=C and C≡C bonds in aliphatic compounds	+	+	+	+	+	+
Hydrogenation of the C=C bond in the ring or aromatic bonds	+	+	+	+	+	
Hydrogen addition at the C=O bond	+	+	+	+	+	
Hydrogen addition at the C=N and C≡N bonds	+	+		+	+	
Destructive hydrogenation with C–C and C–O bond cleavage	+	+		+	+	
Destructive hydrogenation with C–N, C=N, C≡N and N≡N bond cleavage	+	+				
Reduction with molecular hydrogen with HHal release (Hal = Cl, Br, I)	+	+				
Reduction of compounds containing NOH, NO and NO_2 groups with H_2O release	+	+	+		+	+
Reductive cyclization	+					
Reductive condensation	+	+		+	+	
Reduction with other agents (ammonia, cyclohexane, hydrazine, sodium borohydride, methanol, *etc*.)	+	+		+		
Reactions involving CO (carbonylation, Fischer–Tropsch reaction)	+				+	
Reactions involving oxygen (oxidation of organic compounds)	+	+	+	+	+	
Catalytic processing of raw materials of complex composition						
Oil hydrogenation and isomerization	+	+	+			
Rosin dehydrogenation and disproportionation	+					
Hydrogenolysis of heavy hydrocarbons		+				
Petrol aromatization		+				
Wood (lignin) hydrogenation				+		
Formation of new carbon–carbon bonds	+	+		+	+	
Polymerization						
of diethylallylsilane, triallylsilane, *etc*.	+					
of di(silyl)- or di(vinylsilyl)arylenes		+				
of ethylene			+			
Electrochemical processes (catalysts for fuel cells)	+	+	+	+		

Table 3. Organic synthesis processes involving Sibunit-supported Pd-containing catalysts.

Catalyst type	Catalytic process
Powdered	hydrogenation of nitroaromatic compounds in the production of biologically active compounds (chemical and pharmaceutical agents, plant protection agents)
	hydrogenation of benzoic acid in caprolactam production
	hydrogenation of vegetable oils in margarine production
	acetoxylation of ethylene and propylene in glycol production
	oxidation of alcohols and formic acid on low-temperature fuel cell anodes; electroreduction of nitrate ions
Pelletized	purification of hydrocarbons (ethylene, propylene, butenes) from acetylene
	amination in the xylidine production from xylenol
	rosin hydrogenation and disproportionation
	purification of terephthalic acid
	decarboxylation of furfural
	hydrodehalogenation of toxic compounds

facilitate the control over selectivity. Furthermore, the discovered transformations of the carbon material under the action of high-energy radiation (laser radiation, electron beam)[582, 583] open up new prospects for the design of catalytic systems, for example, for the use of laser irradiation of the nanoglobular carbon–metal complex suspensions. This type of treatment can serve for controlled change of both the internal structure of the carbon globule and the sites of location of the deposited metal nanoparticles.

Yet another novel approach to the synthesis of CM-supported catalysts is liquid-phase dehalogenation of polychlorovinylene complexes with transition metal compounds, giving rise to systems with strong metal–carbon interaction.[584] One can expect that this interaction would considerably change the electrophysical and catalytic properties of both the metal nanoparticle and the carbon cluster.

The Pt/C catalysts with high Pt content are key components of low-temperature fuel cells based on the proton-conducting electrolyte (FC-PCE), which are high-performance environmentally friendly power sources. In this regard, the key features of the formation of Pt/C electrocatalysts are now being vigorously studied and approaches to the preparation of samples containing up to 40 mass %–80 mass % of the deposited metal are being developed.[585–590]

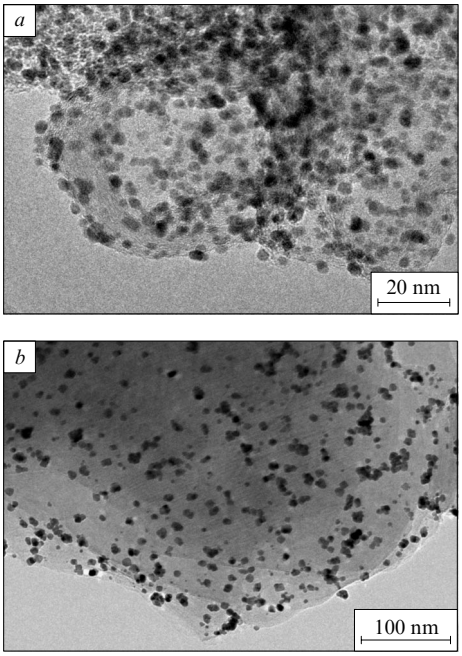


Figure 23. Photomicrographs of catalysts: 40% Pt/Sibunit 1562 (S_{sp} = 590 $m^2 g^{-1}$) (*a*), 0.5% Pt/graphite (S_{sp} = 2 $m^2 g^{-1}$) (*b*) (authors' data).

A number of effective procedures have been proposed for the synthesis of Pt/C electrocatalysts by hydrolytic and/or reductive deposition of platinum from H_2PtCl_6 solutions [590] and by additional formation of platinum binding sites on the PCM surface.[589] In the latter case, the resulting catalysts have a very narrow platinum particle size distribution. A photomicrograph of a surface fragment of such sample is shown in Fig. 23 *a*. It was shown experimentally [587] that the efficiency of cathodes based on this catalyst is close to that of the best commercial material, 40% Pt/Vulcan XC 72R – Hispec 4000 (Johnson Matthey); however, the activity per unit weight is twice higher for 40% Pt/sibunit 1562 than for the commercial sample owing to a higher degree of dispersion of platinum, which opens up the way for further advancement of electrocatalysts based on Sibunit supports.

Methods for control of the platinum degree of dispersion and particular size distribution developed for electrocatalysts were successfully tested for the preparation and regeneration of the 0.5% Pt/graphite catalyst (2 $m^2 g^{-1}$) in the synthesis of hydroxylamine sulfate by NO hydrogenation in sulfuric acid solutions (see Fig. 23 *b*), because the surface concentrations of Pt particles in these catalysts are similar.

XI.2.b. Formation of new carbon – carbon bonds

A special place in the modern organic synthesis is occupied by the reactions resulting in the formation of new C–C bonds. First of all, this is the palladium-catalyzed cross-coupling reactions. One more way of forming C–C and C–X bonds (X is a heteroatom) in aromatic systems is based on nucleophilic substitution of hydrogen.

Reactions of the first type are couplings of organic halides with organometallic compounds in the presence of Pd^0 complexes (Scheme 141).

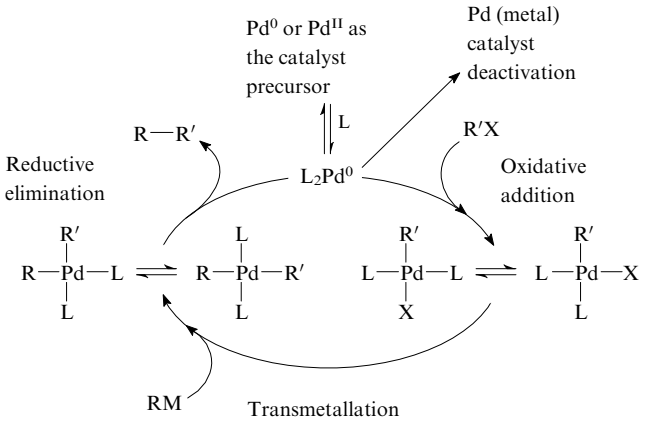
Scheme 141

$$R'X + RM \xrightarrow{[Pd]} R'—R + MX$$

R′ = Ar, All, Bn, CH=CH_2; M = Mg (Kumada reaction), Sn (Stille reaction), Zn (Negishi reaction), B (Suzuki reaction)

The mechanism of cross-coupling can be depicted as a four-step catalytic cycle (Scheme 142) [591] in which the first step is the oxidative addition of R′X (X = Hal) to the Pd^0 complex followed by transfer of the group R from the metal M to Pd. The palladium(0) complex can be either directly introduced into the reaction medium or prepared from a precursor *in situ*. The catalytic cycle is completed by reductive elimination of the R–R′ product and recovery of the Pd^0 complex.

Scheme 142



The homogeneous catalysts used in these reactions are, most often, palladium complexes: $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, $Pd_2(dba)_3$ and so on. Due to the increasing demand for valuable products obtained in this way, the development of efficient heterogeneous analogues of cross-coupling catalysts becomes a topical task. This would increase catalyst stability, the problems of product separation would be avoided and reuse of the catalyst would become possible. These catalysts can be fabricated, for example, by targeted formation of palladium complexes directly on the surface of carbon supports.[592] Attempts are being made to attach palladium complexes to polymers, gels or inorganic supports, to use ionic liquids and so on.[591, 592] However, catalysts prepared in this way show lower activity.

XI.2.c. Reactions involving oxygen

Due to the low corrosion stability of traditional carbon supports in oxidative atmosphere at elevated temperatures, the percentage of M/C catalysts promising for selective oxidation of organic compounds has been rather low until recently. However, during the last two decades, quite a few publications dealing with the use of such catalysts for environmental protection processes appeared (the number of publications still increases).[592, 593] For purification of liquids and gases from hazardous compounds (phenol, organochlorine compounds, *etc.*), various combinations of metals and their salts supported on carbon materials have been proposed. The percentage of studies devoted to the Au/C catalysts is growing.[594, 595] The key applications of these catalysts are related to oxidation of functional groups

containing O, N and Si heteroatoms, namely, transformations of amines, oxidation of organic silanes, alcohols and aldehydes, epoxidation of propylene and so on.

A vivid example of efficient use of the M/C catalysts in fine organic synthesis is selective oxidation of sugars. In an alkaline medium, the Pd–Bi/C catalyst can be used to oxidize glucose with air to sodium gluconate with 99.8% selectivity at 96.6% conversion.[596] Subsequently, it was found that this bimetallic catalyst is less active than monometallic Au/C.[597] In this and in some other oxidation reactions, Au-containing catalysts are more efficient than platinum group metals, but recent results indicate that bimetallic particles containing Au and Pt, Pd or Rh can be more perfect catalysts.[595]

In the development of processes that help to protect the environment, Sibunit-supported Fe and Ru catalysts are currently studied in extensive oxidation of organic ecotoxicants in aqueous solutions.[598]

XI.2.d. Activation of unsaturated C=C and C≡C bonds

Most of modern organic synthesis processes using M/C catalysts comprise steps of activation of unsaturated C=C and C≡C bonds.[592, 593] Some reactions of this type are listed in Table 2. Below we consider some characteristic features of these reactions in relation to the industrially important partial hydrogenation of vegetable oils catalyzed by Pd/Sibunit systems.

The Pt/C and Pd/C catalysts with low metal contents are considered to be promising in hydrogenation of vegetable oils for the production of foodstuffs. The use of these catalysts is caused by the necessity of replacing the traditional nickel systems, as they can contaminate the hydrogenation products (hydrogenated fats) by toxic nickel, which does not comply with the modern manufacturing requirements. Vegetable oils contain 95%–97% of fatty acid triglycerides (FAT), which are bulky molecules of >2 nm size. Therefore, to efficiently hydrogenate these compounds on supported catalysts, macro- or mesoporous supports should be used, in particular, Sibunit-type PCMs.

The hydrogenation of unsaturated carbon–carbon bonds catalyzed by M/C systems is described by the Horiuti–Polanyi mechanism according to which the reaction can proceed simultaneously along three pathways: hydrogenation and formation of geometric (*cis–trans* isomerization) and positional (migration of double bonds along the carbon chain of the molecule) isomers of unsaturated acids. Therefore, the activity and selectivity control of FAT hydrogenation receives enormous attention; however, this issue is beyond the scope of the review. We would like to note only that lately, additional requirements have been placed on the products formed on hydrogenation catalysts. According to modern world trends,[599] edible hydrogenated fats should contain, all other factors being the same, minimized amounts of *trans*-isomers and products of complete hydrogenation of unsaturated C–C bonds (Fig. 24; the area marked by dashed line). However, as can be seen from the Figure, new approaches to oil processing for obtaining products of the required composition are still to be developed or new, in principle, catalysts for partial oil hydrogenation are to be devised.

During the last decade, new efficient methods for the synthesis of supported M/C catalysts with a broad range of concentrations of active component have been proposed. In particular, a number of Pt/C electrocatalysts with active

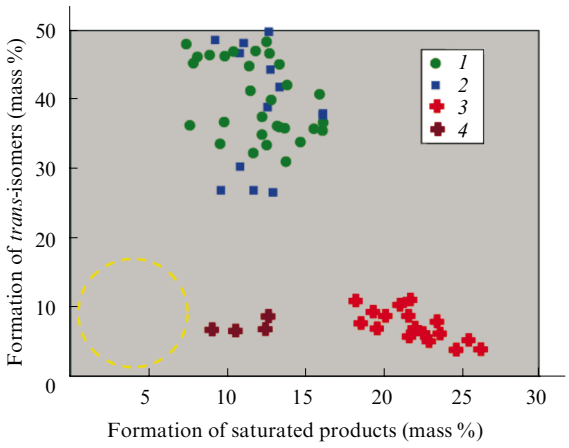


Figure 24. World trends in oil partial hydrogenation processes (see the text).[599]
(*1*) Ni, (*2*) Pd, (*3*) Pt (1st generation), (*4*) Pt (2nd generation).

component contents of 40 mass % – 60 mass % have been devised. Apart from the development of methods for deposition of the active component, some new approaches imply the preparation of catalysts by simultaneous formation of the support and the active component on exposure of a suspension of nanoglobular carbon in solutions of metal complexes to laser radiation or an electron beam or by means of liquid-phase dehalogenation of polychloroinylene complexes with transition metal compounds.

In turn, low-percentage mono- and bimetallic catalysts based on palladium, platinum and ruthenium have successfully passed tests, including pilot tests, for purification of terephthalic acid, hydrogenation of some nitroaromatic compounds in the manufacture of herbicides and anesthetic agents, in partial and exhaustive hydrogenation of vegetable oils for food and technical purposes, in the hydrogenation of benzoic acid or NO to produce caprolactam and for rosin disproportionation in the plastics technology.

One can expect that by using chemically modified porous carbon materials in combination with metal complexes or nanoparticles deposited on these materials, it would be possible to devise catalytic systems that meet the requirement of multiple-function character and could play a significant role in the transition from multistep synthetic processes to one-pot procedures.

XII. Heterogeneous catalysts in the industrial production of organic compounds

Conventionally, by fine organic chemistry products are meant compounds that cost >10 US dollars per kg and are manufactured in amounts of <10 000 tonnes per year.[600] Catalytic processes are widely used in the production processes of large-tonnage products, whereas processes for manufacture of complex organic compounds still rely on classical organic chemistry including multistep syntheses, stoichiometric amounts of oxidants and reductants ($KMnO_4$, $K_2Cr_2O_7$ and so on). The expansion of green chemistry principles and legislative regulation of production and environmental safety of industrial plants in some countries stimulate the development of catalytic processes of industrial organic synthesis using environmentally clean

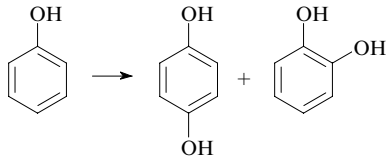
oxidants (oxygen, hydrogen peroxide) and reductants (hydrogen), which would increase the selectivity of transformations and reduce the number of steps and amounts of industrial wastes.

A huge number of scientific publications are devoted to various aspects of the use of heterogeneous catalysts for the transformation of organic compounds, whereas information about the practical use of a particular catalyst for industrial organic synthesis processes is seldom encountered in publicly available literature. This is due to tough competition between chemical companies and to enormous expenses needed to develop the production process of one or another chemical. This Section describes examples of relatively new catalytic processes demonstrating advantages of the use of heterogeneous catalysts for oxidation and hydrogenation of organic molecules in industrial organic synthesis.

XII.1. Heterogeneous catalysts in oxidative processes

A successful example of application of heterogeneous catalysts in oxidative processes is the use of the titanosilicate TS-1-based zeolite material in the hydroxylation of phenol, epoxidation of propylene and ammoximation of cyclohexanone (in the presence of NH_3) with hydrogen peroxide.[600–603] The works were started by the Eni company in order to advance the process of hydrogen peroxide oxidation of phenol to give a mixture of hydroquinone and pyrocatechol (Scheme 143), which was previously carried out in the presence of an iron(II) and cobalt(II) salt mixture and had low efficiency, resulting in the formation of resins and non-optimal pyrocatechol : hydroquinone ratio (2 – 2.3).

Scheme 143



Screening of a large number of samples revealed a catalyst that exhibited high activity and selectivity in the hydroxylation of phenol with hydrogen peroxide, namely, titanosilicate TS-1 [$x\,TiO_2 \cdot (1-x)\,SiO_2$, $0.0001 < x < 0.04$]. The industrial application of this process was preceded by a long period of research aimed at the development of a reproducible method for the synthesis and commercialization of the catalytic material, optimization of oxidation conditions and development of a method for catalyst regeneration. The process was commissioned in 1986 at the EniChem Synthesis plant (Ravenna, Italy); in 2010, Camlin Fine Chemicals (India) became the owner of the production unit. The process changed little since the commissioning: the oxidation is performed in an acetone, methanol and water mixture at 80 – 100 °C, the H_2O_2 : phenol ratio is 0.2 – 0.3. For phenol conversion of 20% – 30%, the selectivity to phenol is 90% – 95%, that to hydrogen peroxide is 80% – 90%, and the pyrocatechol : hydroquinone ratio in the phenol hydroxylation products is 1.1 – 1.2. The annual demand for hydroquinone is ~55 000 tonnes and that for pyrocatechol is ~35 000 tonnes.

