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Metal oxides and silica as efficient catalysts for the preparative organic chemistry

Yu A Titova,[a, b] O V Fedorova,[a, b] G L Rusinov,[a, b] V N Charushin [a, b]

[a] *I Ya Postovsky Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences ul. S Kovalevskoi/Akademicheskaya 22/20, 620990 Ekaterinburg, Russian Federation*
[b] *Ural Federal University named after the First President of Russia B N Yeltsin ul. Mira 19, Ekaterinburg, 620002 Russian Federation*

Data on the use of metal oxides and silica as catalysts of reactions that are most in demand in laboratory organic synthesis are summarized. The potential of oxide catalysts for optimization of organic reactions is demonstrated, and some mechanistic aspects of oxide action are considered. Available publications on the synthetic use of single and mixed, as well as bulk and nanosized, metal oxides and silica are presented.
The bibliography includes 189 references.

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I. Introduction

The vast majority of reactions in modern organic chemistry are catalytic. Advantages of heterogeneous catalysts over homogeneous catalysts are evident. First, a solid catalyst is easy to separate from the reaction mixture by filtration or centrifugation, which considerably simplifies the synthesis technology and reduces the synthesis time. Second, a heterogeneous catalyst after regeneration can be repeatedly used. Third, the cost of most heterogeneous catalysts is relatively low, which makes their use economically attractive.[1]

Metal oxides and silica represent an important class of heterogeneous catalysts owing to their high durability, environmental safety, ease of use, availability and low cost.[2] They are able to enhance the chemoselectivity of various chemical reactions. In this respect, the best known and studied are natural and synthetic aluminosilicates, both amorphous and crystalline (zeolites). In our opinion, synthetic oxides of other metals are of no less interest to researchers, since the differences in the nature of metal cations and a variety of known synthetic methods make it possible to modify the properties of oxide catalysts within wide limits. One of such properties is specific surface area, which can increase as the oxide particle size decreases. Therefore, this review deals with synthetic metal oxides and silica, both single and mixed, bulk and nanosized.

The surface structure of oxide catalysts, as well as the nature of their catalytic active sites, has been studied in detail and considered in several modern monographs (see, *e.g.*, Refs 2 – 5). The following types of active sites are discerned: Lewis acid sites M^{n+}; Lewis basic sites represented by oxide oxygen atoms and hydroxyl groups, as well

Yu A Titova Candidate of Chemical Sciences, Researcher at the IOS UB RAS, and the UrFU.
Telephone: +7(343)362 – 3058, e-mail: titova@ios.uran.ru
Current research interests: heterocyclic compounds, nanosized metal oxides, catalysis, enantioselective synthesis.
O V Fedorova Candidate of Chemical Sciences, Senior Researcher at the IOS UB RAS, and the UrFU.
Telephone: +7(343)362 – 3058, e-mail: fedorova@ios.uran.ru
Current research interests: heterocyclic compounds, multicomponent reactions, podands, crown ethers, antituberculosis drugs, catalysis.
G L Rusinov Candidate of Chemical Science, Leading Researcher at the IOS UB RAS and Senior Lecturer at the UrFU.
Telephone: +7(343)362 – 3201, e-mail: rusinov@ios.uran.ru
Current research interests: heterocyclic compounds, azines, nucleophilic substitution, supramolecular compounds, medicinal chemistry.
V N Charushin Academician, Head of the IOS UB RAS, Professor at the UrFU.
Telephone: +7(343)369 – 3058, e-mail: charushin@ios.uran.ru
Current research interests: nucleophilic substitution of hydrogen atoms, heterocyclic chemistry, medicinal chemistry.

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as by ion pairs of the $M^{n+}-O^-$ type; Brønsted acid sites — hydroxyl protons of a metal hydroxycarbonate formed on the oxide surface as a result of sorption of carbon dioxide. A combination of acid and basic active sites and their number and activity depend essentially on the nature of the oxide and the method and conditions of its synthesis and can vary within rather wide limits, which is responsible for the catalytic properties of oxide materials.

The concentration and strength of Brønsted and Lewis acid sites considerably increase on the surface of mixed oxides, for example, TiO_2-SiO_2, which is attributed to the presence of Ti—O—Si moieties. Supported bifunctional catalysts like Pt/Al_2O_3 have metal sites, in addition to acid (basic) sites. The oxide surface acidity can be changed through fluorination or sulfation.[6]

The content of active sites of an oxide catalyst can increase with increasing its surface area either through creation (enhancement) of porosity or as a result of a decrease in the particle size (nanosized oxides). The most popular method for the preparation of metal oxides with a developed surface is the precipitation from aqueous salt solutions with subsequent calcination of the resulting compounds. Disadvantages of the precipitation method are the large consumption of the required reactants and large amounts of wastes. Oxide catalysts with high specific surface area are also produced by mechanochemical methods, which require special equipment. The sol–gel method can produce both nanosized and mesoporous metal oxides. However, the latter are synthesized in the presence of matrix molecules, which should be removed.[7,8]

Metal oxides have been long and successfully used as catalysts of commercially important processes, such as the water-gas-shift reaction (steam conversion of carbon monoxide into carbon dioxide and hydrogen),[9–11] polymerization,[12,13] the Fischer–Tropsch reaction,[14–20] synthesis of acids,[21,22] alcohols[23] (and their dehydration to formaldehyde[24–28]), acetone,[29] methyl ethyl ketone,[30,31] cyclohexanone,[32] dehydrogenation of alkylaromatic compounds,[33–35] hydrocarbons, *etc*.[36–45] These well-known reactions are not covered in the present review since our interest as organic chemists focuses on the use of metal oxides in the laboratory practice, for example, on the processes indispensable in organic synthesis, such as condensation, formation of C—N and C—O bonds and multicomponent reactions.

The up-to-date published monographs and reviews dealing with the application of oxide catalysts in organic synthesis either cover only model reactions or focus on industrial organic synthesis. For example, in monographs addressing oxide catalysts, the chapters describing their application in organic chemistry have mainly focused either on redox processes or on the application of zeolites.[2,5,46–49] The catalytic action of mixed metal oxides,[50] transition metal oxides,[51] alkaline-earth metal oxides,[52] as well as of metal oxides modified with sulfuric and vanadic acids,[53] has been covered in various reviews. However, the range of organic reactions presented in these publications is fairly limited. One chapter of a review published in 2013 deals with the use of nanosized metal oxides in multicomponent reactions.[54]

The aim of the present review is to demonstrate the wide applicability of oxide catalysts in fine organic synthesis. Available data are classified according to the types of reactions, with special attention paid to the C—C, C—N and C—O bond formation reactions and multicomponent reactions. An essential role of metal oxides and silica in optimization of these reactions and prospects for the use of these versatile catalysts in research and practice are discussed. The review presents publications dealing with the application of single and mixed oxides. A special focus is put on the use of nanosized oxides, which become increasingly available, especially with development of sol–gel synthesis. The level of detail in the description of characteristics of oxide materials is dictated by the degree of comprehensiveness in the original papers.