The process of propylene epoxidation with hydrogen peroxide was commissioned in 2001 at a pilot unit with 2000 tonnes per year capacity belonging to the Eni group (Ferrara, Italy). In the same year, the plant was purchased by Dow Chemical, which established a joint venture with BASF in 2002 for commercialization of the process of propylene oxidation with hydrogen peroxide. Currently this process is known as BASF/Dow HPPO (Hydrogen Peroxide for Propylene Oxide), the propylene oxidation to propylene oxide (PO) being conducted in the presence of the TS-1 catalyst. The first industrial production of propylene oxide by the new process with 300 000 tonnes per year capacity was started in 2008 (Antwerp, Belgium). In October 2011, propylene oxide production by the BASF/Dow HPPO process was started at a plant with 390 000 tonnes per year capacity (Map ta phut, Thailand). The Evonic and Unde Gmbh companies also developed a propylene oxide production process using hydrogen peroxide. The process was implemented in South Korea (Ulsan); a plant of 100 000 tonnes per year capacity was commissioned in July 2008.[604]

Comparison of the key characteristics of alternative processes currently used to produce propylene oxide is given in Table 4. The HPPO process, unlike the other two catalytic processes, does not require organic peroxides (ethylbenzene or styrene hydroperoxide); therefore, today it is most environmentally attractive.[602] Nevertheless, in 2009, only ~8% of propylene oxide was produced in this way, the rest being distributed approximately in equal parts among the non-catalytic chlorohydrin method and catalytic methods using organic peroxides.[600]

Development of the catalytic process of cyclohexanone ammoximation in cyclohexylamine in the presence of titanosilicate TS-1 formed the basis for environmentally

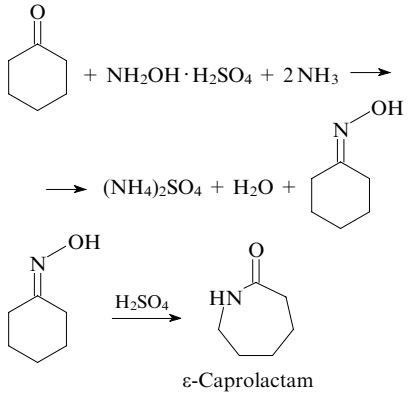
Table 4. Modern alternative industrial processes for propylene oxide production.[602]

Process	Catalyst	Reagents	By-product [a]	PO yield (%) (see [b])	Wastes, tonnes per tonne of PO
Chlorohydrin	none	$Ca(OH)_2$, Cl_2 or NaOH, Cl_2	A solution of $CaCl_2$ or NaCl	89	2
Co-production of PO and styrene	Ti/SiO_2	ethylbenzene hydroperoxide	styrene	⩾90	2.5
Cumene process	Ti silicate	cumene hydroperoxide	water	⩾90	–
Peroxide process	TS-1	H_2O_2	water	⩾90	–

[a] Waste water treatment is required (for water and salt solution); [b] the yield was calculated in relation to the reagent.

friendly method for the production of caprolactam to be used as the monomer for nylon 6. The conventional industrial methods for the manufacture of caprolactam start from cyclohexanone, which first reacts with an excess of an aqueous solution of hydroxylamine sulfate at 0–100 °C. In the second step, cyclohexanone oxime is converted to caprolactam in the presence of sulfuric acid *via* the Beckmann rearrangement (Scheme 144). The production of caprolactam is accompanied by the formation of a large amount of the ammonium sulfate by-product (~4.4 kg per kg of caprolactam); the synthesis of hydroxylamine comprises several steps and produces nitrogen oxide and sulfur oxide effluents.

Scheme 144



ε-Caprolactam

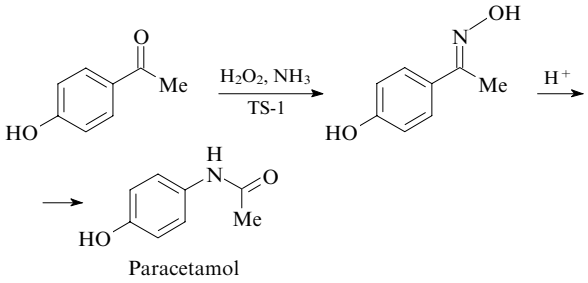
The reaction of cyclohexanone with ammonia and hydrogen peroxide in the presence of the microspherical TS-1 catalyst is free from by-products and gas effluents and requires much less complicated equipment. It is commonly accepted that ammoximation involves hydroxylamine, which is formed *in situ* upon oxidation of ammonia with hydrogen peroxide in the presence of the TS-1 catalyst.[603] The reaction with ammonia and hydrogen peroxide, resulting in cyclohexanone oxime and called ammoximation, was first performed by Lebedev and Kazarnovsky[605] in the presence of sodium tungstate. The possibility of process commercialization was demonstrated on a pilot unit with a capacity of 12 000 tonnes per year in 1994 at the Porto Marghera plant (Venice, Italy). The reaction was carried out in a flow type slurry reactor on a modified TS-1 catalyst; cyclohexanone, ammonia and hydrogen peroxide were fed to the reactor in 1.0 : 2.0 : 1.1 molar ratio, the reaction was carried out at 80–90 °C with a *tert*-butyl alcohol and water mixture as the solvent. Under these conditions, cyclohexanone was converted almost completely (conversion >99.9%) to cyclohexanone oxime with >98% selectivity.

Approximately at the same time, the Sumimoto company developed a heterogeneous catalyst for the Beckmann rearrangement. In this process, cyclohexanone oxime reacts in the vapour phase at a temperature of 300–400 °C under atmospheric pressure on a fluidized catalyst bed (MFI zeolite). Upon optimization of the catalyst composition, it was possible to reach a 95% selectivity towards caprolactam at a virtually complete conversion of cyclohexanone oxime.

Sumimoto purchased the license for hydroxylamine production process and in 2003, commissioned the caprolactam production unit with a capacity of 65 000 tonnes per year at the Niihama plant (Ehime, Japan). In this process, both steps (ammoximation of cyclohexanone and Beckmann rearrangement) make use of heterogeneous catalysts. To our knowledge, there are no other analogous processes. Since the annual production of caprolactam is ~4 million tonnes (data for 2010), the contribution of the heterogeneous catalytic process is < 2%.

The patent and scientific literature describe examples of successful implementation of ketone ammoximation to give products holding good prospects for commercialization. For example, ammoximation of *p*-hydroxyacetophenone has been reported (Scheme 145), the resulting oxime being the precursor of *N*-(4-hydroxyphenyl)acetamide (paracetamol).[606, 607]

Scheme 145



Paracetamol

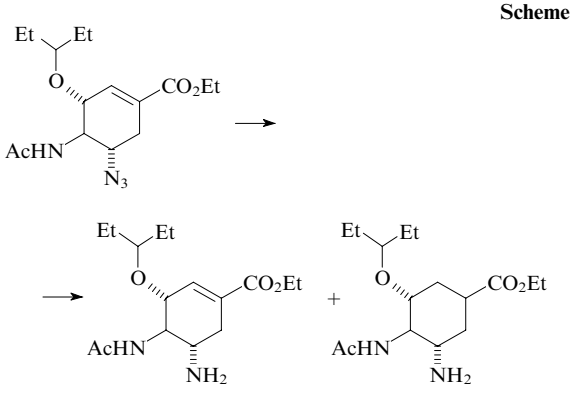
The reaction selectivity is 100% for a 50% conversion of the starting compound. The preparation of laurolactam, the monomer for nylon 12 production, has also been reported.[608, 609] No data on the industrial implementation of these reactions are available.

XII.2. Catalytic methods for the reduction of organic compounds

It is impossible to describe the whole diversity of catalytic methods for the reduction of organic compounds within a single section; therefore, we will consider reactions that proceed on Pd-containing catalysts and fall into the area of research interests of the authors. It is known that palladium catalysts are used in numerous hydrogenation reactions;[600] however, most active users of expensive catalysts are still pharmaceutical and defence industries.

For example, the last step in the 10-step synthesis of oseltamivir (antiviral drug efficient against the H5N1 bird flu virus) was implemented as reduction of the azide group to the amino group with hydrogen in the presence of the Pd/Sibunit catalyst (5% Pd/C) to give the necessary stereoisomer (Scheme 146). The industrial yield of the target product was 63%; the use of highly active palladium

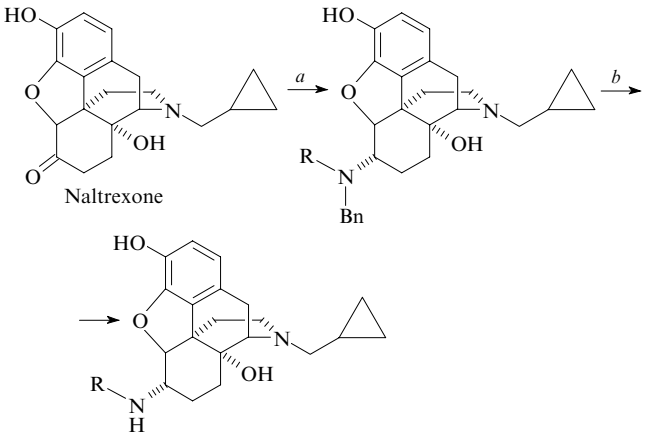
Scheme 146



catalyst resulted in reduction of the double bond, too, to give the side product.[610]

Naloxone, naltrexone and its derivatives are opioid receptor antagonists used to treat narcotic and alcohol addictions. Carbon-supported palladium is used to prepare intermediates for the synthesis of naloxone and naltrexone and for the synthesis of naltrexone derivatives (Scheme 147).[611]

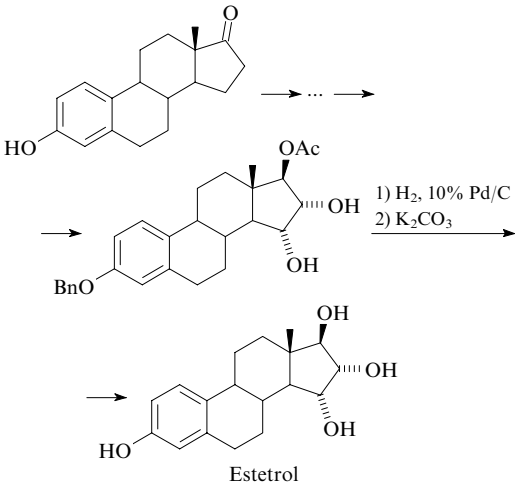
Scheme 147



R = H, Me, CH_2CH_2OH, Et, Bu^n;
(*a*) HNBnR; (*b*) H_2 (1–2 bar), 10% Pd, AcOH

In the six-step pilot procedure for the synthesis of estetrol, a versatile hormonal agent, the benzyl and acetyl groups are used to protect the active hydroxy groups. Deprotection is accomplished in the final step of the synthesis. First, O-debenzylation is carried out and then the acetyl group is removed by alkaline hydrolysis under mild conditions (Scheme 148).[612]

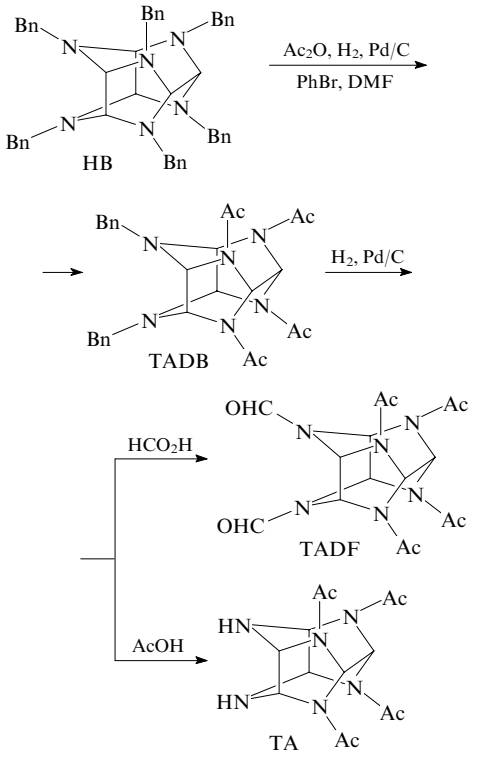
Scheme 148



The most widely used large-scale industrial process involving palladium catalysts in industry is the production of 2,4,6,8,10,12-hexanitro-2,4,6,8,10,12-hexaazaisowurtzitane (HNIW, CL-20). This is a promising and powerful explosive — a component of explosive formulations and composite solid propellants.[613,614] The key step of the HNIW preparation is Pd-catalyzed reductive debenzylation (Scheme 149).[615] The most convenient starting compounds the nitrolysis of which gives the best yields and product quality are 2,6,8,12-tetraacetyl-4,10-diformyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADF) and 2,6,8,12-tetraacetyl-2,4,6,8,10,12-hexaazaisowurtzitane (TA).

In the two-step catalytic debenzylation, a catalyst containing 5%–10% palladium on carbon and bromobenzene as the co-catalyst are used.

Scheme 149

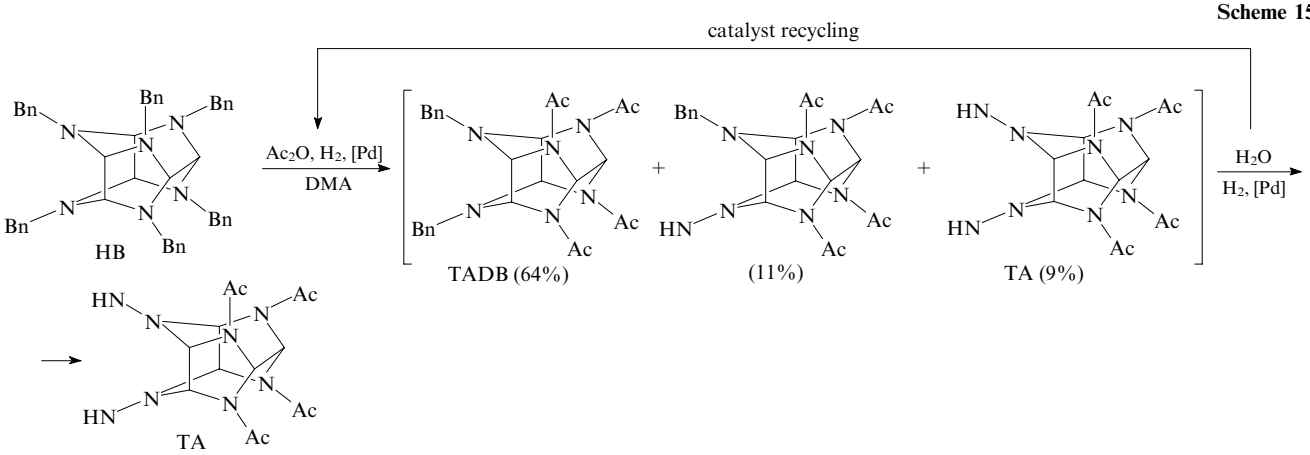


The catalyst is employed successively in two debenzylation steps, the key problem faced by the practical implementation of these steps being fast catalyst deactivation. The known methods for regeneration of heterogeneous catalysts do not restore the activity to the initial level, which precludes repeated use of the catalyst. From the spent catalyst, palladium is isolated and used to prepare the new catalyst. The cost of the palladium catalyst can amount to 35%–40% of the HNIW prime cost. Therefore, lots of studies have been devoted to the search for catalytic systems that would allow repeated use of the expensive catalyst.

Using the modern industrial production of HNIW, we will consider the scope and limitations of the catalytic chemistry for solving industrial problems. The industrial production process of this compound with a capacity of 5 to 100 tonnes per year is demanded for solution of important practical problems. An attempt of repeated use of the palladium catalyst in the step of 2,4,6,8,10,12-hexabenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (HB) debenzylation has been patented.[616] It was shown that some commercially available Degussa catalysts used in the two-step reductive debenzylation of HB (Scheme 150) can be reused (see Scheme 149, HB → TADB → TADF). However, in the second catalyst cycle, the yield of 2,6,8,12-tetraacetyl-4,10-dibenzyl-2,4,6,8,10,12-hexaazaisowurtzitane (TADB) considerably decreases and subsequently tends to zero.

A method for TA preparation with repeated use of the catalyst containing up to 10% palladium (see Scheme 150) has been described in patents.[617,618] When ten debenzyla-

Scheme 150



tion runs were performed, the TA yield was not less than 80% in each step. This debenzylation method formed the basis of an industrial process for the synthesis of HNIW.[617] However, this process proved to be of low utility for the preparation of the diformyl derivative (TADF), used most often in HNIW synthesis.

Studies of the catalytic debenzylation–formylation step (HB → TADB → TADF) have been reported.[619,620] The studies concerned the effects of the preparation procedure of heterogeneous catalysts, components of the reaction mixture and process conditions on the catalyst stability against deactivation in the catalytic debenzylation. Using modern methods of analysis, the authors established the optimal degree of dispersion of Pd on the support surface for debenzylation. It was shown that in the two-step catalytic debenzylation, redistribution of palladium particles on the carbon support takes place and the particle size markedly increases. The researchers concluded that the decrease in the Pd/C activity is due to plugging of the metallic palladium in the support pores by the by-products resulting from oligomerization of intermediates and to agglomeration of metal particles.

A known method for increasing the stability of palladium metal particles in the Pd/C catalysts is introduction of the stabilizing metal into the catalytic system.[621] Stabilization can be attained due to both the electronic effect (change in the electronegativity of the active metal) and modification of the carbon support surface.

A patent [622] describes a series of bimetallic systems that were tested in the two-step hydrodebenzylation reaction (HB → TADB → TADF). Particular attention was paid to the possibility of conducting the second hydrodebenzylation cycle (recycle) with spent catalysts. According to the results presented in Table 5, the addition of stabilizing metal ions during the catalyst preparation resulted, in some cases, in increased catalyst productivity for the target product owing to enhancement of the catalyst stability against deactivation. However, the overall yield of TADF per gram of the catalyst remained rather low.

Table 5. Use of bimetallic catalysts in the synthesis of tetraacetyldiformyl hexaazaisowurtzitane.[622]

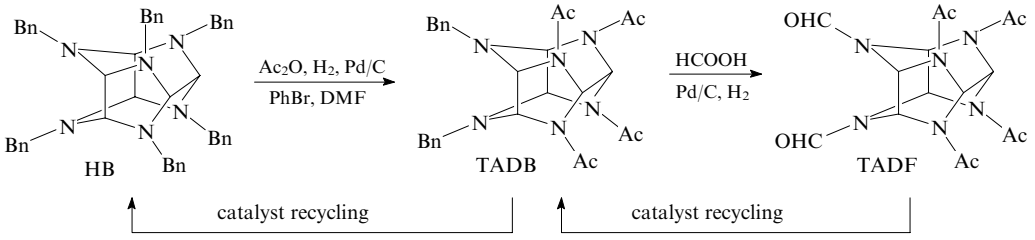
Catalyst [metal content (%)]	TADF yield (%)		
	freshly prepared catalyst	1st recycle	2nd recycle
Pd/C (6)	69	0	0
Pd/C (10)	75	0	0
Pd : Ir/C (6 : 3)	76	70	59
Pd : Pt/C (6 : 3)	72	73	0
Pd : Pt : Ir/C (6 : 1.5 : 1.5)	60	51	22
Pd : Ir/C (4 : 3)	0	0	0
Pd : Ir/C (6 : 1)	73	0	0
Pd : Ir/C (6 : 4)	72	67	55
Pd/C (6) + Ir/C (3)	69	0	0
Pd : Ir/CFC (6 : 3) [a]	70	66	50

[a] CFC is catalytic fibrous carbon.

Proceeding from the assumption that the use of the catalyst only in one debenzylation step stabilizes the catalyst operation, a process chart for separate use of the catalyst was proposed (Scheme 151).[623–625] The data presented in Fig. 25 illustrate the possibility of repeated use of the catalyst containing 5.6%–5.9% palladium in the first debenzylation step (HB → TADB).

The second debenzylation step is less sensitive to the quality and morphology of the catalyst. When the process employs the reused catalyst, the TADF yield decreases noticeably only in the 14th cycle. Also, the catalyst that has already served for ten cycles in the first step was able to

Scheme 151



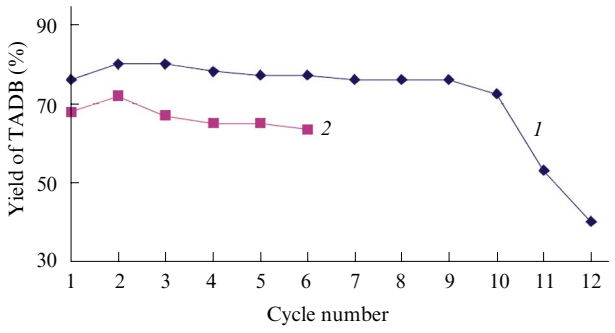


Figure 25. Yield of TADB upon repeated use of Pd/C catalyst.[623,625]
(*1*) Hydrogenation at $P_g = 2-5$ kg cm^{-2} for 6 h, (*2*) hydrogenation at $P_g = 0.05$ kg cm^{-2} for 18 h.

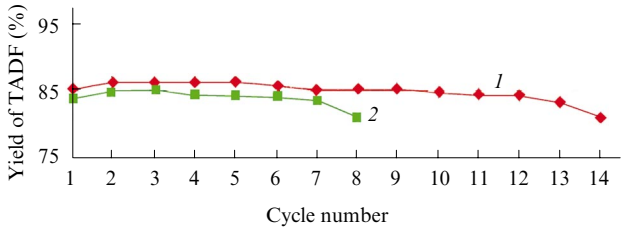


Figure 26. Yield of TADF upon repeated use of the Pd/C catalyst.[623,625]
(*1*) Freshly prepared catalyst, (*2*) catalyst after ten cycles of TADF preparation (*2*).

perform seven more cycles in the second step to give TADF yields of 84% – 85% (Fig. 26). In order to eliminate the step of isolation of crystalline TADB from the solution in acetic acid, conduction of the second debenzylation step in a mixture of formic and acetic acids was proposed.[626]

A TEM study of catalyst samples demonstrated that in the repeated use of the catalyst, palladium particle size considerably increases and, hence, the active metal surface area decreases. The coarsening of palladium particles in both the first and second debenzylation steps occurs from one cycle to another to reach a definite threshold value after

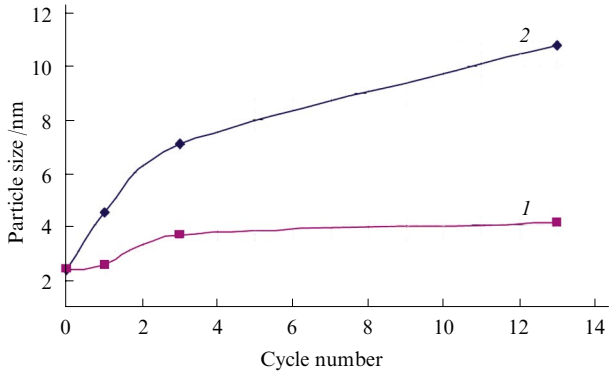


Figure 27. Change in the palladium particle size upon repeated use of the Pd/C catalyst.[623,625]
(*1*) HB → TADB, (*2*) TADB → TADF.

which the catalyst completely loses activity. These values are considerably different for the first and second debenzylation steps (Fig. 27). It was found that for the first step of HB debenzylation, the optimal average palladium particle size of the catalyst is 2.3 – 2.5 nm and the catalyst completely loses the activity when the average particle size is > 4 nm. For the second step, the optimal catalyst particle size is 4 – 6 nm and the activity is lost as the average particle diameter has increased to 10 – 11 nm.

Thus, the key solution to the problem of repeated use of the catalyst in the HB debenzylation steps is its separate use: the first process (HB → TADB) is performed with one catalyst sample, while the second process (TADB → TADF) is performed with another catalyst sample (either freshly prepared or already used in the first step). On the basis of these data, a chart for two-step HB debenzylation with repeated use of the catalyst was proposed (Fig. 28).[625]

This debenzylation chart was tested under pilot conditions. The average product yields in steps 1 and 2 were 80% and 84%, respectively, and the overall yield of the final product (TADF) per gramme of the catalyst used was 16.6 g, which is much greater than the values obtained earlier.[625]

The use of Pd-containing catalysts formed the basis for the new 'green' methods for the preparation of the drugs ibuprofen (isobutylphenylpropionic acid) and sertraline (Refs 600, 627 and 628). The conventional synthesis of

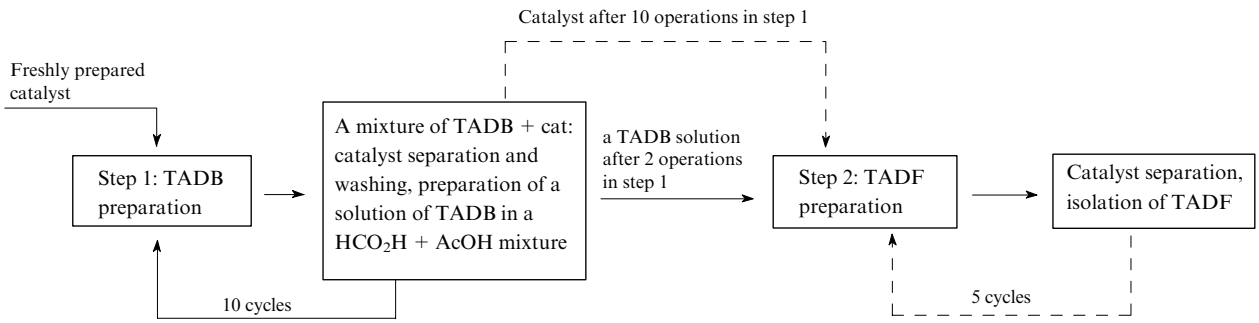
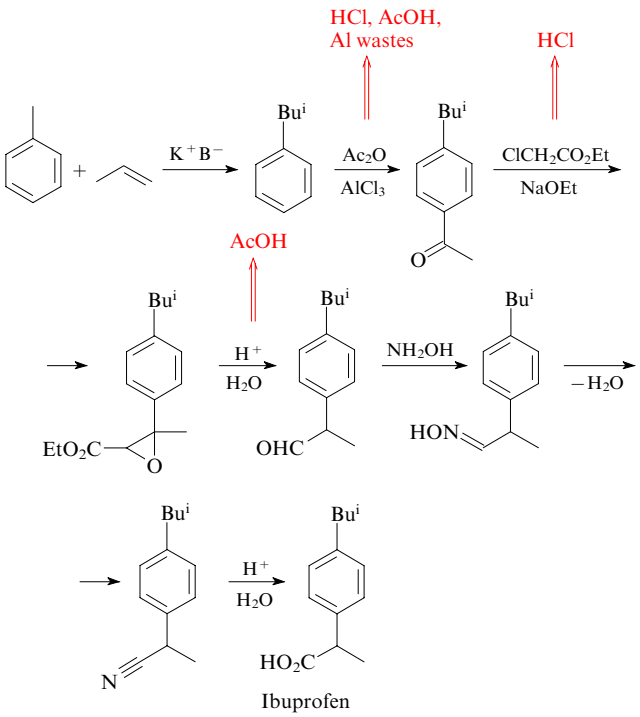


Figure 28. Diagram of application and regeneration of the Pd/C catalyst.[625]

ibuprofen, an anti-inflammatory drug (annual production of about several thousand tonnes), included seven steps (Scheme 152), the yield in each step being lower than 100%, which gave rise to huge amounts of diverse wastes (acetic acid, ethyl chloroacetate, hydroxylamine).

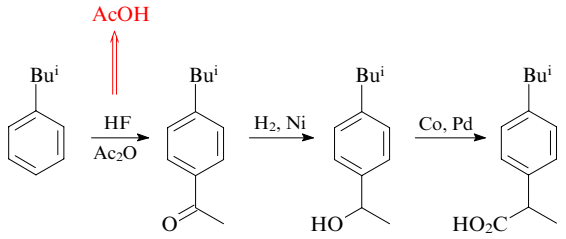
Scheme 152



Ibuprofen

According to the new process developed by the Hoechst-Celanese company, ibuprofen is produced in two catalyzed steps — hydrogenation and carbonylation (Scheme 153). As a result, the amount of wastes per 206 kg of ibuprofen decreased from 308.5 to 60 kg, acetic acid being the only by-product.

Scheme 153

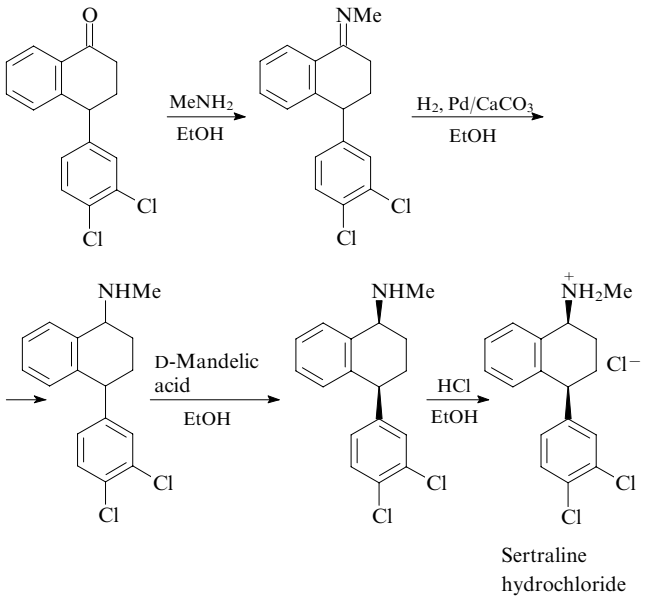


Ibuprofen

The antidepressant drug sertraline was initially produced over three steps, each using a different solvent, with intermediate isolation of products of each step.[600, 604]

In the new process developed by Pfizer, the three steps are performed in the same solvent, ethanol, and no isolation of the intermediate products between the steps is required (Scheme 154). The yield of the final product increased twofold (to 37%) and ethanol replaced toluene, tetrahydrofuran and hexane solvents, the total solvent consumption was reduced from 240 to 24 litres per gramme of the product. In addition, implementation of this process makes it possible to avoid the large amount of wastes, which was up to 440 tonnes of titanium dioxide, 150 tonnes of 35% hydrochloric acid and 100 tonnes of sodium hydroxide annually in the initial sertraline production process.

Scheme 154



Sertraline hydrochloride

The presented examples demonstrate the efficiency of using heterogeneous catalysts in industrial production of organic compounds. The increase in cost efficiency (higher yield, fewer number of steps, no protecting groups, simpler isolation, lower material consumption) and environmental safety (lower amounts of wastes and effluents, replacement of toxic reagents by catalysts) in industrial organic synthesis processes stimulates commercialization of catalytic reactions. This is promoted by development of new catalytic materials (supported mono- and bimetallic nanoparticles, grafted metal complexes and enzymes) able to catalyze selective transformations of complex organic molecules. Apart from extension of the use of heterogeneous catalysts, modern trends of organic synthesis include the implementation of flow type reactors, attempts to use supercritical carbon dioxide and ionic liquids as solvents and intensification of organic reactions upon physical action on the reaction mixture (ultrasound, microwave radiation).[600, 604]

In the 20th century, heterogeneous catalysts were actively introduced mainly in large-tonnage production processes of fuels and semi-products at large plants. The goal for the 21st century is the development and commercialization of heterogeneously catalyzed processes in fine organic synthesis.

XIII. Studies of the mechanisms of catalytic reactions by the nuclear spin hyperpolarization technique

The immense potential of heterogeneous catalytic reactions and high demand for heterogeneous catalysts in fine organic synthesis determine the increasing interest in the research in this area. However, a serious obstacle comes from the considerable complications in the studies of reaction mechanisms caused by specific nature of heterogeneous systems (see Section IX). It is the development of new methods for investigation of mechanisms of complex catalytic reactions that will predetermine the progress in this area for selective

organic synthesis. A highly interesting investigation method for reactions involving molecular hydrogen (see Sections IX–XII) is the nuclear spin hyperpolarization method considered in this Section.

Molecular hydrogen (H_2) has two nuclear spin isomers, orthohydrogen and parahydrogen, which are chemically identical but differ by a number of physical properties. Therefore, physical methods (*e.g.*, heat capacity measurement) can be used to determine their ratio in the mixture. In the equilibrium state at room temperature, hydrogen exists as a 3 : 1 mixture of ortho- and para-isomers. A relatively simple procedure can be used to produce various degrees of parahydrogen enrichment of H_2 up to almost pure parahydrogen. In the 1930s, parahydrogen was actively used to study the mechanisms of heterogeneous catalytic processes.[629, 630] It is well known that hydrogen can be dissociatively chemisorbed on contact with the surface of a catalytically active metal. Upon the subsequent recombination of the pairs of random H atoms on the surface, the ortho- and para-isomer ratio for the resulting H_2 molecules is equal to the thermodynamically equilibrium ratio for the given temperature. Therefore, upon metal activation, parahydrogen is converted to an equilibrium mixture of ortho- and para-isomers. The rate of this transformation is believed to be a direct measure of the H_2 dissociation rate on the catalyst surface.[631] Thus, comparison of the rates of reactions of substrate with H_2 and D_2, the $H_2 + D_2 \rightarrow 2\,HD$ exchange rate and the ortho–para hydrogen conversion rate provides important information about the mechanisms of H_2 activation and chemical transformations in heterogeneous hydrogenation processes.[630–632]

In combination with the NMR technique, parahydrogen provides even more useful and diverse information on catalytic processes. Analytical methods based on NMR have become an indispensable tool for numerous advanced applications in physics, chemistry, biology and medicine. For example, NMR spectroscopy is widely used in modern chemical investigations, in particular, to study the mechanisms of homogeneous[633] and heterogeneous[634–637] catalytic reactions by detecting the reaction intermediates and products, dynamic processes involving them, reaction kinetics and so on. The spatially resolved NMR technique (NMR imaging, MRI), which has acquired wide use in medical diagnosis and biological studies on animals, is also successfully used in chemical engineering and catalysis, in particular for *in situ* and *operando* studies of catalytic reactions and reactors.[638] However, a factor that impedes further extension of the scope of applicability of NMR is low sensitivity caused by a small difference between the populations of energy levels of nuclear spins in the magnetic fields of modern NMR and MRI instruments. Therefore, in recent years, considerable attention in NMR has been paid to development of the methods of nuclear spin hyperpolarization, which can increase the intensity of NMR signals by 3–4 orders of magnitude or even more.[639–641] One of these approaches is based on the use of parahydrogen in catalytic hydrogenation of unsaturated organic compounds.[642–645]

From the NMR standpoint, a significant difference between the hydrogen spin isomers is the different value of the total nuclear spin of the H_2 molecule, which is 1 for orthohydrogen and 0 for parahydrogen. Thus, the parahydrogen molecule itself does not produce a ^1H NMR signal. However, H_2 enriched in the para-isomer shows a high degree of nuclear spin correlation. As both H atoms add to a substrate molecule, the symmetry of the initial H_2 molecule disappears, which may result in a pronounced enhancement of NMR signals owing to the so-called parahydrogen induced polarization (PHIP).

The PHIP effect was first demonstrated in the hydrogenation of acrylonitrile to propionitrile.[642] Since then, this approach has been widely used to study the mechanisms and kinetics of homogeneous processes in solution, which include the step of H_2 activation by transition metal complexes.[643, 644, 646–648] Owing to the high sensitivity of NMR in combination with PHIP and the unusual line shapes in the spectra (the presence of antiphase multiplets or signals with different signs), these experiments can provide a lot of information about hydrogenation reactions. Therefore, of considerable interest is to extend the PHIP technique to heterogeneous catalytic processes. However, this area has remained unexplored until recently, mostly, due to the belief among specialists that heterogeneous hydrogenation processes cannot preserve the molecular nature of H_2 upon addition to the substrate, *i.e.*, two hydrogen atoms of the same H_2 molecule cannot end up in the same product molecule due to the specific character of reaction mechanism on metal catalysts. Since pairwise addition of H_2 is necessary for the PHIP effect to arise, there was the opinion that PHIP cannot be observed in heterogeneous catalytic reactions. Only in 2007–2008, it was demonstrated experimentally that heterogeneous catalysts, including supported metal catalysts, are able to add hydrogen to multiple bonds of unsaturated substrates in the pairwise fashion and give rise to PHIP effects.[649, 650] Since then, the PHIP technique has been developed as a highly sensitive tool for studying not only homogeneous but also heterogeneous hydrogenation processes. This Section briefly outlines the recent advances in this research area.

XIII.1. The use of parahydrogen to study the catalytic hydrogenation processes

As has already been noted, the PHIP effect is widely used to considerably enhance the NMR signal in the studies of the mechanisms and kinetics of reactions in which molecular hydrogen is activated by metal complexes in solution.[643, 644, 646–648] The observation of PHIP for NMR signals of hydrogenation products usually attests to pairwise addition of hydrogen to the substrate, which, in the case of mononuclear metal complexes, implies homolytic hydrogen activation by the catalyst to give an intermediate dihydride complex. Conversely, monohydride complexes perform non-pairwise addition of hydrogen (*i.e.*, two H atoms that end up in the same product molecule have belonged previously to different H_2 molecules), and no PHIP appears. In some cases, the observation of PHIP served to identify the true dihydride nature of the catalytically active complex, although a monohydride complex is used as the precursor.[651] The PHIP effect can also help to distinguish between the hydrogen atoms that were inherited from the substrate and those that came from H_2 in the product molecule. In particular, in the hydrogenation of alkynes, it is possible to distinguish between the *syn*- and *anti*-addition of hydrogen even if the resulting alkenes are chemically identical (for example, in the hydrogenation of propyne or but-1-yne to the corresponding alkenes). For conjugated dienes, this can be used to identify processes such as 1,4-addition.[652] In the hydrogenation of styrene catalyzed by some cationic rhodium complexes, polarized

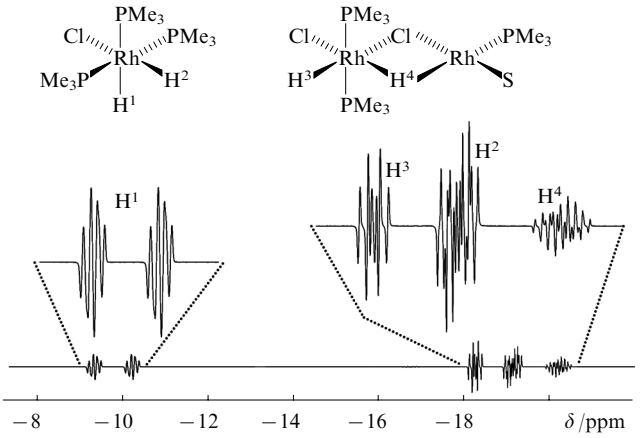


Figure 29. Hydride region of the ^{1}H NMR spectrum recorded for a solution of $[Rh(NBD)Cl]_2$ and PMe_3 in acetone-d_6 after bubbling parahydrogen at 320 K.[655]
The spectrum shows signals for the hydrides $Rh(H)_2Cl(PMe_3)_3$ and $H(Cl)Rh(PMe_3)_2(\mu\text{-}Cl)(\mu\text{-}H)Rh(PMe_3)S$ (S is acetone-d_6, NBD is norborna-2,5-diene).

ethylbenzene formed in the reaction was observed not only in the free state in solution but also being η^6-coordinated to rhodium(I).[653, 654]

The PHIP effect can also serve to enhance the NMR signals of short-lived intermediates and thus to establish their structure and the role in the reaction mechanism (Fig. 29). This made it possible to record the NMR spectra of some mono- and binuclear dihydride complexes for the first time.[655–657] In some cases, this resulted in the detection of dihydride complexes containing a substrate molecule as one of the ligands and monohydride complexes formed after the addition of one hydrogen atom to the substrate,[658, 659] which demonstrates the possibility of using PHIP to gain important information about reaction mechanisms.