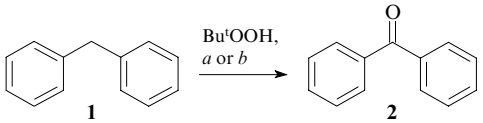
II. Oxidation and reduction reactions

Commercial oxide catalysts of oxidation reactions are, as a rule, complex multicomponent systems composed of Group V–VIII metal oxides. As already mentioned, their application in redox reactions has been considered in several monographs.[2,46,47] In the present review, we give examples of laboratory procedures of oxidation and reduction reactions of simple molecules (alcohols, ketones, ethers, saturated and unsaturated hydrocarbons, *etc*.) catalyzed by single and mixed oxides.

Oxidation reactions catalyzed by metal oxides often involve the activation of an oxidant molecule on the oxide surface. The activation mechanism depends on the oxide and oxidant nature. This activation can be through the radical initiation of an oxidation reaction, formation of peroxide compounds, *etc*.

In particular, activation of *tert*-butyl hydroperoxide (TBHP) in the presence of bulk MnO_2 (Ref. 55) and V_2O_5 (particle size 0.1–0.2 μm)[56] leads to the efficient oxidation of alkylaromatic substrates to ketones [for example, diphenylmethane (**1**) is converted into diphenyl ketone (**2**), Scheme 1].

Scheme 1



(*a*) V_2O_5, AcOH, 60 °C, 1 h (92.5% yield);
(*b*) MnO_2, MeCN, 80 °C, 10 h (92% yield)

A series of alkylarenes have been oxidized using the Bu^{t}OOH–MnO_2 catalytic system (Table 1).

In the course of oxidation of the initial diphenylmethane, the metal oxide promotes the decomposition of *tert*-butyl hydroperoxide to free radicals. The latter react with alkylarene to give the desired aryl ketone. The essential role in this reaction is attributed to the hydroxyl radical, which

Scheme 2

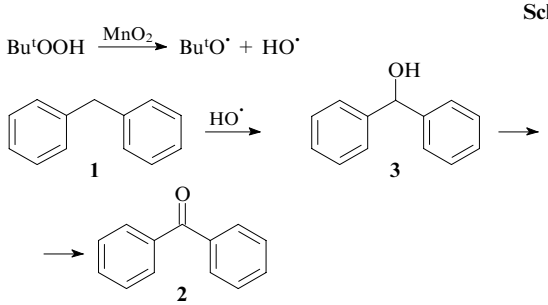
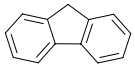
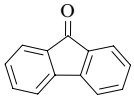
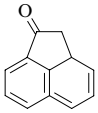
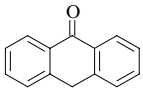
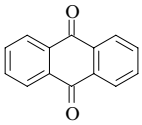
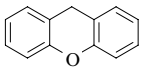
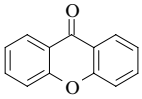
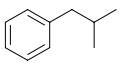
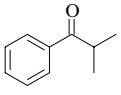


Table 1. Oxidation of arenes and alkylarenes by the $Bu^tOOH - MnO_2$ system.[55]

Reactant	Product	Conversion (%) [a]
		92
		89
		100
		88
		100
		100
		85

[a] According to gas chromatography data.

reacts with diphenylmethane to form benzhydrol (**3**), and the latter is oxidized to diphenyl ketone (**2**).[55] (Scheme 2).

At the same time, other researchers[56] believe that it is precisely *tert*-butylperoxy and *tert*-butoxy radicals that promote further oxidation of diphenylmethane (Scheme 3).

Scheme 3

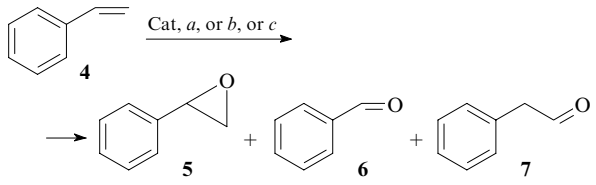
$$Bu^tOOH + V^V \longrightarrow Bu^tOO^{\bullet} + H^+ + V^{IV}$$

$$Bu^tOOH + V^{IV} \longrightarrow Bu^tO^{\bullet} + HO^- + V^V$$

$$\mathbf{1} \xrightarrow{Bu^tOO^{\bullet}\ \text{or}\ Bu^tO^{\bullet}} \mathbf{2}$$

The oxidation of styrene (**4**) with *tert*-butyl hydroperoxide to a mixture of epoxide **5** (styrene oxide), benzaldehyde (**6**) and phenylacetaldehyde (**7**) (Scheme 4) has been accomplished over a large number of bulk alkaline earth,

Scheme 4



(*a*) TBHP, MeCN, 80 °C, 8 h; (*b*) TBHP, PhH, 80 °C, 3 h; (*c*) TBHP, MeCN, 60 °C, 6 h

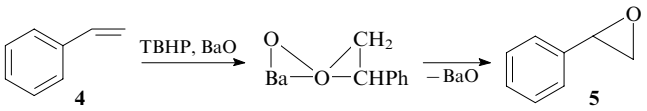
Table 2. Oxidation of styrene with *tert*-butyl hydroperoxide in the presence of different catalysts (see Scheme 4).

Oxide	Conditions	Conversion of **4** (%)	Selectivity (%)			Ref.
			5	**6**	**7**	
MgO	*a*	15	32	60	7	58
2.5% TiO_2-MgO	*a*	25	33	52	14	58
7.5% TiO_2-MgO	*a*	27	30	56	13	58
15% TiO_2-MgO	*a*	34	19	60	20	58
TiO_2-SiO_2	*c*	52	3	88	2	60
TiO_2	*b*	6	26	4	6	57
Cr_2O_3	*b*	44	48	12	25	57
Fe_2O_3	*b*	18	61	3	5	57
CoO	*b*	47	73	0.1	6	57
NiO	*b*	52	86	2	4	57
MoO_3	*b*	42	76	0	11	57
BaO	*b*	41	78	1	8	57
CeO_2	*b*	29	39	4	6	57
Nd_2O_3	*b*	20	63	1	8	59

rare earth and transition metal oxides: NiO, CoO, MoO_3, Cr_2O_3, Fe_2O_3, ZnO, TiO_2,[57] MgO,[58] BaO, CaO, SrO, La_2O_3, Ce_2O_3, *etc.*[59,60] The conversion of styrene and reaction selectivity are different in the presence of different oxides (selected results are presented in Table 2).