Also, in a number of studies, the PHIP technique was used to explore the hydrogen activation processes, the formation of dihydride complexes, their structure and transformations including isomerization and ligand exchange in the absence of a substrate with a multiple bond. In particular, binuclear dihydride complexes with bridging hydride ligands were detected (see Fig. 29). For numerous Rh, Ir, Ru, Pd and Pt complexes, isomers of dihydride complexes were detected upon the reaction with parahydrogen, and their dynamic transformations were studied.[647, 660–662] These studies are often performed with free ligands added to the solution.

An interesting result that opens up the way for the development of a new direction in PHIP research was the first observation of PHIP in the system comprising a sterically separated (frustrated) Lewis acid–Lewis base pair of ansa-aminoborane.[663] Activation of parahydrogen with these 'molecular tweezers' results in enhancement of the NMR signals of not only the exchanging but also other hydrogen atoms in a molecule, as well as of ^{11}B NMR signals, which demonstrates the applicability of the method to study the H_2 activation mechanism by systems containing no metal atoms.

Considerable progress in the use of the PHIP technique for studying homogeneous catalytic hydrogenation processes demonstrates that the approach could be useful for obtaining information about the mechanisms of heterogeneous catalytic processes. One of the methods for 'bridging the gap' between homogeneous and heterogeneous catalysis is immobilization of metal complexes on solid supports. A multitude of methods for attaching homogeneous catalysts to various supports have now been developed including covalent, ionic or hydrogen bonding, physical adsorption, encapsulation, dissolution in a supported liquid phase (water, ionic liquid) and so on. This provides a broad range of options for converting a homogeneous catalyst into a heterogeneous analogue.

It is usually postulated that the reaction mechanism does not change significantly upon immobilization of the complex. Therefore, one could expect that the ability of transition metal complexes to perform the pairwise addition of hydrogen would also be retained upon immobilization and, hence, the PHIP effect would be manifested in heterogeneous hydrogenation processes catalyzed by immobilized metal complexes.

Immobilized metal complexes were successfully used for the first time to generate PHIP in liquid-phase hydrogenation of styrene in the presence of Wilkinson's complex $[Rh(Cl)(PPh_3)_3]$ immobilized on modified silica gel or on the styrene–divinylbenzene copolymer.[649, 664] The same catalysts were applied to generate PHIP in the gas-phase hydrogenation of propylene, which unambiguously demonstrated the possibility to observe PHIP using heterogeneous catalysts. The immobilized Wilkinson's complex was later studied in another work.[665] The results of control experiments confirmed the formation of PHIP effects in the heterogeneous reaction but the effect was weak (the ^{1}H NMR signal increased 3.5–4.4-fold). The PHIP observed for propyne hydrogenation in deuteriobenzene on Wilkinson's complex immobilized on modified silica gel allowed researchers to establish the *syn*-addition of hydrogen to the triple bond to give propylene, which is also typical of homogeneous hydrogenation of alkynes on this complex.[666] This indirectly supports the assumption that the mechanism of hydrogenation does not change much upon immobilization of the complex on a support. A similar behaviour was also established for a freshly prepared immobilized complex in the gas-phase hydrogenation of propyne. However, immobilized catalysts based on Wilkinson's complex and other rhodium complexes proved to be unstable under the reaction conditions. In particular, in the gas-phase hydrogenation, they tend to undergo reduction at temperatures above 70 °C, while in the case of liquid-phase hydrogenation, the complex can be leached into the solution. Deactivation of the immobilized rhodium complexes during gas-phase hydrogenation may be associated with the loss of the phosphine ligand, formation of binuclear complexes, interaction of the Rh centre with silanol and siloxane groups on the support surface and cleavage of the Rh–P bond resulting in detach-

ment of the complex from the support. Reactivation of the catalyst at higher temperatures is caused by partial reduction of the complex.[666]

The behaviour of some immobilized iridium complexes has also been studied. Indeed, with Vaska's complex $[IrCl(CO)(PPh_3)_2]$ immobilized on silica gel, substantial levels of conversion in the gas-phase hydrogenation of propylene were achieved; however, the PHIP effects were minor. The same catalyst provided substantial ($\sim 10^2$-fold) enhancement of the NMR signal of propylene in the hydrogenation of propyne at 110 °C but at low conversion levels. While recording the magic angle spinning NMR spectra, the PHIP effect was detected not only for propylene in the gas phase but also for propylene adsorbed on a porous catalyst. This catalyst remained stable in a hydrogen atmosphere even at 140 °C. Other immobilized catalysts based on iridium have also been studied. Some of them produced up to 400-fold enhancement of the NMR signal; however, the catalysts were deactivated in several minutes under the reaction conditions.

Supported ionic liquids can be used as an alternative approach to immobilization of metal complexes on a porous support. Catalysts based on supported ionic liquids are successfully used in various catalytic reactions, in particular, hydrogenation.[667, 668] Attempts to use these catalysts for hydrogenation of unsaturated compounds with parahydrogen have been reported. In the presence of a cationic rhodium complex dissolved in an ionic liquid supported on silica gel, hydrogenation of propylene was accompanied by substantial PHIP effects on propane.[669] However, the catalyst showed unstable behaviour with time, which is likely due to reduction of the complex at elevated temperature to give metal particles. The possibility of this reduction *in situ* has been confirmed.[670] In the organic phase–ionic liquid two-phase system, hydrogenation of ethyl acrylate on a cationic rhodium complex showed no PHIP effects.[671]

One more example of observing PHIP with a metal complex immobilized on a porous support is the use of Au^{III} Schiff base complex attached to a metal-organic coordination polymer.[672] Hydrogenation of propylene and propyne at 130 °C did not result in catalyst deactivation and allowed for observing PHIP effects on propane and propylene, respectively; propyne hydrogenation to propylene proceeded stereoselectively as *syn*-addition of hydrogen atoms.

It has been considered for a long period of time that hydrogenation according to the Horiuti–Polanyi mechanism rules out the pairwise addition of hydrogen to a substrate and, hence, the PHIP effect for metal catalysts should be impossible. Nevertheless, it was demonstrated[650] that PHIP can be observed in hydrogenation of unsaturated compounds with parahydrogen on supported metal catalysts. While using $Pt/\gamma\text{-}Al_2O_3$ catalysts with a metal particle size of 0.6–8.5 nm, a considerable PHIP effect on the reaction product, propane, was detected, being most pronounced for the metal particle size of 0.6 nm. The particle size effect in this reaction was later studied in more detail (see below). Subsequently, it was shown that PHIP also arises in the hydrogenation of other unsaturated hydrocarbons. For propyne hydrogenation over the $Pt/\gamma\text{-}Al_2O_3$ catalyst, propylene was shown to be formed upon both *syn*- and *anti*-addition of hydrogen atoms to the triple bond. Similar non-stereoselective addition of hydrogen was observed also in the hydrogenation of but-1-yne to but-1-ene.[645] In this reaction, PHIP was also observed on but-2-ene (*cis*- and *trans*-isomers) and butane. The same products were detected upon buta-1,3-diene hydrogenation. In both cases, the appearance of PHIP allowed researchers to propose the reaction scheme for the pariwise hydrogen addition. It is noteworthy that PHIP effects were much higher for metal nanoparticles supported on TiO_2.

The PHIP formation is structurally sensitive. The influence of the platinum particle size on the PHIP has been studied in detail for propylene hydrogenation catalyzed by $Pt/\gamma\text{-}Al_2O_3$ with various metal particle sizes.[673] The dependence of the magnitude of PHIP on the particle size proved to be non-monotonic: the effect was least pronounced for particles of diameter 2–4 nm and increased for both larger and smaller particles (Fig. 30). The most pronounced effect was observed for the smallest metal particles (< 1 nm). Based on analysis of the data, it was concluded that the pairwise addition of hydrogen catalyzed by particles of < 3 nm size occurs predominantly on low-dimensional sites, *e.g.*, kink or corner Pt atoms, whereas for larger particles, the pairwise addition occurs on polyatomic active sites. The major reaction channel is non-pairwise, being accomplished on active sites of the most close-packed faces of metal particles. Similar dependences of PHIP on the nanoparticle size were elucidated for Pt on ZrO_2 and SiO_2. A different result was obtained in analysis of the structure sensitivity for buta-1,3-diene hydrogenation on $Pt/\gamma\text{-}Al_2O_3$.[645] In this case, both the major reaction channel and the pairwise addition of hydrogen were associated with the active sites located on flat nanoparticle faces.

Palladium-based catalysts are known for their ability to perform selective partial hydrogenation of

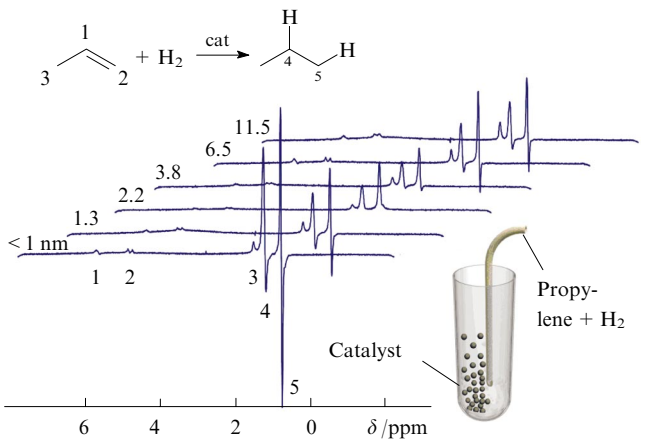


Figure 30. ^1H NMR spectra recorded during hydrogenation of propylene with parahydrogen over the of $Pt/\gamma\text{-}Al_2O_3$ catalysts with different metal particle size.[673]

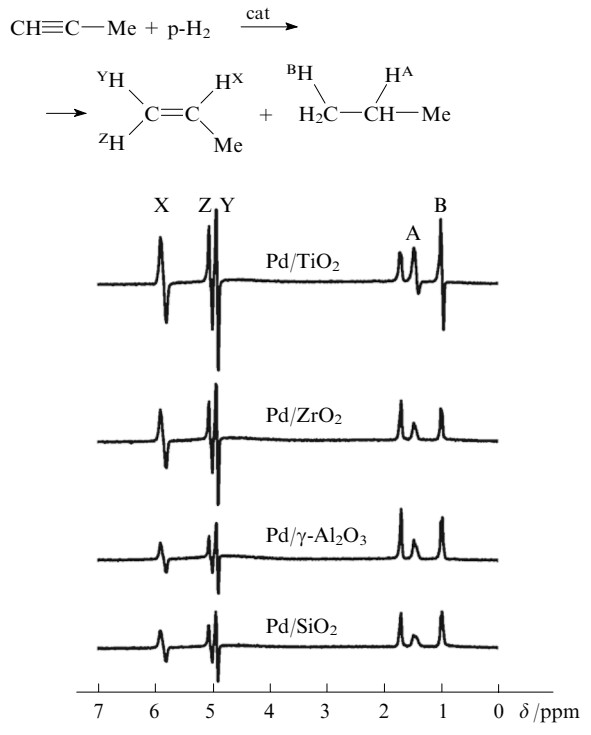


Figure 31. ^{1}H NMR spectra recorded during hydrogenation of propyne with parahydrogen in the presence of Pd/TiO_2, Pd/ZrO_2, Pd/SiO_2 and Pd/γ-Al_2O_3 catalysts with metal particle sizes of 1.5–3 nm.[674]
All of the spectra are given on the same vertical scale.

alkynes and dienes to alkenes. To elucidate the mechanistic details of the selective hydrogenation of unsaturated hydrocarbons, it is pertinent to use parahydrogen. Detailed investigation using monodisperse supported palladium catalysts with various Pd particle sizes demonstrated that gas-phase hydrogenation of propylene on the Pd/ZrO_2, Pd/SiO_2 and Pd/γ-Al_2O_3 catalysts results in the formation of considerable amounts of propane but does not produce the PHIP effect.[645, 674] Meanwhile, hydrogenation of propyne (Fig. 31) and buta-1,3-diene on the same catalysts results in PHIP on partial hydrogenation products (propylene and but-1- and but-2-enes, respectively) and gives no PHIP on the fully hydrogenated products (propane and butane).

According to existing views, a Pd-catalyzed reaction may involve not only the surface hydrogen but also subsurface hydrogen (dissolved in the metal lattice). The latter is considered to be highly reactive but non-selective and, therefore, provide complete hydrogenation of the substrate to the alkane. Conversely, surface hydrogen is less reactive but more selective towards the formation of partial hydrogenation products (alkenes). The results of PHIP experiments are generally consistent with this hypotheses. Indeed, for PHIP to be manifested, after the dissociative chemisorption of H_2, the two hydrogen atoms should stay close to each other to retain high probability of their pairwise addition to the substrate during lifetime of the coherent state of their nuclear spins. An increase in the distance between them due to diffusion or dissolution in the metal bulk should rapidly decrease this probability. Thus, hydrogenation involving dissolved hydrogen should not give rise to PHIP, while reaction with only surface hydrogen may partly occur *via* pairwise addition of hydrogen and, hence, may give rise to PHIP. This conclusion is in principle consistent with the fact that in the Pd/ZrO_2-, Pd/SiO_2- and Pd/γ-Al_2O_3-catalyzed hydrogenation of buta-1,3-diene and propyne, polarization is observed only for alkenes but not for alkanes. Reaction conditions can substantially influence the observed phenomena. An important factor is the amount or the accessibility of hydrogen dissolved in the Pd lattice. Indeed, coking of the catalyst can accelerate the diffusion of hydrogen atoms into the lattice through nanoparticle edges but simultaneously it can prevent hydrogen from emerging freely on most of the surface. One can expect that in this case, the contribution of surface hydrogen to alkene hydrogenation would increase, thus increasing the percentage of the pairwise reaction pathway. Indeed, when the Pd/γ-Al_2O_3 catalyst pre-coked in propylene hydrogenation was used, the PHIP was observed.[650] One more example is the use of a catalyst representing Pd nanoparticles embedded in an ionic liquid film supported on the surface of activated carbon fibres. In the presence of these catalysts, the gas-phase hydrogenation of propyne at 130°C afforded mainly propylene, the PHIP effect being observed only for propylene.[670] In control experiments, similar catalysts but containing no ionic liquid layer were employed. In this case, propane was mainly formed but the a small PHIP effect was observed for propylene only. These results suggest that the diffusive transport of hydrogen through an ionic liquid layer limits the amount of hydrogen dissolved in Pd nanoparticles, and, together with different solubilities of propylene and propyne in the ionic liquid, this affects the reaction selectivity.

The situation is quite different with the Pd/TiO_2 catalyst, which, when being used in propylene, buta-1,3-diene or propyne hydrogenation (see Fig. 31) with parahydrogen, gives rise to the PHIP effect for all of the reaction products including alkanes.[645, 674] This attests to importance of the support in these processes and to the possible presence of strong metal–support interactions for metals supported on TiO_2. In addition, in the hydrogenation of but-1-yne, polarization was observed for all reaction products and for all of the four catalysts (Pd/ZrO_2, Pd/SiO_2, Pd/γ-Al_2O_3 and Pd/TiO_2). Thus, the nature of the substrate can also substantially affect PHIP formation.

A number of studies have been performed with rhodium-based supported metal catalysts. In particular, to verify the hypothesis according to which reduction is one of the factors responsible for the lack of stability of immobilized complexes, Wilkinson's complex immobilized on various porous supports was intentionally reduced *in situ* at 373–573 K in a mixture of propylene and hydrogen.[666] The highest signal enhancement factors were 180–210. A specific feature of rhodium-based catalysts is the formation of PHIP not only on the product (propane) but also on the vinylic protons of the substrate (propylene). The origin of this effect requires further investigation. In

the propyne hydrogenation, PHIP was observed for propylene but was nearly absent for propane although the latter formed in substantial amounts. Since the hydrogenation of propyne catalyzed by reduced catalysts is non-stereoselective, while that catalyzed by immobilized complexes leads mainly to *syn*-addition of hydrogen to the triple bond, this can serve as the criterion to verify the stability of immobilized complexes in hydrogenation reactions with parahydrogen. Chitosan-supported Rh nanoparticles were used in the hydrogenation of buta-1,3-diene and but-1-yne in the gas and liquid phases.[675] The catalysts showed selectivity towards the formation of but-1- and but-2-enes and provided PHIP effects. The Rh/TiO_2 and Rh/AlO(OH) catalysts demonstrated PHIP effects for dissolved propane in the liquid-phase hydrogenation of propylene[645,676] and in the hydrogenation of styrene to ethylbenzene in acetone.[676] Substantial PHIP effects were observed in the hydrogenation of methyl propiolate to methyl acrylate in methanol catalyzed by Pd/SiO_2, Pt/SiO_2 and Pt supported on mesoporous materials, Al- SBA-15 and Al-MCM-48, and in hydrogenation of styrene and phenylpropyne catalyzed by Pt/SiO_2.[677]

A key issue in the investigation of PHIP is to estimate the contribution of the pairwise hydrogen addition channel to the overall hydrogenation mechanism. This information is necessary for understanding of the pairwise addition mechanism and for the search for ways to attain the maximum PHIP-induced enhancement of the NMR signal with the use of heterogeneous catalysts. These estimates were made based on comparison of the theoretically calculated maximum possible enhancement of the NMR signal when parahydrogen is used in the reaction and the experimentally measured enhancement of the ^1H NMR signal of the reaction products.[645,664] This method is likely to underestimate the contributions of the pairwise addition, because some polarization is inevitably lost due to nuclear spin relaxation effects between the instants of formation and observation of the polarized reaction products. Nevertheless, even this lower-bound estimate of the pairwise contribution appears quite useful.

For propylene hydrogenation to propane catalyzed by $Pt/\gamma\text{-}Al_2O_3$ with metal nanoparticles of 0.6 nm size, the contribution of the pairwise route was estimated as $\sim$3%.[650,664] A similar value ($\sim$2.4%) was also found for the Pt/TiO_2 catalyst with Pt particle size of 0.7 nm.[673] For most of other catalysts, substrates and experimental conditions, lower values were found. This implies that the metal-catalyzed addition of hydrogen to the substrate is mainly non-pairwise, which is generally consistent with the Horiuti–Polanyi mechanism. In another work,[678] owing to the use of 4-sulfanylbenzoic acid for stabilization of the supported Pt nanoparticles, higher percentages of pairwise addition in the propylene hydrogenation to propane may have been achieved. However, the authors made an experimental mistake; therefore, the actual percentage of pairwise addition is unknown for these experiments. In addition, the use of the sulfur-containing ligand considerably lowered the yield of the reaction product.