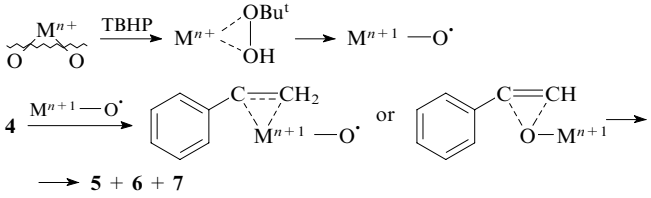
Since the redox properties of the above oxides are different, the epoxidation mechanisms in their presence differ from one another. For example, it is suggested[59] that the high activity of BaO is due to the ease of its reaction with TBHP to give barium peroxide, which then reacts with styrene (Scheme 5).

Scheme 5



According to other researchers,[61] the initiating stage of the reaction is coordination of TBHP on the oxide surface to give a metal oxide radical, which subsequently reacts with styrene (Scheme 6).

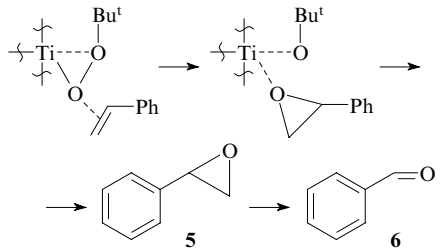
Scheme 6



The introduction of TiO_2 nanoparticles into the MgO structure enhances the catalytic activity of the latter. It has been reported that as the content of nano-titania in the catalyst increases, the selectivity toward styrene oxide (**5**) decreases, the selectivity toward benzaldehyde (**6**) increases, and there is no linear dependence of selectivity to phenylacetaldehyde (**7**). Mesoporous TiO_2-SiO_2 also exhibits high activity and selectivity to benzaldehyde. At the same time, bulk TiO_2 almost does not catalyze the reaction. It is known that epoxidation of compounds with double bonds over supported titania involves the formation of hydro-

peroxide intermediates (Scheme 7).[62] However, it is likely that the redistribution of Ti^{4+} over the oxide support surface increases the number and strength of basic sites of the catalyst, which promotes the conversion of epoxide **5** into aldehyde **6**.

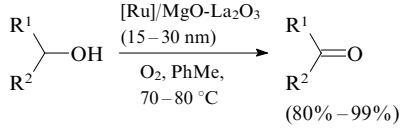
Scheme 7



Bulk mixed oxide TiO_2-SiO_2 turned out to be an efficient catalyst of oxidation of unsaturated alcohols and ketones with alkyl hydroperoxides.[8]

Selective oxidation of alcohols to ketones or aldehydes has been accomplished using ruthenium(IV) oxide supported on nanosized mixed magnesium–lanthanum oxide $MgO–La_2O_3$ as the catalyst and molecular oxygen as the oxidant (Scheme 8).[63]

Scheme 8



R^1, R^2 = Ar, Alk, Het, H

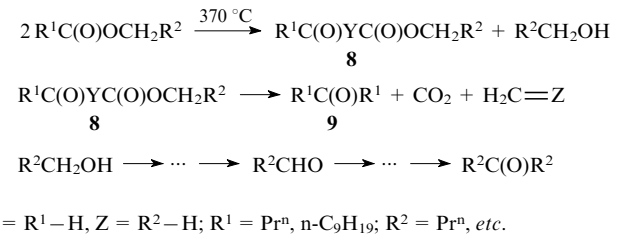
The oxidation reaction involves an oxygen atom bonded to ruthenium atoms as a hydroxy group. An alcohol molecule is bonded to the coordinatively unsaturated ruthenium atom, which is accompanied by splitting-off of a water molecule. The resulting aldehyde (ketone) is desorbed leaving an oxygen vacancy at the surface. The reduced sites are regenerated by the oxygen migrating from the reaction medium bulk.[64]

The authors believe that immobilization of the ruthenium catalyst on the surface of nanosized $MgO–La_2O_3$ oxide favours the stabilization of the former since ruthenium in an oxygen atmosphere is readily oxidized to ruthenates, which, being anions, can be stabilized at highly basic sites of the $MgO–La_2O_3$ surface. This is responsible for the lack of washing-out of the ruthenium-containing catalyst into the solution.

Nanosized $MgO–La_2O_3$ turned out to be the best support for the ruthenium catalyst as compared with single oxides MgO, La_2O_3, TiO_2, Al_2O_3 and SiO_2, owing to its high basic properties (80%–99% yield depending on the substrate used). To achieve analogous yields of ketones in oxidation of aliphatic alcohols under homogeneous catalysis conditions, the presence of hydroquinone as a cocatalyst, in addition to the $RuCl_2(PPh_3)_3$ catalyst, trifluoromethyltoluene as a solvent and K_2CO_3 as a base is required.[65]

Klimkiewicz *et al.*[66] have synthesized ketones from esters over the $SnO_2–CeO_2–Rh_2O_3$ catalyst (90 : 9 : 1 particle size 0.6–1.2 mm) in a flow reactor. The reaction occurs as condensation of two ester molecules to form unstable β-ketoester **8** (Scheme 9), which is then decomposed to the corresponding ketone **9**.

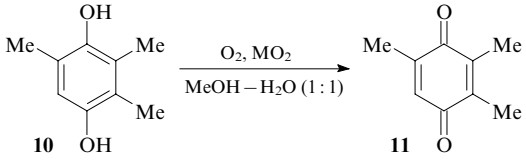
Scheme 9



Y = R^1–H, Z = R^2–H; R^1 = Pr^n, n-C_9H_{19}; R^2 = Pr^n, *etc.*

The oxidative dehydrogenation of 2,3,5-trimethyl-1,4-hydroquinone (**10**) with air oxygen in the presence of stable hydrogels SiO_2,[67,68] TiO_2,[68] SnO_2[68,69] and ZrO_2 has been studied (Scheme 10).[70]

Scheme 10



The introduction of dioxides into this reaction has enhanced the oxidation selectivity, but has somewhat decreased the rate: the initial substrate consumption rate was 0.24 mol litre^{-1} h^{-1} (against 0.26 mol litre^{-1} h^{-1} in the absence of the gel).

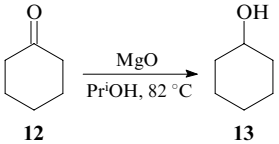
In this case, the catalyst interacts with the substrate rather than with the oxidant. This interaction leads to the formation of hydrogen bonds between the hydroxyls of hydroquinone **10** and surface hydroxyl groups or water molecules of the oxide, which implies the decrease in electron density on the aromatic ring and hydroxyl oxygen atoms attached to the ring.

In addition, the presence of hydrogels suppresses the self-retardation of the reaction, which is caused by the binding of the resulting 2,3,5-trimethyl-1,4-benzoquinone (**11**) to initial hydroquinone **10** to give quinhydrone.

It is worth noting that the role of metal oxides in catalytic hydrogenation reactions can consist in activating the hydrogenation catalyst — an oxide-supported noble metal. This makes it possible to carry out catalytic hydrogenation under mild conditions. Currently, such catalysts are actively used, for example, in the arene hydrogenation reaction.[71–74]

The activation of the substrate and(or) hydrogen source through their sorption onto the metal oxide surface allows performing hydrogenation reactions under mild conditions. In this case, the decrease in the metal oxide particle size improves the reaction chemoselectivity. In particular, the Meerwein–Ponndorf–Verley reduction of cyclohexanone (**12**) to cyclohexanol (**13**) is carried out in isopropyl alcohol at 82 °C over the heterogeneous catalyst MgO (Scheme 11).[75] With decreasing the oxide particle size from 200 to 3 nm, the yield of the product increases from 21% to 97%.

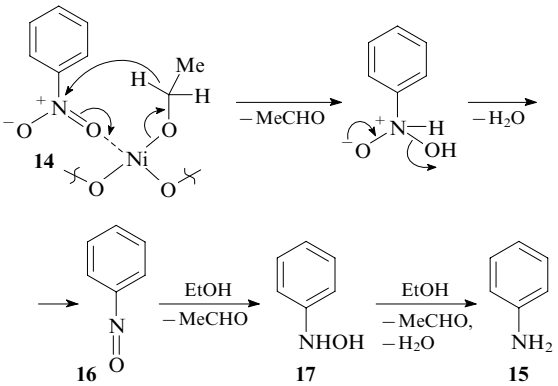
Scheme 11



It is likely that an increase in the catalyst surface area (S_{sp}) is accompanied by an increase in the number of basic and acid sites on the catalyst surface, which is responsible for the increase in the yield of the product. The basic sites of the surface bind the hydroxyl proton of Pr^iOH, while the acid sites bind the keto group of cyclohexanone, thus facilitating hydrogen transfer.

A simple and convenient method for the production of aromatic amines is the microwave-assisted reduction of the corresponding nitro derivatives over nano NiO (particle size 12 nm, $S_{sp} = 88.5\ m^2\ g^{-1}$) in the presence of KOH and EtOH as the hydrogen donor.[76] An advantage of this method is its high regio- and chemoselectivity (the product yield is 85%–98%) of the reduction for nitro compounds with various functionalities, such as OH, OMe, CHO, Ac, CO_2H, CO_2Et, $C(O)NH_2$, CN, $CH{=}CH_2$ and NHAc. Although the mechanism of this reaction in the presence of nano NiO is not completely clear, the authors assume that it is analogous to the mechanisms described in the literature for reactions over other heterogeneous catalysts. Catalytic reduction (Scheme 12) is initiated by coordination of the nitro group of substrate **14** and the alcohol hydroxyl to the Lewis acid sites on the nano-oxide surface. The alcohol molecule is readily converted to the alkoxide in the presence of KOH. Hydrogen transfer occurs either directly from the alcohol or from the alkoxide promoted by KOH. Formation of target amine **15** proceeds through nitrobenzene (**16**) and *N*-phenylhydroxylamine (**17**). Since the nitro group is a stronger electron acceptor than the other functional groups, it withdraws electrons more strongly from the aromatic ring and, thus, is better adsorbed onto the catalyst surface and reduced. This can account for the high selectivity of the reaction in the presence of nano NiO.

Scheme 12



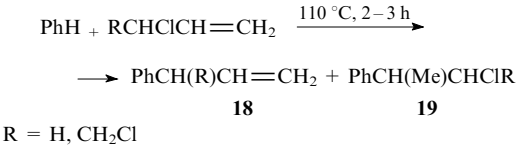
Bulk transition metal oxides have been studied in the reduction of *p*-nitrophenol at room temperature with the use of $NaBH_4$ as a hydrogen source.[77] In this system, CuO, Co_3O_4, Fe_2O_3 and NiO ($S_{sp} = 0.63–25.7\ m^2\ g^{-1}$) are active, while TiO_2, V_2O_5, Cr_2O_3, MnO_2 are ZnO inactive. Transition metal oxides activate the hydrolysis of $NaBH_4$ to release gaseous H_2.

III. C- and O-alkylation of arenes

Favourable effect of metal oxides on the rate and selectivity of C- and O-alkylation reactions has been reported. Nanosized metal oxides are more active than their bulk counterparts. Some researchers state that sorption of the participants of an alkylation reaction on the catalyst surface leads to their activation.

Heating solutions of allyl chlorides in benzene (5 : 1) at 100 °C for 4 h under anaerobic conditions with bulk iron oxide Fe_2O_3 leads to a complex mixture of products, including the products of benzene alkylation with C–Cl (1- and-2-propenylbenzenes) or C=C [(1-methyl-2-chloroethyl)benzene, 3-chloropropylbenzene] bond cleavage of chloroalkene, as well as considerable amounts of products of dimerization and further transformations of allyl chlorides. In air, the process also occurs with low selectivity to give ~ 2% of the allyl chloride dimer and 10% of high-boiling products under the same conditions in 3 h. Silica-supported iron oxide nanoparticles — Fe_2O_3/SiO_2, FeO/SiO_2 and Fe_3O_4/SiO_2 (particle size 2–15 nm) — catalyze this reaction more electively[78] to produce only alkylation products **18** and **19** in approximately a 1 : 1 ratio *via* C–Cl and C=C bond cleavage, respectively (Scheme 13). The yield of other products is no higher than 1% in all cases. In the absence of oxygen, the reaction gives 2-propenylbenzene (**18**, R = H) in low yield (1%–5%).

Scheme 13



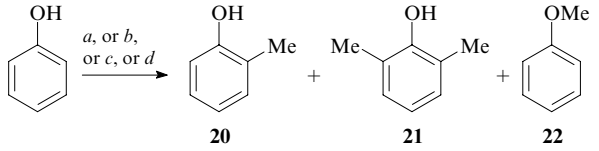
R = H, CH_2Cl

The catalytic properties of nanosized iron oxides in alkylation reactions depend on the oxide phase composition and reaction temperature and duration. In particular, a catalyst based on iron(III) oxide is most active in alkylation *via* C–Cl bond cleavage. At low conversions, the reaction mainly yields 2-propenylbenzene (**18**, R = H), a product of alkylation *via* C–Cl bond cleavage; then, there is observed an increase in the content of the product formed through allyl chloride double bond cleavage, (1-methyl-2-chloroethyl)benzene (**19**, R = H). The latter is also predominantly formed over the reduced catalyst, which can be due to the appearance of $Fe^{3+}(Cl^-)$ sites when Fe^{2+} interacts with the chlorine atom of a chloroalkene molecule. Indeed, the alkylation catalyzed by anhydrous iron(III) chloride, a strong Lewis acid, occurs mainly with double bond cleavage.