An important open question related to the formation of PHIP on heterogeneous catalysts is the nature of the active sites able to perform the pairwise addition of hydrogen to multiple bonds. For metals, the rate of diffusion of hydrogen atoms on the surface is so high that in the absence of additional restrictions on the mobility of newly chemisorbed hydrogen on the surface, the probability of pairwise addition should be very low. The initial interpretation of PHIP on supported metal catalysts was based on the assumption of the existence of static or dynamic partitioning of the metal surface into small islands due to the presence of various sorts of adsorbates.[650] This may result in localization of active sites upon formation of obstacles to free diffusion of hydrogen across the metal surface. The existence of numerous surface structures such as carbonaceous deposits,[679–681] reaction intermediates and side low-activity species[682,683] in hydrogenation reactions is well-known. However, other explanations can also be proposed. For example, for supported metal catalysts, several types of active sites operating in parallel can simultaneously exist, and some of them may be able to perform the pairwise addition of hydrogen to the substrate. These sites can be represented by some low-dimensional structures such as corners, edges and some faces of metal nanoparticles and the interfaces between the metal and the support. For supported metal catalysts, the support surface may bear not only metal nanoparticles but also other active phases (metal oxide, single metal atoms and so on). A fundamentally different possibility is participation of molecular hydrogen in hydrogenation, when an H_2 molecule (possibly physisorbed) reacts with the adsorbed substrate molecule without dissociative chemisorption of hydrogen.

As noted above, metal oxides used as the supports for the production of finely dispersed supported metal catalysts can have a pronounced influence on the activity and selectivity of these catalysts. Furthermore, many oxides exhibit the catalytic activity themselves. From the standpoint of development and application of the PHIP technique, of interest is the activity of some oxides in heterogeneous hydrogenation of unsaturated compounds.

Hydrogenation using metal oxides has a number of distinctive features. For example, the rate of hydrogenation of conjugated dienes is often higher than the rate of alkene hydrogenation. Indeed, hydrogenation of buta-1,3-diene catalyzed by alkaline earth metal oxides occurs at 273 K to give butenes rather than butane, whereas butene hydrogenation becomes significant only at 473 K.[684] The reaction proceeds mainly as 1,4-addition of hydrogen atoms to buta-1,3-diene to give but-2-enes, whereas using metal catalysts, but-1-ene resulting from 1,2-addition is formed as the major product. Finally, many researchers point to retention of the molecular identity of hydrogen atoms in the reaction, *i.e.*, they point out that two hydrogen atoms that have ended up in the same product molecule belonged to the same H_2 molecule before the reaction.[685] As noted above, this is crucial for the formation of the PHIP effect for the products (and intermediates). Therefore, one could expect that

unlike metal catalysts where the percentage of pairwise addition of hydrogen to the substrate is in principle relatively low (see above), metal oxides could produce much higher enhancements of the NMR signal when being used as catalysts in hydrogenation of unsaturated compounds with parahydrogen.

However, the mechanism of hydrogen activation and substrate hydrogenation on metal oxides remains obscure. The dissociative chemisorption of hydrogen can be heterolytic (involving metal and oxygen atoms to give $O-H^+$ and $M-H^-$ structures) or homolytic (one-centre to give the metal atom dihydride or two-centre involving two oxygen atoms). The catalytic activity depends substantially on the metal oxidation state and the possibility for the oxidation state to change during the reaction. In addition, the possibility of selective hydrogenation catalyzed by oxides is also of interest.[684]

Until very recently, only a single indication that PHIP can be detected upon activation of parahydrogen by metal oxides was reported in the literature.[686] The researchers studied the interaction of ZnO with parahydrogen by pulsed (50–200 ms) supply of parahydrogen into a sample tube filled with ZnO calcined at ~700 K *in vacuo*. By recording the ^{1}H NMR spectrum of the solid phase, the presence of PHIP effect was detected. This indicates that after activation of an H_2 molecule, two hydrogen atoms remain close to each other for a considerable period of time (at least 10^{-4} s), which enables noticeable magnetic interactions between them. Based on the published data, the authors interpreted the results as being due to heterolytic activation of H_2 to give an intermediate of the $H-Zn-O-H$ type. The adsorption resulting in PHIP was reversible because after evacuation of the sample, a new pulse of parahydrogen supply produced the same results.

Only in 2014, the possibility of detecting PHIP upon the use of metal oxides as catalysts for hydrogenation of unsaturated compounds was demonstrated experimentally for the first time.[687] In the hydrogenation of buta-1,3-diene with parahydrogen in the presence of CaO at 130 °C, polarization was observed for all reaction products (but-2-ene, but-1-ene, butane) (Fig. 32). However, CaO had a very low activity towards propylene hydrogenation under the same conditions. A temperature rise to ~300 °C increases the activity and gives rise to considerable PHIP effects for propane. In the case of Cr_2O_3, CeO_2 and ZrO_2, a noticeable activity and PHIP effects were observed as the temperature was increased to 300–600 °C.

Successful detection of PHIP effects is the most direct proof for the possibility of oxide-catalyzed pairwise addition of hydrogen atoms to unsaturated compounds. Presumably, the high contribution of pairwise addition is due to much lower diffusivities for hydrogen atoms on the oxide surface as compared with the metal surface. Slow surface diffusion of hydrogen atoms should increase the probability of the pairwise addition of hydrogen to the substrate. Thus, much more pronounced enhancement of the NMR signal could be expected. However, in reality, the highest enhancement factors for metals and for

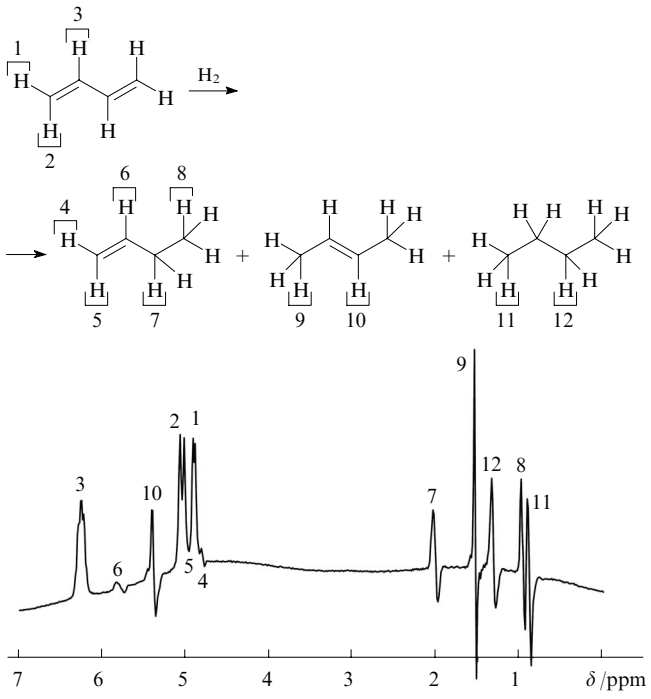


Figure 32. ^{1}H NMR spectrum recorded during hydrogenation of buta-1,3-diene with parahydrogen catalyzed by CaO at 403 K inside the NMR probe.[687]

oxides were comparable. Among other reasons, this may be due to the fact that oxides show noticeable activity at higher temperatures, which accelerates the diffusion of hydrogen atoms on the oxide surface and diminishes the PHIP effects.

It should be noted that the results are considerably affected by preactivation of the oxide catalysts, the activity without preactivation being usually negligibly low. All of the oxides were calcined in air or *in vacuo* at 400–700 °C. Further, the calcination conditions can affect the catalyst activity and selectivity and the magnitude of PHIP in different ways. For Cr_2O_3, the behaviour was also different depending on the method of oxide synthesis. It was shown in the same study[687] that the PHIP effects can also be observed in the hydrogenation of unsaturated compounds in the presence of PtO_2, PdO, $Pt(OH)_2$ and platinum black.

The results of PHIP experiments with heterogeneous catalysts obtained to date clearly indicate that this approach has extensive application prospects and also a number of problems that are still to be solved. The use of transition metal complexes immobilized on a solid support in parahydrogen experiments, although seems to rely on a simple concept, is faced with quite a number of practical difficulties including accelerated deactivation of the catalyst, leaching of the complex off the support to the solution and a number of other problems. The use of such catalysts in PHIP experiments requires the design of more efficient and stable catalysts. A similar challenge is faced by industrial catalysis where numerous attempts to develop such systems have only partly met with success as yet. The PHIP effect observed on supported metal catalysts requires elucidation of the mechanism of pairwise

addition of hydrogen to the substrate. The understanding of this mechanism should form the grounds for the design of catalytic systems capable providing an extra 30-100-fold NMR signal enhancement compared to the values attained to date. Besides, this would enable more rational utilization of the PHIP technique to study the mechanisms of heterogeneous catalytic reactions, including not only hydrogenation but also other catalytic processes important from the industrial standpoint.

The achievements and the potential of the PHIP technique are quite significant. However, the use of parahydrogen has a number of limitations. In particular, the method requires that hydrogen participates in the reaction in question, while the necessary condition of pairwise addition of two hydrogen atoms of the H_2 molecule to the substrate is in conflict with fast migration of hydrogen atoms on the metal surface after H_2 dissociation. Therefore, to understand the PHIP mechanism, it is important to theoretically study the H_2 activation processes on metals and the subsequent fate of hydrogen atoms under reaction conditions with allowance for lateral interactions of adsorbed species. Yet another promising line of development of this area is the use of nuclear spin isomers of other molecules. However, to produce them in amounts sufficient for NMR is a complex scientific and technological problem which remains unsolved.[688] Nevertheless, it was demonstrated experimentally for the first time[689] that nuclear spin polarization can be generated by using nuclear spin isomers of the ethylene molecule for which isomer enrichment was accomplished by chemical synthesis (hydrogenation of normal acetylene with parahydrogen).

The methods for signal enhancement by nuclear spin hyperpolarization become highly demanded in a variety of NMR and MRI applications, including biomedical ones. Indeed it has already been demonstrated that this approach is highly promising in the studies of metabolic processes in a living body on a real time basis by introducing hyperpolarized compounds into the body and observing the products of their metabolism.[640, 641] This opens up new, in principle, possibilities for early diagnosis of various pathologies, including cancer, and early detection of response to therapy. A recipe for success in the development of biomedical applications of PHIP is obviously transition from homogeneous to heterogeneous catalysis to implement the possibility of obtaining solutions of hyperpolarized contrast agents containing no dissolved catalyst. Thus, biomedical applications form a powerful impetus for the development of the PHIP technique based on heterogeneous catalysis.

XIV. Preparation of materials for organic electronics

The preceding Sections considered issues of the strategic progress of organic synthesis and elaboration of new synthetic methods. For correct analysis of the prospects for the development of this area, it is also necessary to take into account the demands of the modern research and production complex and the application area of developed methods. The preparation of biologically active compounds and applications of organic synthesis to solve problems of pharmaceutical and biomedical chemistry are considered in Sections II–XII. Yet another highly practically important application of fine organic synthesis is the fabrication of molecular building blocks for the design of a new generation of smart materials. The most interesting trends in this area are briefly considered in Sections XIV and XV.

Owing to the development of organic synthesis, since the beginning of the 21st century, organic electronics has been actively developed based on the ability of some π-conjugated oligomers and polymers to conduct electrical current and to exhibit semiconductor and luminescence behaviour.[690, 691] These compounds are prepared, as a rule, by forming aryl or hetaryl C–C bonds using organometallic reactions. The enormous progress in this area is, beyond doubt, related to advances of organic and organometallic synthesis, which may provide diverse and more and more complex conjugated compounds with predetermined chemical structure and with control over molecular-mass characteristics, solubility and morphology of conjugated polymers. It is also necessary to do justice to the design of new devices based on these compounds and new methods for fabricating them, which is a necessary condition for the development of this area.[692, 693] This Section deals with the chemical aspects of this area related to the achievements and prospects of using organometallic synthesis for the preparation of π-conjugated oligomers and polymers for organic electronics. Among such reactions, one can distinguish four key types used most widely and giving the best results. These are Suzuki, Kumada and Stille reactions and, in recent years, direct C–H arylation. Below these reactions are considered in more detail using numerous particular examples.

XIV.1. Selective catalytic reactions for the preparation of organic semiconductors and luminophores

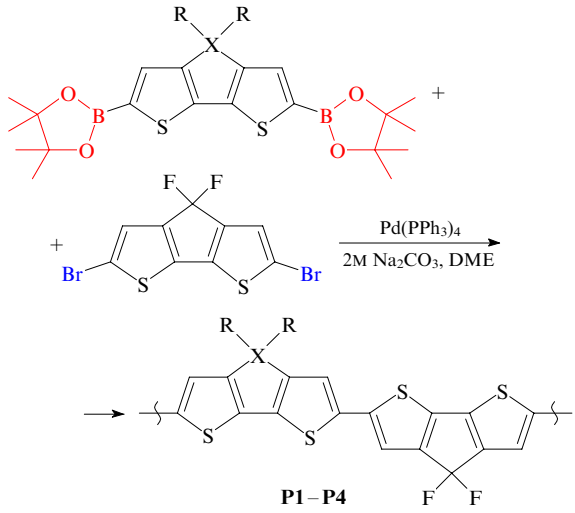
XIV.1.a. Application of the Suzuki reaction

The key advantages of the Suzuki reaction include the almost complete absence of undesirable side reactions, due to the fact that the boronic acid residues cannot be exchanged with a halogen atom, and high yields of the reaction products (see Sections VI.2 and X.2). The absence of heavy elements, apart from palladium, makes this approach suitable for the synthesis of compounds of various classes used to fabricate devices for organic electronics. For example, the Suzuki reaction served to prepare a number of polymers[694, 695] and star-shaped oligomers[696–698] for photovoltaic cells, linear[699, 700] and star-shaped oligomers[701] for thin-film field effect transistors, dendrimers for photonics[702–705] and materials for monolayer field effect transistors.[706] By selecting appropriate catalytic systems, polymers possessing both p-type (hole conduction)[707, 708] and n-type (electron conduction)[709] semiconductor properties have been prepared by pseudo-living polymerization. The polymers had a narrow molecular-mass distribution and controlled terminal groups, which is important for good semiconductor properties. Using this approach, it was possible to

prepare a polymer combining semiconductor (charge mobility of 3.5×10^{-3} cm^2 V^{-1} s^{-1}), electroluminescence (luminance of up to 385 cd m^{-2}) and photovoltaic (solar cell efficiency of up to 0.77%) properties. It should be noted, however, that these values are rather far from the current record characteristics.

The Suzuki reaction is widely used to prepare polymers with a narrow band gap to be used in organic photovoltaic cells[695, 710] (polymers **P1**–**P4**, Scheme 155). It was shown[707] that optimization of the purification methods and techniques for solar cell fabrication based on these polymers substantially increases their operation efficiency.

Scheme 155



P1–**P4**

X = C: R = n-C_8H_{17} (**P1**), $CH_2CHEtBu^n$ (**P2**);
X = Si: R = n-C_8H_{17} (**P3**), $CH_2CHEtBu^n$ (**P4**)

Apart from the solar cells, polymers obtained by the Suzuki reaction are used as electroluminescent materials in organic light emitting diodes (OLED). Copolymers have been reported[711] in which electroluminescence properties can be changed by varying one of the blocks; hence, blue, green and red light emitting devices have been devised. Copolymers obtained from the organoboron derivative of 9,9-dioctylfluorene and 2,7-dibromospiro[fluorene-9,9′-(2′,7′-di-n-octyloxyxanthene), had a large molecular mass according to polystyrene standards (> 100 kDa) and a narrow molecular-mass distribution (1.04); apart from electroluminescence, they exhibited electrochromic properties.[712]

The absence of side exchange reactions accounts for the extensive use of the Suzuki reaction in the synthesis of so-called conjugated 'small molecules' — oligomers having relatively low molecular mass. These compounds have a number of advantages over polymers, for example, the possibility to prepare extra pure materials, which is especially important for organic electronics. Conjugated oligomers are used as semiconductor materials in organic field effect transistors,[713, 714] phosphorescent molecules in organic light emitting diodes[715] and active layers in organic solar cells.[716] A comparison of two methods for preparation of the oligomers, by the Suzuki reaction and by direct C–H-arylation, has been reported[717] (Scheme 156). With the use of organoboron compounds, the yield of the target product was 1.5 times higher than in the direct arylation reaction (60% and 40%, respectively).

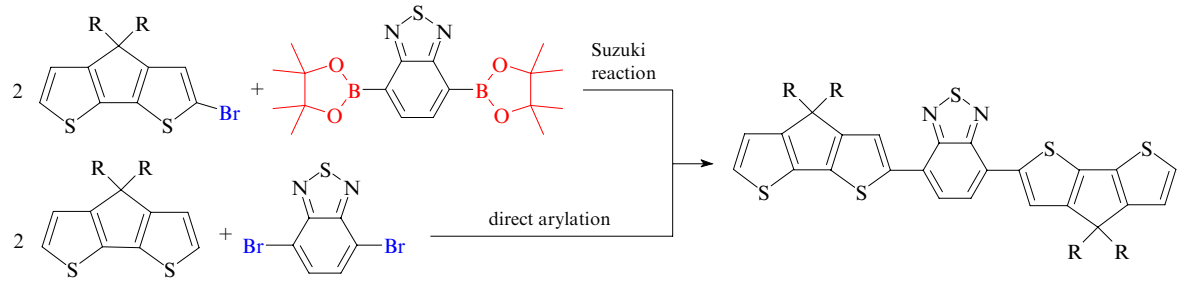
The Suzuki reaction was used to synthesize star-shaped molecules with a triphenylamine moiety as a branching unit and dicyanovinyl groups connected by bithiophene π-conjugated spacers. The molecules differed only by the length of the terminal aliphatic groups, which was employed to study the effect of these groups on photovoltaic properties. It was shown that short alkyl substituents decrease the solubility but increase the operation efficiency of organic solar cells; the best efficiency approached 5%.[697]

XIV.1.b. Application of the Kumada reaction

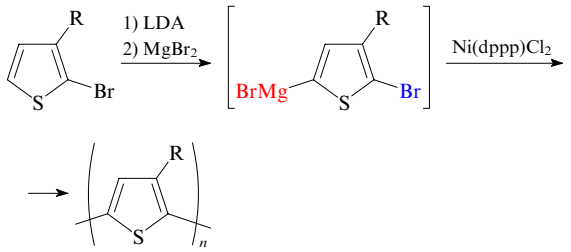
Along with the Suzuki reaction, the Kumada reaction plays a significant role in the synthesis of various functional materials for organic electronics. As a rule, the Kumada cross-coupling is inferior to the Suzuki cross-coupling as regards the product yield, which may be related to exchange processes, and as regards the applicability to the synthesis of complicated structures. However, the preparation simplicity of the starting organomagnesium compounds can make up for these drawbacks. The modern achievements in the use of the Kumada reaction for the synthesis of various compounds have been reported in a monograph.[718]

Poly(3-alkylthiophenes), which are among the most popular types of polymers used as functional material in organic photovoltaic cells, are usually prepared by the Kumada reaction. In 1992, McCullough and Lowe[719] synthesized for the first time regioregular poly(3-alkylthiophene) using Ni(dppp)Cl_2 as the catalyst (Scheme 157).