The alkylation of phenol with methanol in the presence of heterogeneous catalysts based on the nanosized $SnO_2–Sm_2O_3$ oxide with weak acid sites on the surface occurs preferably *ortho*-selectively to give *o*-cresol (**20**) (Scheme 14, conditions *a*). At the same time, the use of the nano oxide modified with sulfate ions leads to the decrease in selectivity and to formation of various C-alkylation products (for example, compounds **20**, **21**, *etc.*, see Scheme 14, conditions *b*).[79] When the Cr (2.5 mass %)–MgO or Pt (0.05 mass %)–Cr (2.5 mass %)–MgO systems are used as heterogeneous catalysts, O-alkylation product **22** is not formed (see Scheme 14, conditions *c*, *d*).[80]

Small amounts of Pt added to Cr–MgO increase the phenol conversion, but deteriorate the reaction selectivity. Sorption of the reactants onto the catalyst surface leads to their activation. Methanol is sorbed on acid sites and phenol, on basic sites as the phenolate ion in such a way that the *orto*-positions of the aromatic ring are located near the catalyst surface.

Scheme 14



(*a*) SnO_2 (80 mass %) – Sm_2O_3 (particle size 2.5 nm, S_{sp} = 102.7 $m^2\ g^{-1}$), PhOH – MeOH (1 : 6), 350 °C;
(*b*) SO_4^{2-}/(SnO_2 (80 mass %) – Sm_2O_3) (particle size 2.1 nm, S_{sp} = 190.7 $m^2\ g^{-1}$), PhOH – MeOH (1 : 6), 350 °C;
(*c*) Cr (2.5 mass %) – MgO (S_{sp} = 46 $m^2\ g^{-1}$), PhOH – MeOH (1 : 10), 440 °C;
(*d*) Pt (0.05 mass %) – Cr (2.5 mass %) – MgO (S_{sp} = 114 $m^2\ g^{-1}$), PhOH – MeOH (1 : 10), 440 °C

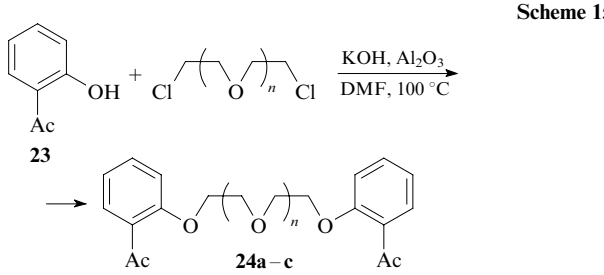
Conditions	Conversion (%)	Selectivity (%)		
		20	**21**	**22**
a	76.1	59.9	36.3	0.1
b [a]	79.1	18.7	30.7	6.5
c	26.0	81.4	18.6	0
d	75.3	34.9	65.1	0

[a] In addition, polyalkylphenols are formed (44.9%).

This is precisely the reason why the methylation occurs at the *ortho*-positions.

The Williamson reaction (O-alkylation of phenols) as applied to *o*-hydroxyacetophenone (**23**) (Scheme 15) is usually accompanied by its self-condensation, which considerably reduces the yield of target product **24**. The introduction of 10 mol.% of bulk Al_2O_3 into the reaction mixture leads to a twofold increase in the yields of compounds **24a** – **c**, while in the presence of the same amount of nano Al_2O_3 (particle size, 20 – 50 nm), the yields increase 2.7 – 3 times.[81]

Scheme 15



n = 0 (**a**), 1 (**b**), 2 (**c**)

Compound **24**	Yield (%)		
	without oxide	with bulk Al_2O_3	with nanosized Al_2O_3
a	29	44	68
b	21	42	57
c	18	39	54

The above effects can be explained by sorption of 2-hydroxyacetophenone (**23**) and(or) its potassium salt on the Al_2O_3 surface being accompanied by the formation of chelate structures. This deactivates the carbonyl group and hinders the competing self-condensation of compound **23**, but not inhibits the Williamson reaction.

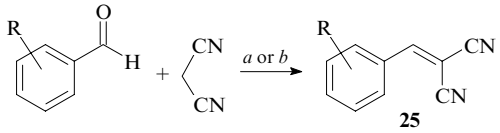
IV. Condensation reactions

IV.1. Knoevenagel condensation

Metal oxides are good catalysts of the Knoevenagel reaction, which is of great importance since its products are key intermediates in synthesis of various pharmacologically active compounds. Although the classical catalysts of the Knoevenagel reaction are bases, acidic and amphoteric oxides turn out to be better. Their advantage is due to the presence of both acid and basic sites so that not only the methylene component but also initial aldehydes are activated, which does not occur in the presence of a base.

In particular, nanosized zirconium oxide promoted by sulfate ions catalyzes the condensation of different aromatic, aliphatic and heterocyclic aldehydes with malononitrile to give product **25** in good yield (78% – 97%) in the absence of a solvent (Scheme 16, conditions *a*).[82]

Scheme 16

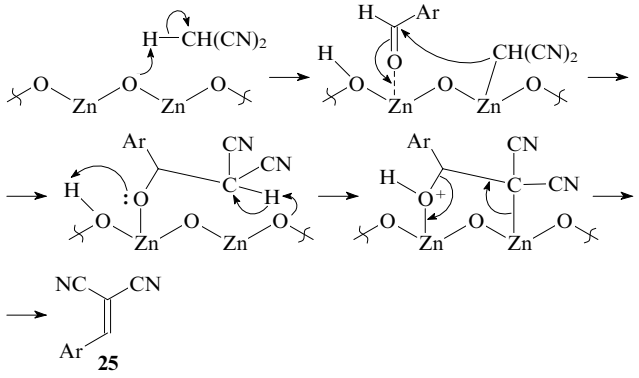


R = 2-NO_2, 4-NO_2, 4-Cl, 4-OH, 4-OMe, 4-Me, 4-CN;
(*a*) SO_4^{2-}/ZrO_2 (particle size 7 – 12 nm, S_{sp} = 100 $m^2\ g^{-1}$), without a solvent, 100 – 150 °C (78% – 97% yield);
(*b*) ZnO (particle size 20 – 30 nm), without a solvent, 23 °C (90% – 98% yield)

The introduction of sulfate groups into the catalyst leads to the increase in the specific surface area and the number of acid sites on the ZrO_2 surface. As compared with Lewis acids, common catalysts of the Knoevenagel condensation, zirconia does not exhibit corrosion activity and can be repeatedly used.

In the absence of a solvent, but at room temperature, the reaction efficiently occurs over nano ZnO (see Scheme 16, conditions *b*).[83] The aldehyde is activated on acid sites Zn^{2+}, and malononitrile is activated on basic O^{2-} sites (Scheme 17). Unfortunately, the authors do not discuss whether the other active sites, such as hydroxy groups and coordinated water molecules typical of the oxide zinc surface, especially of the nano ZnO surface, are involved in reactant activation.