Scheme 156

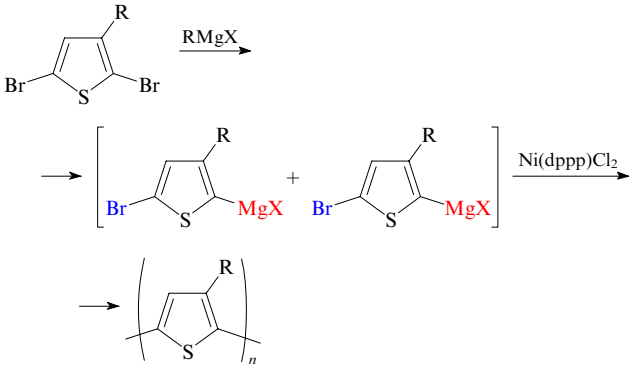


Scheme 157



Later on, McCullough from the same research team proposed a more economical route to poly(3-hexylthiophene) from dibromides (Scheme 158).[720] Subsequently, it was shown that this reaction occurs as a living polymerization when catalyzed by nickel catalysts. This approach is suitable for the preparation of kilogramme amounts of a fairly high-molecular-mass polymer (M_n = 20 000 – 35 000) with a narrow molecular mass distribution (1.2 – 1.4). The use of palladium catalysts results in stepwise polycondensation.

Scheme 158



R = n-C_6H_{13}

The Kumada reaction can serve to prepare not only homopolymers but also copolymers with different monomer ratios. The 3-octylthiophene copolymers with 3-decyloxythiophene synthesized by Shi *et al.*[721] were used to design organic solar cells.

The synthesis of the bithiophenesilane dendrimer by the Kumada reaction was reported.[702] It was shown that unlike the Suzuki reaction, this approach provides the desired product over a short period of time and without incomplete substitution products. However, in this case, by-products having higher molecular mass than the desired dendrimer were formed. This was due to the exchange of the halide and magnesium halide reacting groups known for the Kumada reaction, which can be only slightly retarded by optimization of the reaction conditions (lowering of the temperature, selection of the optimal catalyst for particular reactants) but cannot be completely eliminated.

Dendronized polymers, which represent a sort of hybrid between polymeric and dendrite macromolecules and combine structural features of both, were synthesized by the Kumada cross-coupling.[722] The narrow molecular-mass distribution (1.22 – 1.23), high molecular masses and the use of nickel catalyst indicate that the process follows a living polymerization mechanism. Thus, it was demonstrated that bulky monomers can also be polymerized by this mechanism.

The Kumada reaction has also been used to prepare star-shaped oligomers, which are used as semiconductor layers in organic field effect transistors obtained by solution processing.[723] The reaction was conducted for trifunctional phenyl bromide branching units and Grignard reagents prepared from α-decyloligothiophenes in the presence of a palladium catalyst.

Analysis of published data indicates that for each substrate, a particular catalyst should be selected. It was found[724] that the palladium catalyst Pd(dppf)Cl_2 is much more suited for the synthesis of linear thiophene oligomers, which are widely used in organic field effect transistors, than the nickel catalyst Ni(dppp)Cl_2. Indeed, even a twofold excess of the Grignard reagent and refluxing for 48 h in the presence of the nickel catalyst does not lead to satisfactory results. Meanwhile, the product is formed in a good yield with a 10% excess of the Grignard reagent after 30 min at room temperature when the palladium catalyst is used.

XIV.1.c. Application of the Stille reaction

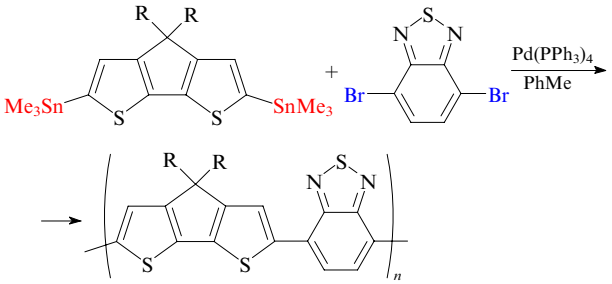
The popularity of this reaction for the synthesis of diverse simple precursors has decreased in the last decade due to some drawbacks as compared with the Suzuki reaction, in particular, the toxicity of organotin compounds and difficulty of purification of reaction vessels from the remains of organotin compounds formed during the reaction. Whereas under laboratory conditions, these drawbacks do not deserve much attention, in the case of large-scale production, they become a significant reason for looking for an alternative. As the tin organic compounds, trimethyltin or tributyltin derivatives are used most often. The former are not only more reactive than the latter but are also an order of magnitude more toxic. A typical Stille reaction is catalyzed by a palladium complex, *e.g.*, Pd(PPh_3)$_4$, and is performed in DMF, toluene, chlorobenzene, *etc.*, as solvents.

The advantages of the Stille reaction include stability of the organotin compounds; therefore, it is used at last steps of multistep syntheses and also in those cases where stability of organoboron compounds is low. Note that recent publications report most often the use of bifunctional organotin derivatives, because their organoboron analogues are less stable. For example, Qin *et al.*[725] described the synthesis of the organoditin benzo[*c*]thiophene derivative in 62% yield by lithiation of benzo[*c*]thiophene with n-butyllithium in tetramethylethylenediamine and THF followed by the reaction with the organotin reagent. The obtained derivative was chemically stable and was used as the monomer in the Stille reaction with the dibromo derivatives of fluorene and oligothiophenes using toluene as the solvent in the presence of Pd(PPh_3)$_4$ as the catalyst to give alternating conjugated copolymers. The yields of the polymers varied from 30% to 70%, while the weight-average molecular masses ranged from 9 to 28 kDa.

According to published data, most often, organoditin derivatives of thiophene, bithiophene and cyclo-

pentadithiophene are used in the synthesis of conjugated polymers for organic photovoltaics and thin-film field effect transistors, as their organoboron analogues are unstable under the Suzuki reaction conditions, which results in the formation of low-molecular-mass polymers. For example, Zhu *et al.*[726] used the Stille reaction to prepare a copolymer based on 4,4-bis(2-ethylhexyl)-4*H*-cyclopenta[2,1-*b*:3,4-*b*′]dithiophene and 2,1,3-benzothiadiazole with M_n of up to 30 kDa and a relatively narrow molecular-mass distribution (1.4–1.6) (Scheme 159).

Scheme 159



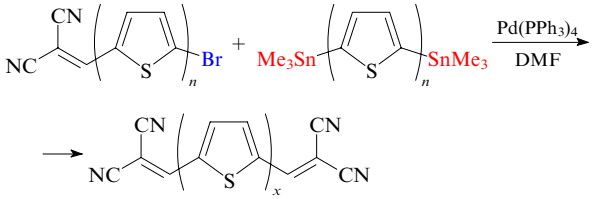
R = Bu^{n}EtCHCH$_2$

By adding one more difunctional monomer, 5,5′-dibromo-2,2′-bithiophene, into this reaction, a series of copolymers with a random distribution of structural blocks and a weight-average molecular mass of up to 30 kDa was prepared. Somewhat later, the Stille cross-coupling successfully served for copolymerization of organoditin cyclopentadithiophene derivatives with a number of monomers such as 4,7-dibromobenzo[2,1,3]selenadiazole,[727] 4,7-bis(5-bromothiophen-2-yl)[2,1,3]benzothiadiazole and 5,8-dibromo-2,3-dioctylquinoxaline.[728]

An example of one more stable organoditin monomer used for the preparation of conjugated polymers is provided by polycondensation of the tributyltin thiophene derivative with the dibromo dithienothiophene derivative under the Stille reaction conditions.[729] The polymer yield was 90%, the weight-average molecular mass was 60 kDa and the polydispersity was 1.8. In a recent study, a similar trimethyltin monomer was introduced in the Stille reaction to produce a block copolymer based on poly(3-hexylthiophene) and poly(diketopyrrolopyrroleterthiophene) blocks (Scheme 160).[730] The weight-average molecular mass of the polymer reached 133.5 kDa at a polydispersity of 1.89.

Bäuerle and co-workers[731] applied the Stille reaction of the same monomer to prepare a number of donor–acceptor π-conjugated thiophene-containing oligomers with dicyanovinyl acceptor groups; these oligomers were employed as effective donor materials in organic photovoltaic cells (Scheme 161). It was also demonstrated in the study that the yield of the reaction products varies from 82% to 99% and decreases if toluene or THF serves as the solvent. This can be attributed to the insufficient solubility of the intermediate monoaddition products in toluene and THF due to which they precipitate and cannot be involved in the further transformations.

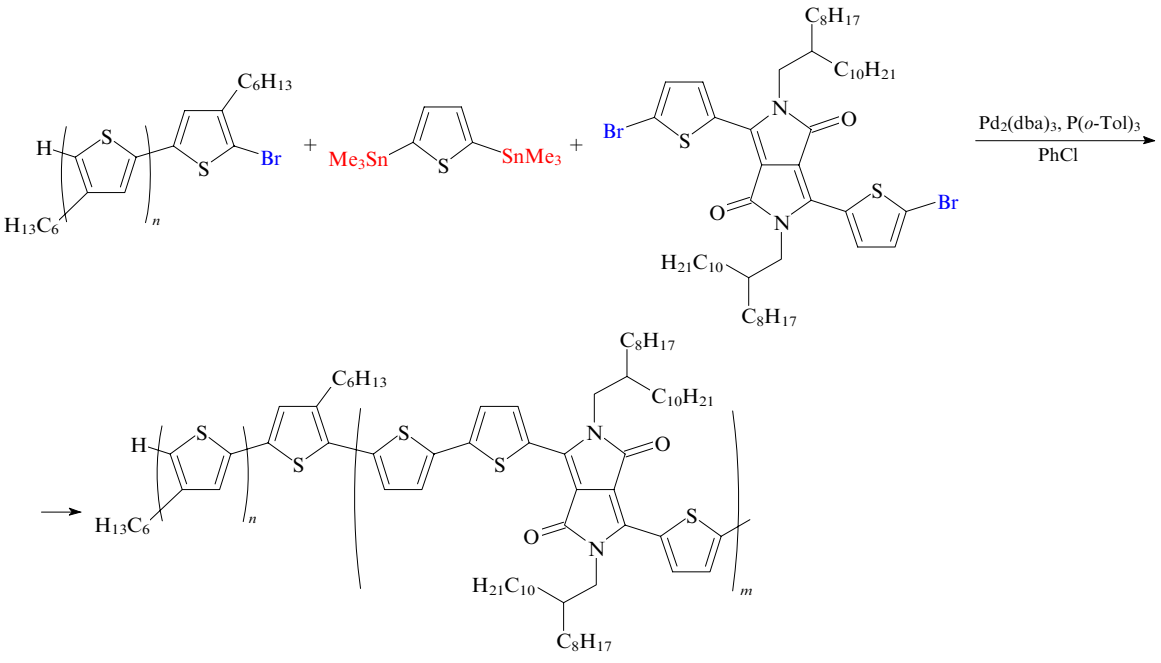
Scheme 161



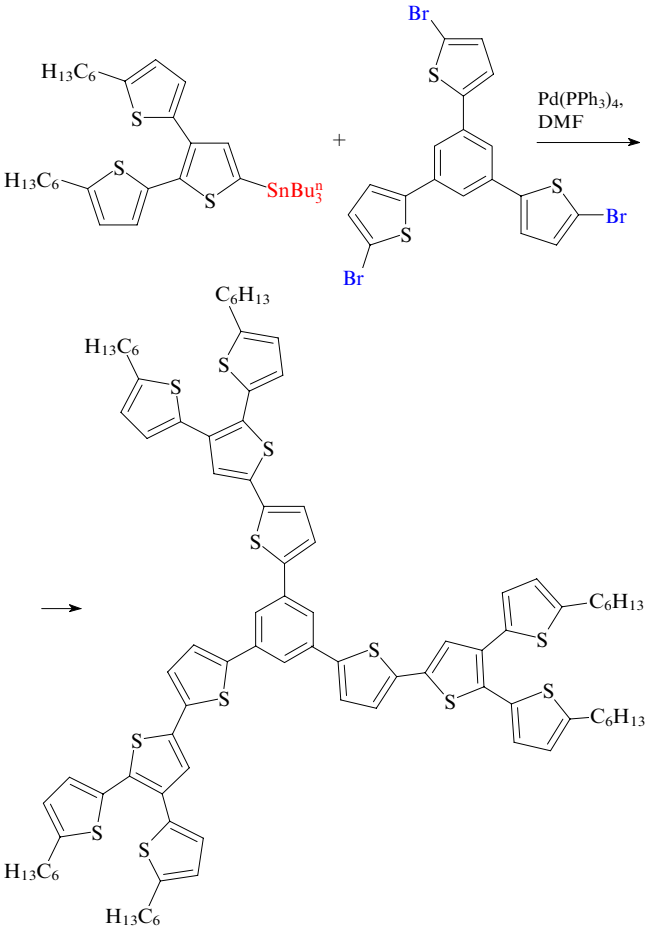
n = 1, 2; *x* = 3–6

An example of the preparation of branched polymers is the convergent synthesis of polythiophene dendrimers with a phenylene nucleus in which organotin derivatives of monodendrones are cross-coupled with brominated thiophene moieties to give den-

Scheme 160



Scheme 162



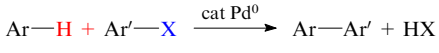
drimers of different generations in 85% to 93% yields (Scheme 162).[732]

Thus, the Stille reaction is still demanded in the synthesis of chemically diversified materials for organic electronics but most often it is utilized to synthesize conjugated polymers. The key factor that holds up the wider use of this reaction, in particular, in industrial production is the lack of environmental safety outlined above. From this standpoint, the development of the direct C–H arylation technique is today most promising.

XIV.1.d. Application of direct C–H arylation

Direct C–H arylation is an economically attractive and more environmentally friendly alternative to the above-described conventional cross-coupling methods. In this method, aromatic or heteroaromatic derivatives are cross-coupled at the C–H bonds directly with one another or with their halogenated derivatives (Scheme 163).

Scheme 163



X = Cl, Br, I

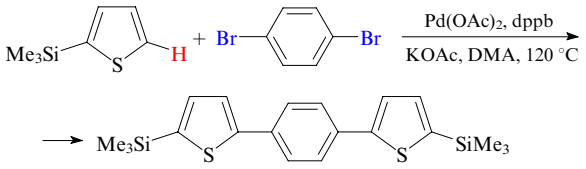
The first direct C–H arylation reactions were demonstrated as thiophene–thiophene coupling used to synthesize symmetrical functional monomers,[733] oligothiophenes[734] and other conjugated oligomers[735] for organic electronics.

Various Ru, Rh and Pd complexes used as catalysts for direct C–H arylation were reported.[736] However, in recent years, $Pd(OAc)_2$ has become most popular for C–H bond activation. Successful and selective direct arylation is often performed in the presence of ligands; as a rule, these are saturated phosphorus compounds, for example, trialkylphosphines, biphenylphosphines, *etc.* Inorganic bases and, often, metal salt additives are also used in this reaction, which, in combination with expensive ligands, markedly reduces the economic benefits and environmental safety of this method. Direct C–H arylation is performed, as a rule, in polar aprotic solvents (DMF, dimethylacetamide, *N*-methylpyrrolidone) or, more rarely, in toluene or THF. The reaction occurs at elevated temperature, microwave heating being often used to accelerate the process.

The key problem of this method is related to selectivity, as one compound may have several C–H bonds comparable in the dissociation energy. Directing groups and substituents and the steric factor can serve as tools for increasing the reaction selectivity. Currently, this area of research is being actively developed. The attention is concentrated on elucidation of the principal regularities and problems of direct C–H arylation and on the adjustment of the optimal conditions of synthesis for various organic substrates (the search for appropriate catalysts, ligands, solvents, bases, reaction temperature and time and so on).

For example, it was shown[737] that the undesirable desilylation of thiophene derivatives during the direct arylation can be avoided by adding the 1,4-bis(diphenylphosphino)butane ligand to the catalytic palladium acetate complex. The efficiency of this approach was demonstrated for a large number of substrates. Scheme 164 shows the preparation of 1,4-bis(5-trimethylsilyl-2-thienyl)benzene in 70% yield.

Scheme 164

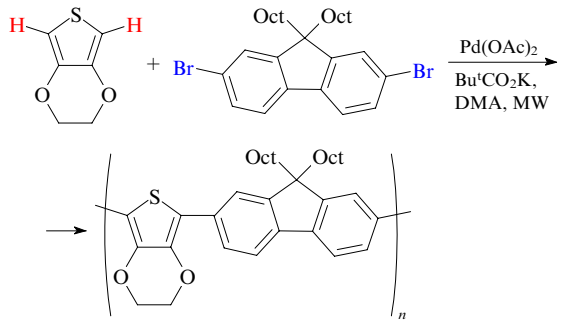


Direct C–H arylation has been developed most appreciably when applied to the synthesis of conjugated polymers for organic photovoltaics by cross-coupling between a monomer with two active protons and a monomer with two halogen atoms. The multistep synthesis of conjugated polymers accomplished by the Suzuki or Stille reactions is reduced here by at least one step, because there is no need to prepare organoboron or organotin monomers. Moreover, more thorough purification by column chromatography can be performed for monomers containing no organoboron or organotin residues. Hence, more accurate stoichiometry between the monomers can be achieved

and polymer samples with higher molecular mass can be prepared.

For example, Choi *et al.*[738] succeeded in the preparation of polymers with a number-average molecular mass of 147 kDa by adjusting the optimal conditions for polycondensation of 3,4-ethylenedioxythiophene and substituted 2,7-dibromofluorene (Scheme 165).

Scheme 165



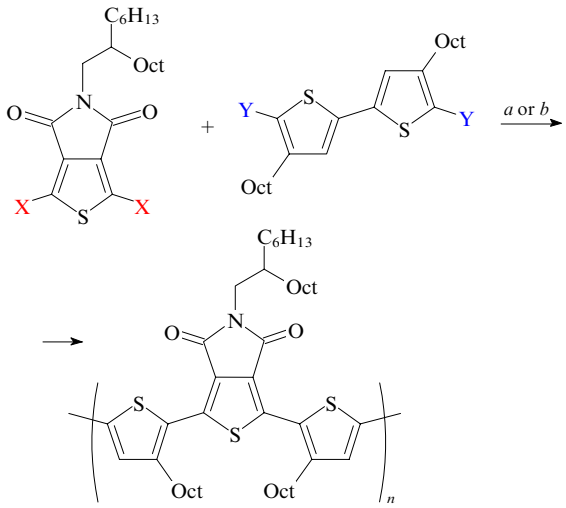
Oct = n-C_8H_{17}

The reaction was assisted by microwave radiation, the reaction time was 30 min and the product yield reached 89%. Dimethylacetamide was used as the solvent, potassium pivalate served as the base and the catalyst (palladium acetate) amount used was as low as 1 mol.%. The polymer obtained demonstrated good film-forming properties, which is important for the fabrication of organic thin-film electronic devices by solution methods.