Scheme 17

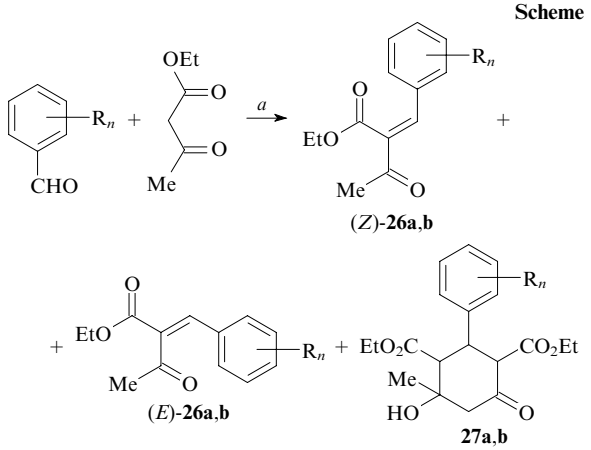


For the condensation of benzaldehyde with ethyl cyanoacetate, CaO supported on activated fly ash (particle size 2–5 m) is used as a heterogeneous catalyst.[84] The activated fly ash is a mixture of silica (54%), alumina, iron, calcium, manganese and titanium oxides and an inert crystalline phase composed of quartz, magnetite and mullite. The major component of the ash — silica — is insufficiently active by itself, but being combined with CaO, which leads to the appearance of Si–O–Ca fragments, exhibits the high activity of a basic catalyst. It is worth noting that the reaction does not occur in the presence of pure CaO or pure ash. The reaction mechanism is analogous to that for ZnO (see Scheme 17), with the difference that the activating acid sites in this case are surface hydroxyl groups.

After the reaction completion, the catalyst is filtered off, washed with acetone, dried at 110 °C and then activated at 700 °C; after that, it is again ready for use.

An efficient catalyst of the Knoevenagel reaction of aromatic aldehydes with ethyl acetoacetate as a CH-active component (Scheme 18) is nanosized alumina in the presence of morpholine.[85] Initially, ketoester **26a** has been synthesized over CuO, Al_2O_3, NiO and MgO nano-oxides (particle size 20–80 nm), the best result being shown by nano alumina (Table 3). Conversely, copper, nickel and magnesium nano-oxides inhibit the reaction. Copper and nickel nano-oxides presumably form a complex with compound **26a**, since the authors note that all ^{1}H NMR signals of the reaction mixtures are broadened.

Scheme 18



R_n = 3-NO_2 (**a**), 2,3-Cl_2 (**b**); (*a*) M_xO_y, morpholine, MeCN, 20 h

Table 3. Synthesis of ketoesters **26** in the presence of different catalysts (see Scheme 18).[85]

Compounds **26**, **27**	Temperature /°C	Metal nano-oxide (0.1 mol)	Yield of **26** (%) (*E*:*Z* ratio) [a]	Yield of **27** (%) [a]
a	60	–	78 (1.0 : 3.1)	8.6
	60	Al_2O_3 (bulk)	71 (1.0 : 3.7)	Traces
	60	MgO	23 (1.0 : 1.0)	45.9
	60	NiO	See [b]	
	60	CuO	See [b]	
	60	Al_2O_3	88 (1.0 : 4.5)	Traces
	40	Al_2O_3	96 (1.0 : 3.7)	Traces
b	25	Al_2O_3	98 (1.0 : 2.4)	–

[a] The yields of compounds **26** and **27** and the ratio of ketoester **26** isomers were determined from ^{1}H NMR spectra. [b] All ^{1}H NMR signals are broadened.

The major product of this reaction over a heterogeneous catalyst is cyclohexanone **27**. For comparison, the catalytic properties of bulk alumina (particle size 0.1–0.16 mm) have been studied. It has been demonstrated that nano Al_2O_3 is a more efficient catalyst of the Knoevenagel reaction as compared with bulk alumina.

The authors do not describe the role of morpholine and the nano-oxide surface in the reaction mechanism; however, it can be suggested that morpholine is sorbed on the acid sites of nano alumina, thus increasing the number of basic groups at the surface.

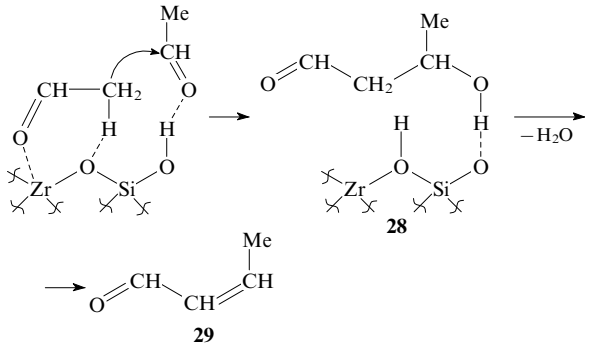
Metal oxides and silica modified with alkali metals also efficiently catalyze the Knoevenagel reaction.[86] In particular, K/Al_2O_3 and K/SiO_2 have shown the best results in condensation of aromatic aldehydes with ethyl acetoacetate (30%–81% yield) on heating under solvent-free conditions. It is likely that modification of oxides with alkali metals, like the addition of morpholine to Al_2O_3, leads to an increase in the content of surface basic groups.

IV.2. Aldol condensation

Acetaldehyde condensation is one of the most common cases of aldol condensation. Traditionally, this reaction is carried out under homogeneous conditions in the presence of an acid and a base. However, in recent time, heterogeneous catalysts have been used more and more often. The best results have been provided by nanosized oxides, both acidic and basic.

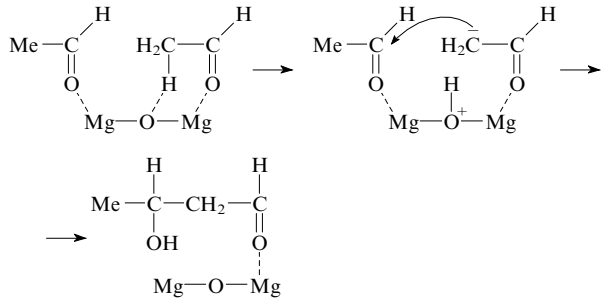
The effect of the basic and acid sites of the catalyst surface on the reaction mechanism has been studied for the acetaldehyde condensation in the presence of SiO_2-supported MgO and ZrO_2 (S_{sp} = 350 m^2 g^{-1}).[87] The acetaldehyde condensation over ZrO_2/SiO_2 occurs on Lewis acid sites (Zr–O) and Brønsted acid sites (silanol groups) (Scheme 19). The suggested mechanism implies the activation of an acetaldehyde molecule on the Zr–O pair, proton transfer from the acetaldehyde methyl group and formation of a C–C bond between the newly formed methylene group and the carbonyl group of the second acetaldehyde molecule protonated on a Brønsted acid site. Then, 3-hydroxybutanal (**28**) is dehydrated to form crotonaldehyde (**29**).

Scheme 19



In the presence of MgO/SiO_2, the reaction can follow two mechanisms. In the first one, the main role is played by strong basic sites represented by the oxygen atoms of magnesium oxide (Scheme 20). The second mechanism is analogous to that suggested for ZrO_2/SiO_2 (see Scheme 19).

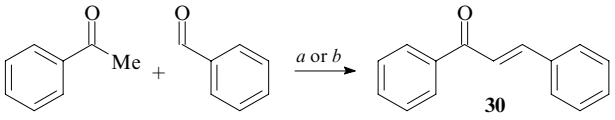
Scheme 20



IR spectroscopy has demonstrated that strong basic sites of the MgO/SiO_2 surface are more reactive in the condensation reaction than the Lewis and Brønsted acid sites of both catalysts. However, the strong basic sites are rapidly deactivated. Therefore, the acetaldehyde condensation in the presence of ZrO_2/SiO_2 and MgO/SiO_2, most likely, occurs by the second mechanism (see Scheme 19).

Nanosized MgO turned out to be an efficient catalyst of the Claisen–Schmidt reaction (Scheme 21).[88,89] Nano MgO with smaller particles and more developed specific surface area affords chalcone **30** with higher chemoselectivity in shorter time. The catalyst is suitable for repeated use without significant loss in activity.

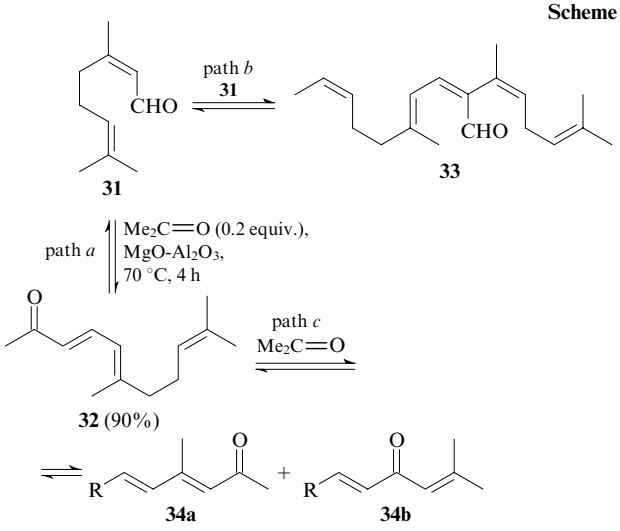
Scheme 21



(*a*) MgO (particle size 6–7 nm, S_{sp} = 115 $m^2\ g^{-1}$), without a solvent N_2, 140 °C, 4 h (99%yield);
(*b*) MgO (particle size 500 nm, S_{sp} = 45 $m^2\ g^{-1}$), PhMe, 100 °C, 8 h (92%)

A catalyst for the condensation of citral (**31**) with acetone (Scheme 22, path *a*) is mixed oxide $MgO\text{-}Al_2O_3$.[90] As distinct from homogeneous catalysis, there is no undesirable self-condensation of acetone in the presence of this catalyst. This is likely due to the sorption of its carbonyl group analogously to 2-hydroxyacetophenone.[81] In addition to product **32**, gas chromatography and mass spectrometry reveal the presence of trace amounts of compound **33**, which is a result of self-condensation of two citral molecules (see Scheme 22, path *b*), as well as a mixture of compounds **34a**,**b** (the ratio is unknown), which are a result of the aldol condensation of compound **32** with acetone (see Scheme 22, path *c*).

Scheme 22

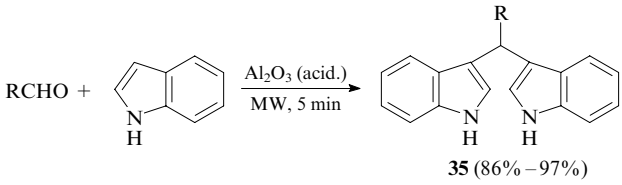


R = 2,6-dimethyl-1,5-heptadienyl

IV.3. Synthesis of bis(indolyl)methane and its derivatives

Bis(indolyl)methane and its derivatives **35** have wide synthetic and biological application. This causes great interest in such compounds and is responsible for a large number of procedures suggested for their synthesis.[91–99] One of these procedures is solvent-free condensation of indole with aldehydes over bulk acidic Al_2O_3 under microwave (MW) irradiation (Scheme 23).[100]

Scheme 23

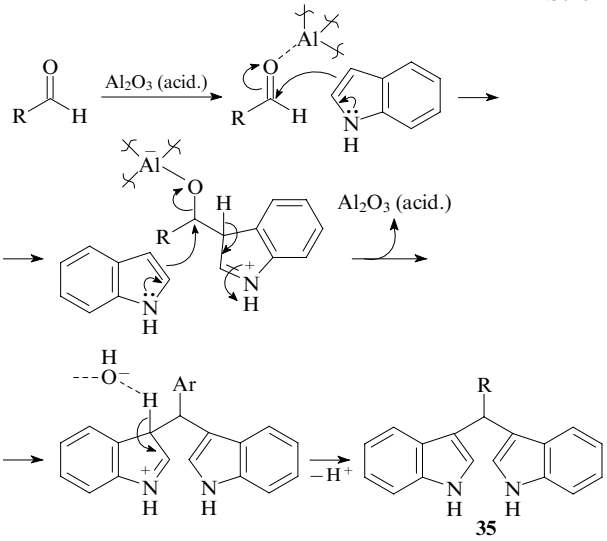


R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-HOC_6H_4, 4-$O_2NC_6H_4$, 2-Py, 2-Fu, 2-Th, 3,4-(methylenedioxy)benzyl; Py is pyridyl, Fu is furyl, Th is thienyl

Although, as stated by the authors, this reaction occurs without a catalyst as well, the use of acidic alumina leads to a twofold increase in the yield and reduces the reaction duration from 25 to 5 min.

To explain the role of alumina in synthesis of bis(indolyl)methane derivatives **35**, a probable reaction mechanism has been proposed in which the key step is coordination of the aldehyde carbonyl group to the Lewis acid sites Al^{3+} (Scheme 24).

Scheme 24

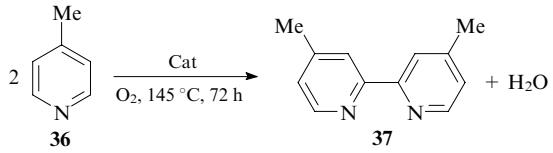


After four cycles of the reaction over alumina, the yield of product **35** decreased only by 7%.