Some papers are devoted to the synthesis by direct arylation of highly efficient polymers for organic photovoltaics, which have been prepared formerly by the Stille reaction.[739] For example, polymers based on thieno[3,4-*c*]pyrrole-4,6-dione,[740] dithienosilole and dithienogermole,[741] cyclopentadithiophene and benzothiadiazole[742] and some other compounds have been synthesized in the presence of the Herrmann–Beller palladium catalyst under various conditions. In each case, the polymer molecular mass was higher than that of analogous polymers obtained by the Stille reaction. The advantages of synthesis of conjugated polymers by direct C–H arylation over the Stille reaction were demonstrated most clearly by Leclerc and co-workers,[740] who considered polycondensation of bithiophene and thienopyrroledione monomers by both methods (Scheme 166). The imide group in the thienopyrroledione monomer acts simultaneously as both a directing and an activating group for the C–H bonds. In the case of direct synthesis, the yield of the polymer proved to be higher, the molecular mass was six times higher, and the amount of wastes was three times lower.

Researchers pin a lot of hope on the direct C–H arylation, further development of which may not only reduce the prime cost of organic semiconductors and increase the environmental safety of the production but also provide new conjugated polymers with high molecular masses and unique properties.

Scheme 166



(*a*) Stille reaction; X = Br; Y = $SnMe_3$; $Pd_2(dba)_3$, P(*o*-Tol)$_3$, PhCl; 71% yield, M_n = 9000;
(*b*) direct arylation; X = H; Y = Br; Pd(OAc)(*o*-Tol), P(C_6H_4OMe)$_3$, Cs_2CO_3, THF; 96% yield, M_n = 56 000

From the material presented, one can see how important is the selection of a particular synthetic chart for the yield of the π-conjugated oligomers and especially for molecular-mass characteristics of π-conugated polymers. Each of the considered organometallic synthesis reactions has its advantages and shortcomings for the preparation of functional materials for organic electronics. A recent trend is a more extensive use of the direct C–H arylation reaction owing to its simpler synthetic chart: there is no need to prepare organoboron, -magnesium and -tin derivatives for the Suzuki, Kumada or Stille reactions, respectively; the problem of stability of these derivatives during the reaction is eliminated and, hence, the molecular mass of the resulting conjugated polymers increases. However, the development of the direct C–H arylation technique is slowed down by the need to use fairly expensive ligands, which are, moreover, not universal and should be often selected anew for each substrate. Therefore, currently, the classical Suzuki, Kumada and Stille cross-couplings are still more popular. The most important tasks for this line of research in the near future are to study the possibility of performing the Suzuki reaction in an aerobic atmosphere, which is barely used now to prepare conjugated oligomers and polymers, and to search for new promising catalysts and ligands for extending the scope of applicability of direct C–H arylation in the synthesis of organic semiconductors and luminophores.

XV. Supramolecular gels as a new class of smart materials

The development of new technologies will result, in the nearest future, in a very broad use of so-called

smart materials — *i.e.*, materials that respond to changes in the environment and change their properties in response to the external stimuli. This stimuli may include temperature, pressure, pH, the presence or absence of chemicals, irradiation, magnetic or mechanical treatment. The ability to finely controlling substance properties by varying the above-mentioned conditions provides researchers with a powerful tool for the design of functional materials of the future. Therefore, the search for systems that behave as smart materials and ways to control them is a topical problem of the modern fundamental and applied science.

One of the methods for the design of controllable materials is supramolecular approach. Supramolecular chemistry is a multidisciplinary field of science combining organic, inorganic and physical chemistry.[743,744] A key problem solved by supramolecular chemistry is the synthesis of intricate multicomponent structures with specified architecture and properties. The essence of the supramolecular approach is in the use of weak intermolecular interactions including hydrogen bonds, ion–ion, ion–dipole, van der Waals and hydrophobic interactions, π–π stacking and charge transfer complexes to combine molecular components bearing binding sites necessary for assembly into a dynamic supramolecular system. The binding site is a part of a molecule able to form intermolecular bonds between appropriate molecular components. The main feature of intermolecular interactions is low energy (as compared with covalent bonds in organic molecules), which accounts for reversibility of the assembly of molecular components. Hence, there is the possibility to control the equilibria by changing the reaction conditions; any of the above-mentioned types of stimuli can be used either separately or in combination.

An important class of smart materials is represented by supramolecular gels — non-rigid soft materials able to change their physical and chemical properties and even the phase state depending on external conditions and external stimulus applied. This Section is devoted to conceptual issues of the synthesis and application of the new class of dynamic supramolecular materials — supramolecular gels and their metal-containing analogues.

More detailed information and specific applications of such systems can be found in reviews,[745–756] collected works[757] and monographs.[758,759]

XV.1. Supramolecular and coordination polymers

XV.1.a. Supramolecular polymers

Supramolecular polymers are ordered polymeric structures consisting of monomeric units that are held together by reversible and highly directional secondary interactions.[760–763] The latter comprise ion–ion and ion–dipole interactions, coordination bonds, hydrogen bonds and cation–π-system, π–π-stacking, dipole–dipole, metallophilic and van der Waals interactions and solvatophobic effects.[764,765] Supramolecular interactions that may combine molecular building blocks (tectons)[766] in a programmed and reproducible manner give rise to supramolecular synthons.[767]

In the first stage of the reaction between complementary tectons, the intermolecular association gives rise to polymeric properties of the associates being manifested both in solutions (dilute and concentrated) and in the condensed state. As a definite degree of polymerization has been attained, spontaneous assembly of supramolecular polymers into a specific phase (film, layer, membrane, vesicle, micelle, gel, mesomorphous phase or crystal) may take place.[768] In supramolecular polymers that are formed upon the reversible assembly of bifunctional monomers, the degree of polymerization (the number of monomers contained in the polymer — an important characteristics of a polymer) is determined by the strength of interaction of the terminal groups. To attain substantial degrees of polymerization at relatively low concentrations, it is necessary to construct monomers with binding sites that can ensure high association constants (K_a). None of the intermolecular interactions taken separately complies with the criteria imposed on interactions suitable for the formation of supramolecular polymers with a high degree of polymerization.[769] Indeed, for a single hydrogen bond, which has the required directionality, the association constants do not exceed 100 litres mol^{-1}. A drawback of the Coulomb interactions between ionic groups is the lack of directionality; therefore, these bonds give rise to insufficiently clearly shaped aggregates. Hydrophobic effects are applicable only in polar media.

XV.1.b. Coordination polymers

One type of intermolecular interactions widely used in the supramolecular synthesis are coordination bonds, which form the basis for coordination polymers (CPs) — supramolecular polymers composed of repeating organic molecules (di- or polytopic ligands) and metal ions.[770–774]

According to the most up-to-date and general definition,[764] coordination polymers are high-molecular-mass compounds composed of repeating organic molecules and metal ions connected by intermolecular interactions. Of these, the strongest type of interaction is coordination bonding between the donor sites of organic molecule (L) and the metal ion (M). If a ligand molecule contains several donor sites arranged in the divergent fashion (divergent binding sites), it can bind several metal centres into one supramolecule. Translation of these bound groups (L–M) along one, two or three directions gives rise to CPs. One-dimensional chains (1D, linear, zigzag-like and helical), two-dimensional networks (2D, non-interpenetrating and interpenetrating networks) and three-dimensional frameworks (3D, non-intersecting and interpenetrating frameworks) can be formed in the crystal (Fig. 33).

The order of arrangement of CP components in three dimensions, the possibility of varying the nature and the size of tectons and dynamic properties of the frameworks impart unique properties to crystalline coordination polymers. These compounds are being actively studied as electric conducting materials; catalysts for a variety of organic reactions including stereo- and enantioselective ones; materials with controllable magnetic properties, in particular, materials capable of cooperative spin-crossover; materials with unusual optical and nonlinear optical properties; sensors for metal ions and small molecules.[775–784]

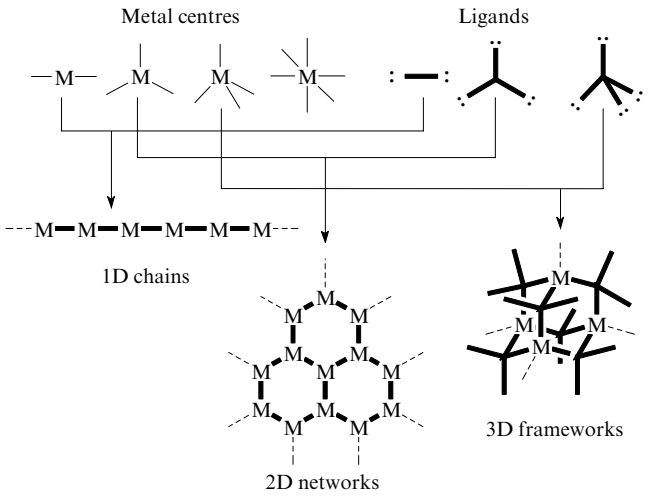


Figure 33. Schematic view of one-, two- and three-dimensional coordination polymers.[775]

It is noteworthy that particular properties of third-generation porous frameworks (the ability to be rearranged under the action of external factors, which include light, temperature or guest molecules) are analogous to the properties of materials based on molecular gels.[785] As noted above, crystalline coordination polymers have been comprehensively studied with the goal of practical application (see, for example, Refs 775 and 777); however, non-crystalline systems having similar structures, first of all, metallogels we are interested in have been rather little studied.[750, 754]

XV.2. Supramolecular gels and metallogels

The search for systems able to reversibly change the structure and properties under the action of external factors (stimuli-responsive materials) is a topical problem of modern materials science and has a broad range of potential applications.[786] One of the ways for producing materials with indicated properties may be the use of monomeric tectons that are self-assembled to a supramolecular polymer. The supramolecular assembly thus formed can change the structure and even be destroyed under a certain external action but can be restored with full recovery of the initial properties after the action has been terminated.[787] This behaviour is based on reversibility of formation of supramolecular bonds.

Examples of stimuli-responsive materials are supramolecular gels (SMGs), which represent a type of supramolecular polymers. Supramolecular gels are able to change their structure (and, hence, properties) under the action of an enormous number of external factors of different nature. Indeed, known SMGs can be anion-sensitive,[788] thermally sensitive,[789–791] metal-sensitive,[792] CO_2-sensitive,[793, 794] redox-sensitive,[795–797] magnetically sensitive,[798] mechanically sensitive,[799] sound-sensitive[800] and light-sensitive.[801–804] Gel formation based on low-molecular-mass components is the dominant subject matter of research of many research teams, first of all, in materials science.

The chemistry and chemical engineering of supramolecular metallogels (SMMGs) have started to be vigorously developed after the publication of Guenet and co-workers.[805] The currently known applications of SMMGs include catalysis[806–810] and design of luminescence,[811, 812] photochromic[813] and spin-crossover materials.[814, 815] Supramolecular gels are applied to obtain films,[816] nanotubes[817] and nanowires,[818] to transport[819] and remove organic compounds from aqueous systems;[820] they serve as porous templates to grow inorganic materials,[821] as templates for organopolymerization;[822] gels based on G-quartet nucleic acids are also known.[823, 824]

Gels based on low-molecular-mass gelators (LMMGs) are usually prepared by heating the gelator in the appropriate solvent followed by cooling the resulting isotropic supersaturated solution to room temperature. The gelation process competes with the formation of crystals and amorphous precipitates. As regards the degree of molecular ordering, a gel can be considered to be an intermediate state (most often, metastable) between these phases. During the gelation, the self-assembly of LMMG affords long polymeric fibrillar aggregates, which are then interwoven to give a three-dimensional template, which traps molecules of the medium, most of all, due to surface tension. As a result, the mobility of the solvent molecule is restricted and the whole material acquires some features of a solid.

A key characteristics of a supramolecular gel is the reversible gel–sol transition, which occurs on heating and distinguishes SMG from a polymeric gel. Owing to this feature, these materials can be used as thermal sensors: above a definite temperature (called gelation temperature, T_{gel}), the non-flowing gel converts to the flowing sol. Apart from this feature called thermotropy, SMGs can change upon replacement of the solvent (lyotropy) and upon mechanical treatment (thixotropy).

A supramolecular gel can respond to other types of external action (light or chemicals) if a light-sensitive or receptor moiety has been incorporated in the LMMG molecule. The diverse opportunities opened up by incorporating chemically different moieties with various physical properties into the LMMG structure are implemented in the design of thermochromic and conducting gels and oriented liquid-crystalline physical gels (see Section XV.3).

At the current stage of development of chemistry, it is impossible to reliably predict the ability of some organic compound to convert a particular solvent into a gel considering only its molecular structure. Examples of low-molecular-mass gelators are shown in Fig. 34. Most of known LMMGs include urea, carbohydrate or amino acid moieties. This is related to the known properties of multiple hydrogen bonds typical of these classes of compounds, in particular, the directionality and energy characteristics. Only a minor portion of LMMGs are prepared by modification of known structures, while the other are discovered serendipitously.[752, 825]

Gels based on LMMGs are often susceptible to spontaneous micro- and macrodestruction or phase separation upon mechanical treatment or on ageing.

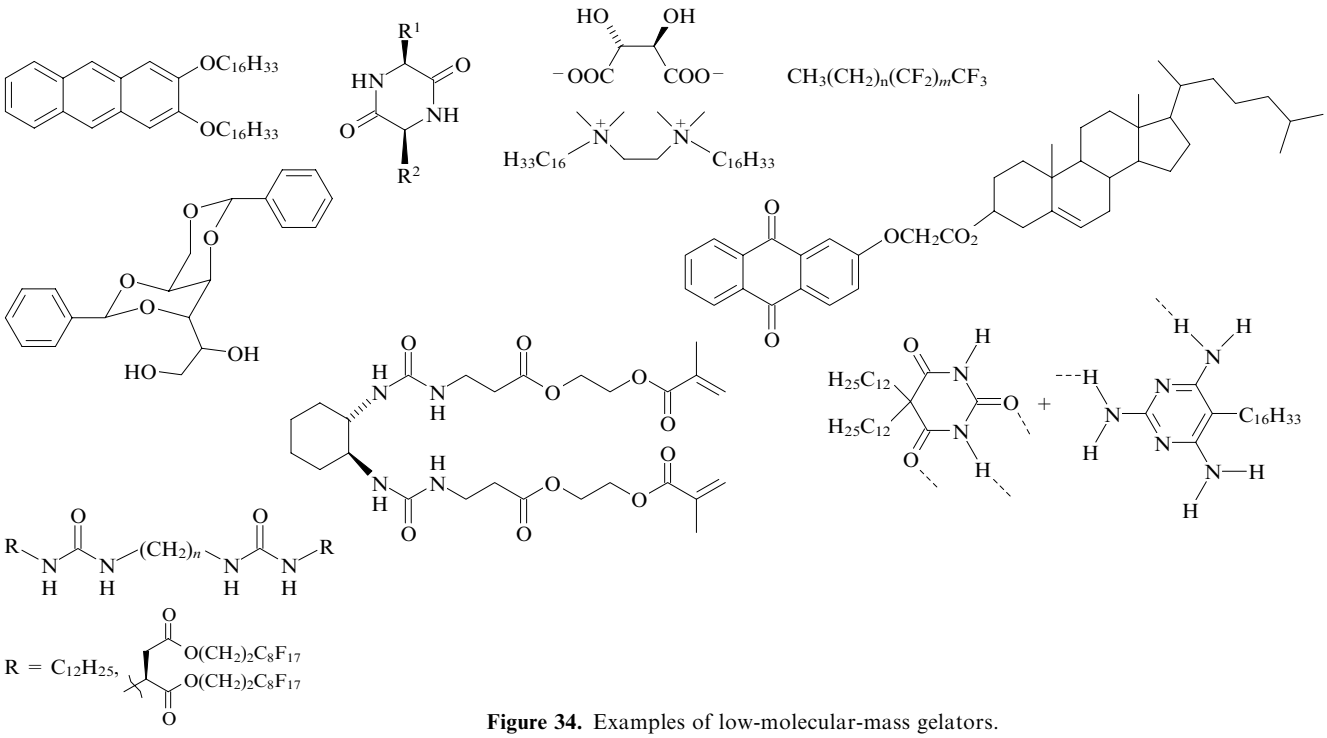


Figure 34. Examples of low-molecular-mass gelators.

To prevent these undesirable processes, the structure of the formed gel could be secured by intermolecular covalent bonds in side chains (*e.g.*, by polymerization involving a double bond or a triple bond; reaction of the hydroxy groups with the diisocyanate linker)[751] or by adding a reinforcing polymer such as cellulose.[826]

While developing new, low-molecular-mass gelators, one should consider the following key factors: (i) the presence of sites for rather strong self-complementary and unidirectional intermolecular interactions for one-dimensional self-assembly; (ii) the possibility of lateral interchain interaction with lower energy than the main interaction along the chain; (iii) the possibility of controlling the nanofibre–solvent interfacial energy in order to regulate the solubility and prevent crystallization; (iv) the existence of ways of affecting the degree of branching during the formation of a 3D network.

XV.2.a. Supramolecular metallogels

The incorporation of a metal atom, ion or cluster into the supramolecular gel structure can give materials having properties caused by the presence of the metal component. First of all, this refers to the design of gel-like catalysts the activity of which can be controlled by external stimuli. The metal-containing catalytically active supramolecular gels combine properties of heterogeneous and homogeneous catalysts — high porosity, accessibility of catalytic sites, easy handling and easy separation from the reaction products.

A metal can be introduced into the structure of a supramolecular gel in three ways. According to the first one, a metal-containing fragment occurs as a part of the low-molecular-mass gelator but does not participate (at least, formally) in the gel formation. The second approach is based on the participation of the metal in the proper gelation process *via* coordination bonding with the donor sites of the exodentate ligand molecules. In this case, the metallopolymer and the whole SMMG can be classified as a coordination polymer. The third approach is based on introduction of a metal-containing component into the structure of the SMG prepared beforehand. All three approaches are schematically shown in Fig. 35.

Examples of using the first approach have been reported in two publications.[806, 827] Dötz and co-workers[806] prepared the Fischer type cobalt carbene complex, which contained groups capable of gel formation, namely, a sugar residue and a hydrophobic alkyl tail. The resulting complex was able to gelate

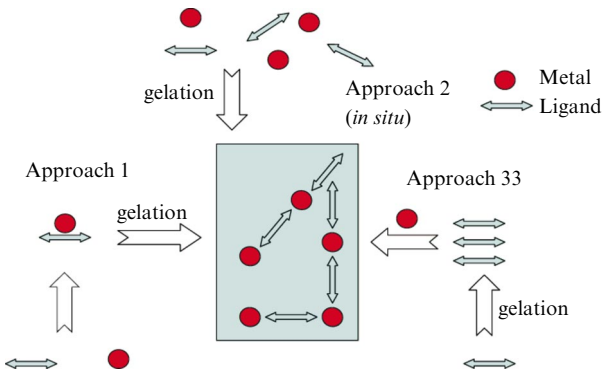


Figure 35. Approaches to the formation of supramolecular metallogels.

chloroform and mixtures of chloroform with toluene or benzene.

The second approach to the preparation of SMMGs was reported by Xu and co-workers.[807] The authors studied gelation processes involving exodentate ligands and palladium complexes. The prepared SMMGs were studied in the oxidation of benzyl alcohol to benzaldehyde. Note that in the vast majority of studies dealing with metallogels, exactly this approach was used.

The third approach to the preparation of catalytically active SMMGs was implemented by Miravet and Escuder.[808] The prepared metal-containing gel was also studied in the catalytic oxidation of benzyl alcohol to benzaldehyde.

XV.2.b. Three levels of structural organization of supramolecular gels

Gelation is believed to occur upon trapping of solvent molecules by interwoven fibres (of diameter from nano- to micrometres) due to surface tension[828–831] and upon physical sorption of solvent molecules on the fibre surface. For understanding of the mechanism of gelation, three levels of gel structure, namely, primary (molecular), secondary (nano) and tertiary (macro) levels, can be distinguished (Fig. 36).[832, 833]

The primary organization level (molecular level, chain diameter from several Ångströms to 1 nanometre) is dictated by intermolecular interactions. Hydrogen bonds, which serve as the key interactions for the formation of most organic gels, lose their strength in water, except for the cases where structures protecting the hydrogen bonds from the solvent are formed.[834] Conversely, hydrophobic effects that have no particular directionality inherent in hydrogen bonds become an important factor in the development of gelators for aqueous medium. The salt bridge and transition metal coordination effects can also play a certain role in the gelation.[835]

At the nanolevel (10–1000 nm), the gels are extended fibre-like structures connected by multiple non-covalent contacts (hydrogen bonds, van der Waals interactions, π–π stacking, *etc.*).

Of special note is self-assembly of disc-shaped molecules (*i.e.*, flat molecules with a rather large surface area), so-called discotics (Fig. 37). As the concentration grows, these molecules form cylindrical oligomeric associates in which bonding occurs, most often, *via* stacking interactions and solvatophobic effects. As a certain degree of polymerization has been attained, the oligomers start to laterally interact with one another, which may result in the formation of either gel or more ordered liquid crystal.

The tertiary structure of the gel (macrolevel, 1–1000 μm) is due to the interaction of particular nanoaggregates (fibres, stacks) with one another. It is the tertiary structure that ultimately determines whether a gel or a precipitate will be formed upon the assembly of nanowires or other aggregates. In other worlds, this stage dictates whether the final phase separation will be microheterogeneous or macroscopic.

The transition from the secondary to tertiary level is governed by the type of interactions between the

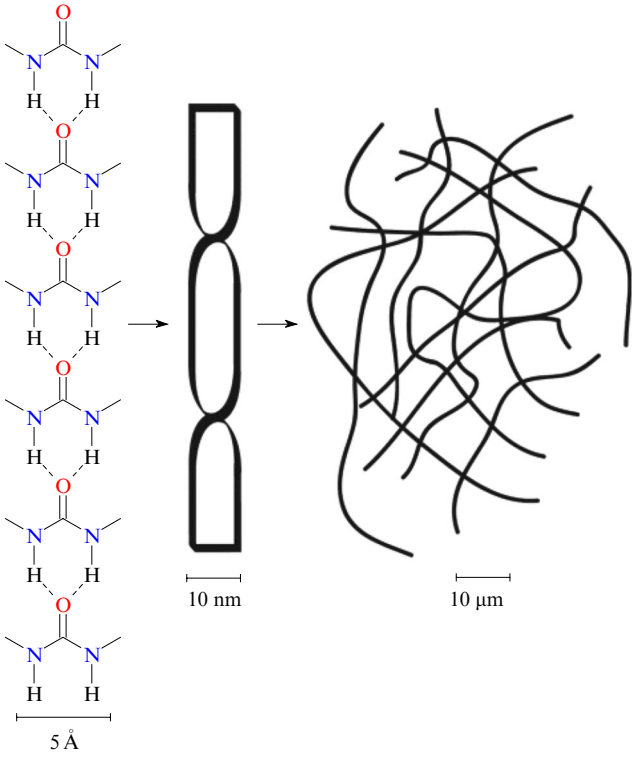


Figure 36. Three organization levels of a supramolecular gel.[747]

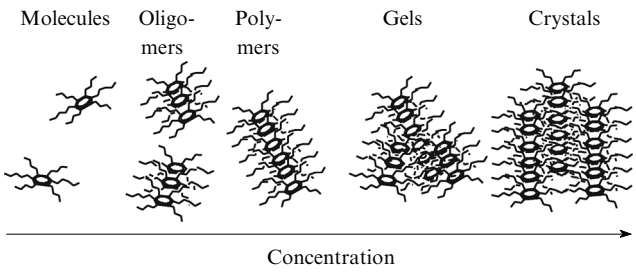


Figure 37. Types of supramolecular structures in solutions of discotic molecules depending on the monomer concentration.

fibres. Gels can be formed by either physically branched fibres or entangled fibres. The type of cross-linking often determines the rheological properties of the gel. Longer, thinner and more flexible fibres have a better ability to capture the solvent molecules than shorter fibres. This means that, depending on the experimental conditions, gels with different morphology and different physical properties can be obtained.

XV.3. Prospective applications of supramolecular gels

Analysis of the available information on the applications of supramolecular gels allows one to distinguish five trends that are currently most promising, in our opinion.

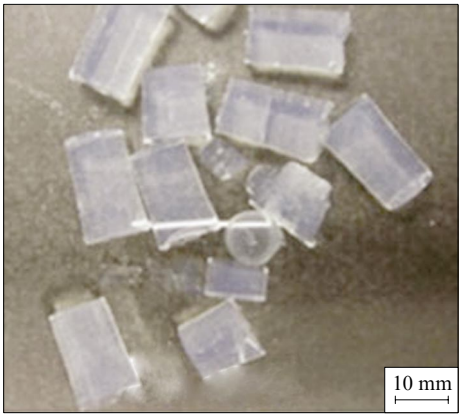


Figure 38. Samples of silica aerogels prepared by supercritical drying.[836]

1. Production of highly porous low-density organic materials for separation processes, as the base for catalysts and for dielectric insulation materials (Fig. 38).[836] These materials are formed when the dispersion medium is replaced by air without destruction of the three-dimensional framework of the disperse phase; usually this is done by drying in supercritical carbon dioxide.

2. The use of supramolecular gels as templates for the formation of organic and inorganic nanostructured materials (Fig. 39).[837]

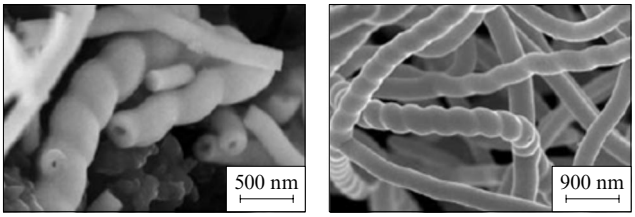


Figure 39. Chiral materials of Ta_2O_5 composition prepared by transcription of chiral supramolecular templates.[837]

3. The use of reversibility of sol–gel transition for the control of smart materials. For example, a change in the structure upon external action results in a change in the interaction between the gel and the immobilized guest. For example, it is possible to control the release of a medical drug from a hydrogel by changing pH, temperature, ionic strength, photoexcitation and so on (Fig. 40).[838] In the design of such materials, the key feature is combining in the same gelation molecule the moieties responsible for supramolecular self-assembly and for switching.

4. Preparation of cytotoxic gels based on metals. It was shown[839] that gels based on Au^{III} complexes exhibit pronounced cytotoxic properties (Fig. 41).

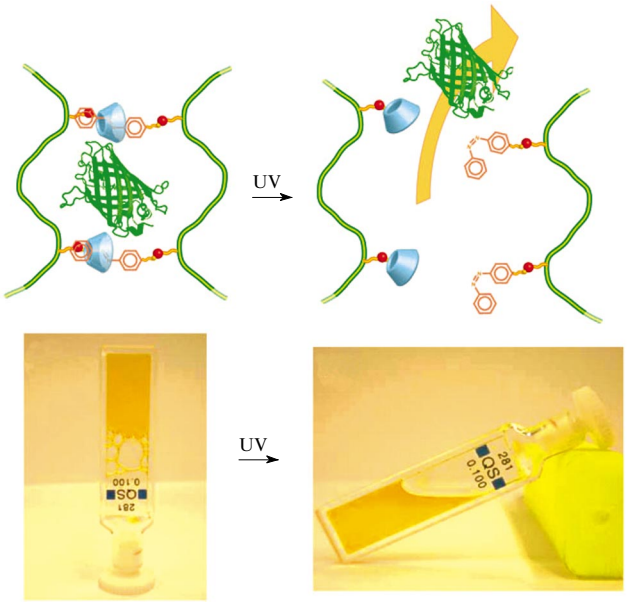


Figure 40. Scheme of application of light-controlled gel–sol transition for UV-induced drug release.[838]

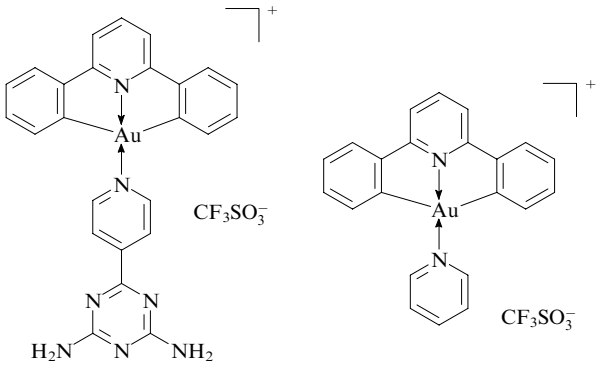


Figure 41. Metal-containing low-molecular-mass gelators exhibiting cytotoxic properties in the gel phase.[839]

5. Development of conducting organic materials. The stacking interactions, which are responsible for polymerization of discotic molecules, account for the ability of such materials to conduct electricity (Fig. 42).[840]

While speaking about the topicality of this research area, one should note that the chemistry of coordination polymers is now at the stage of vigorous development. The order of 3D arrangement of components, the possibility of varying the tecton nature and size and the framework dynamic properties provide the crystalline coordination polymers with unique properties. The key areas in which these systems can be useful include catalysis (also asymmetric); design of molecular ferromagnets, chemical and electrochemical sensors, redox active materials, photoluminescent and

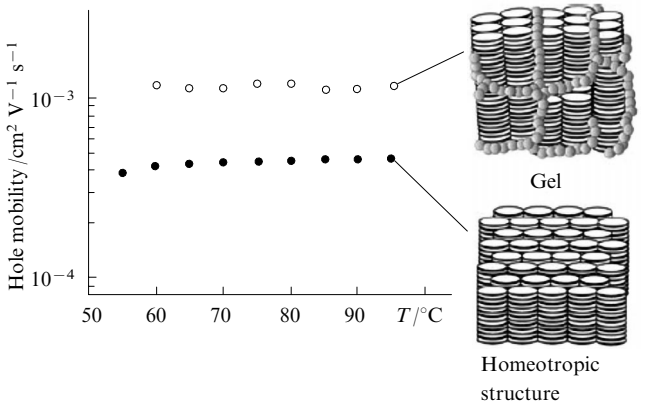


Figure 42. Example of conducting organic materials based on discotics.[840]

photochromic materials and chiral materials; molecular recognition processes; design of conducting, semiconducting and superconducting, nonlinear optical and ferroelectric materials and functional sorbents for the storage, exchange, separation and conversion of gases.

It is important to note that some properties of the third-generation porous frameworks (the ability to be rearranged under the action of external factors, including light, temperature, guest molecules) and high diffusion coefficients are analogous to the properties of materials based on molecular gels. Thus, the research in the field of supramolecular gels becomes a logical continuation and development of the studies of supramolecular polymers as new materials.

The search for new low-molecular-mass gelators and study of gelation processes and applied properties of supramolecular gels are topical up-to-date problems. Note that there are no general approaches to the design of low-molecular-mass gelators, *i.e.*, this field of science still remains almost wholly empirical. It is also important to emphasize that study of the gel structure requires the obligatory use of a set of various physicochemical methods of analysis, and the answer to the question of how the gel is constructed is never exhaustive.

A supramolecular gel can respond to external stimuli (light or chemicals) if a light-sensitive or receptor group has been incorporated into the LMMG molecule. Indeed, SMGs are already used as sensor and photochromic substances. The diverse opportunities provided by incorporation of chemically different moieties with various physical properties into LMMG structure are implemented in the design of thermochromic and conducting gels and oriented liquid-crystalline physical gels. Mention should also be made of gelation of ionic liquids, involvement of nanoparticles into the structure of SMG-based hybrid materials, the use of gels as components for solar cells and media for organic reactions, which has remained beyond the scope of our review. Obviously, preparation of various aerogels as separate materials or as media for reactions and as catalyst supports is among the most promising lines of research.

XVI. Conclusion

The vigorous development observed now for organic chemistry is due to the important practical applications of new organic compounds for pharmacology, agriculture, materials science and for paint and varnish, perfume, cosmetic and other industries. Known reactions already make it possible to obtain almost all types of organic compounds; however, the required reagents are either expensive or hazardous when handled. The former circumstance restricts the industrial use and the latter restricts the broad laboratory use of these processes.

A general problem faced by modern synthetic methods is related to the need to introduce a functional group or a structurally complex substituent into an organic molecule with unprecedented level of accuracy, *i.e.*, complete control over the course of chemical reactions is needed. Analysis of the modern achievements in selective organic synthesis allows one to consider a new trend: the synthesis of organic molecules, biologically active compounds and pharmaceutical blocks with absolute selectivity. In view of the prospects of development for coming years, the essence of methodological development of approaches of organic synthesis may be defined by the term 'atomic accuracy' of chemical reactions.

In order to attain these goals, it is necessary to clearly understand the state-of-the-art of the considered field. The production processes of complex organic compounds that rely on classical organic chemistry consist of many steps and require intermediate separation of the target and side products, which inevitably increases the cost of the resulting commercial products. The considerable amount of wastes also requires development of processes for effective separation and for disposal of some organic compounds, which makes the production even more expensive.

Under these conditions, an important task is to develop clean processes of organic synthesis based, from the very beginning, on green chemistry principles. The examples of processes giving rise to carbon–heteroatom bonds presented in the review (synthesis of fluorine-, oxygen- and phosphorus-containing organic compounds) demonstrate that the use of catalytic processes is a highly promising way for solving these problems, which not only increases the product yields but also decreases the number of steps and minimizes the amount of wastes. Among other advantages of catalytic processes, the following deserve special attention: (i) the possibility to replace reagents in order to avoid formation of hazardous wastes (for example, the use of hydrogen instead of reducing agents in hydrogenation; the use of oxygen or hydrogen peroxide as the oxidants and so on); (ii) guiding reactions along shorter and more effective routes (*e.g.*, direct synthesis without the use of protecting groups); (iii) the possibility to combine several successive catalytic and non-catalytic steps in one process (one-pot reactions); (iv) preparation of compounds that are difficult to synthesize by conventional methods.

One of the objectives of this review was to demonstrate the listed advantages by examples of particular catalytic reactions of organic synthesis the range of which is being constantly extended. One more problem faced by catalysis in organic synthesis is practical implementation of enantioselective methods for the preparation of organic compounds, which is a very large and highly promising area. Obviously, catalytic methods will predominate along this line including both classical methods (involving transition metals) and organocatalysis.

However, despite the enormous scientific and practical interest in catalytic transformations of organic molecules, the industrial use of these processes is still not very extensive. One reason is that most of the discovered catalytic reactions of organic synthesis are homogeneous, *i.e.*, they involve soluble organic complexes of transition (including noble) metals as catalysts. The advantages provided by these processes (high selectivity to target products, which often reaches 100%, in particular in the synthesis of definite stereoisomers and enantiomers) are difficult to implement in industry due to the problems of catalyst separation from other reaction components (reactants, products and solvents).

Therefore, a highly important direction in this research area is to develop approaches to catalytic reactions of organic synthesis in the presence of heterogeneous catalysts in which metal complexes or even metal nanoparticles supported on various solid materials serve as the active components. Transition to heterogeneous catalysts provides additional advantages, including effective separation of the catalyst from the reaction medium for repeated use; a wider range of applicable solvents because in this case, the problem of solubility of metal complexes, which serve as catalysts in homogeneous reactions, is eliminated; implementation of cascade or one-pot processes owing to the design of sites having various functionality on the surface of a heterogeneous catalyst (bimetallic catalysts, support modification and the like).

The second half of the review devoted to characteristic features of reactions of organic synthesis on heterogeneous catalysts indicates that the above-listed advantages of heterogeneous catalytic processes cannot be embodied unless high selectivity to the target reaction products is achieved. Solution of this problem lies in the molecular design of the optimal catalyst. This procedure should be based on the knowledge gained from detailed investigation of the mechanisms of catalytic reactions and structure of active sites, in particular, using model catalysts. Therefore, a highly important modern trend is development of new physical methods for investigation of heterogeneous catalysts including methods that are suitable for *in situ* studying the state of the surface, *i.e.*, during the catalytic process. Elucidation of the relationship between the properties of the catalyst surface and the activity and selectivity of transformation of organic compounds in particular reactions would allow for the manufacture of catalysts of optimal composition for low-waste and waste-free processes of organic synthesis to prepare compounds of various classes.

Among the currently developed approaches to increasing the selectivity of heterogeneous catalysts, most of which are discussed in this review, the following approaches appear to be most promising (i) development of methods for grafting noble and transition metal complexes on solid porous matrices of various nature in order to increase their stability; (ii) study of the size effects in selective organic reactions catalyzed by supported monometallic catalysts in order to determine the size of supported metal particles that ensures the highest level of selectivity and development of methods for the preparation of catalysts with a narrow (in the ideal case, monodisperse) particle size distribution; (iii) study of the effect of the nature of the support (metal–support interaction) and the second metal (synergistic effects) for fine tuning of the electronic state of the active metal in order to minimize the side reactions.

Despite the necessity to carry out huge research along this line, it is possible even now to cite quite a number of examples of heterogeneously catalyzed organic reactions implemented in practice. This conclusion is supported by the review chapter devoted to analysis of the recently commissioned industrial processes of organic synthesis on heterogeneous catalysts.

The final part of the review outlines one more modern trend of the development of organic chemistry, which finds more and more extensive practical application: the use organic reactions for the synthesis of functional materials, including the materials that change properties in response to external influence.

Thus, the challenges of the modern society and the increasing demands of high-technology-based sectors of modern industry stipulated a new phase in the development of organic synthesis. The increase in the efficiency of catalytic processes, especially the selectivity of heterogeneous catalytic systems and stability/regeneration of homogeneous catalytic systems, is the key trend of the development of catalytic technologies in the near future.

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