IV.4. Synthesis of bipyridines

The direct reaction of two molecules of 4-methylpyridine (**36**) to give 4,4′-dimethyl-2,2′-bipyridine (**37**) in the presence of palladium oxide (Scheme 25) is a simple and environmentally safe one-stage method of synthesis of bipyridines.

Scheme 25



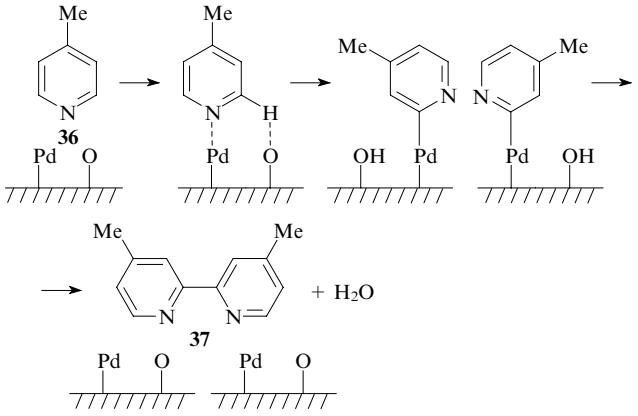
However, the palladium catalyst is deactivated in the course of reaction. Therefore, to improve the economic efficiency of the large-scale bipyridine synthesis by this method, the catalyst has been optimized, namely, palladium catalysts have been produced in which 5% Pd has been supported on different bulk and nano metal oxides: Al_2O_3, MgO, TiO_2, CaO, ZnO, CeO_2, ZrO_2, SnO_2 and CuO (Table 4).[101–105]

Table 4. Search for the optimal catalyst for synthesis of bipyridines (see Scheme 25).

Support	S_{sp} /m^2 g^{-1}	Yield of **37** g g^{-1} of catalyst	Ref.
Activated carbon	600	1.8	104
nano-Al_2O_3	695	2.5	104
nano-MgO	685	2.3	102
nano-TiO_2	505	1.6	102
Porous TiO_2	120	1.6	103
nano-CaO	100	0.15	101
nano-ZnO	70	2.1	101
nano-CeO_2	60	1.5	101
nano-ZrO_2	35	2.3	103
nano-SnO_2	35	0.5	101
nano-ZrO_2 + 10% nano-CeO_2	45	2.45	101
nano-CuO	35	0	101

The first step in the catalytic cycle of this reaction is most likely the coordination of the nitrogen atom of 4-methylpyridine (**36**) to the nano-oxide-supported palladium atoms (Scheme 26). The C–H bond is activated through the coordination of the hydrogen atom to a surface oxygen atom to give a surface hydroxyl group, and the pyridine molecule is coordinated to the surface through a carbon atom rather than the nitrogen atom. Then, two coordinated 4-methylpyridine molecules are eliminated to form product **37**. The authors believe that two surface hydroxyl groups form a water molecule, and its desorption leaves a vacant site filled with an oxygen molecule. Thus, the catalyst surface is regenerated.

Scheme 26



The reaction turned out to be sensitive to the characteristics of the support surface. The active catalysts can be classified into two types: (1) palladium supported on a material with a very large surface area (Pd/nano-Al_2O_3 and Pd/nano-MgO) and (2) palladium supported on a metal oxide with a small surface area but responsible for a strong palladium–support interaction [Pd/ZrO_2, Pd/(nano-ZrO_2 + nano-CeO_2) and Pd/nano-ZnO]. The most economically attractive supports (providing high yield of the product at a relatively low cost of oxides) are nano ZnO and porous TiO_2.

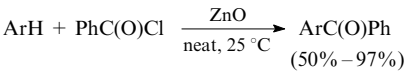
More complex catalytic systems of general formula PdO/M^1O_y/nano-$M^2_xO_y$ (M^1O_y = ZnO, CeO_2, CrO_2; nano-$M^2_xO_y$ = Al_2O_3, MgO, TiO_2) also show rather high chemoselectivity in this reaction.[102]

IV.5. Friedel–Crafts reaction

In the classical Friedel–Crafts reaction, an aromatic compound is subjected to an electrophilic attack of an acylating agent in the presence of >1 equiv. of an acidic catalyst (for example, $AlCl_3$) to give the appropriate ketone. In this case, the catalyst is difficult to separate from the reaction mixture, activate and use again. In addition, the reaction leads to environmentally hazardous by-products.

Metal oxides with active acid sites can be successfully substituted for traditional Lewis acids in this reaction. In particular, in the presence of bulk ZnO, the reaction occurs at room temperature with high yields of the product (Scheme 27). Zinc oxide has all advantages of a heterogeneous catalyst as distinct from traditional Lewis acids.[106]

Scheme 27



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-methoxynaphthyl, 2-Fu

This method provides fast (in 5–10 min) and selective reactions of aromatic compounds. Only in a few cases, weak resonance lines of the remaining reactants are observed in ^{1}H NMR spectra. Even unreactive benzene derivatives, such as chlorobenzene, are converted into corresponding ketones in high yield over ZnO.

It is worth noting that acylation occurs selectively in the *para*-position to the OMe, Me and Cl substituents in nearly quantitative yield. If the *para*-position is blocked, the acyl group occupies the *ortho*-position. This procedure is also suitable for acylation of heterocyclic compounds. The reactions of benzene and anthracene with benzoyl chloride turned out to be less efficient: even after stirring for 2 h, the yield of the target product was only 50%.

An advantage of using ZnO as a catalyst of the Friedel–Crafts reaction is the absence of elimination of one of the ether groups in 1,4-dimethoxybenzene as distinct from the procedure where BF_3 is used as a catalyst.[107]

Study of the reaction mechanism in the presence of ZnO has shown that the reaction of the catalyst with hydrochloric acid leads to the *in situ* formation of $ZnCl_2$, which catalyzes the reaction. In the absence of a chlorine-containing agent, for example, when acid anhydride rather than acid chloride and ZnO as a catalyst are used, acylation is not observed.[106] Other oxides (HgO, Al_2O_3, SiO_2, Ag_2O, Fe_2O_3) turn out to be inefficient catalysts of this reaction.

As mentioned above, macroporous metal oxides are more catalytically active than their bulk counterparts. The same yield of the target product is achieved when 0.5 mmol of bulk ZnO or 0.25 mmol of macroporous ZnO is loaded.

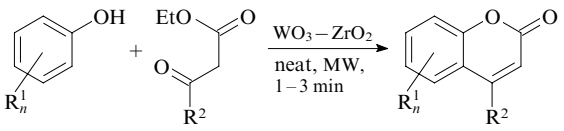
The CuO, NiO and Mn_2O_3 oxides, despite their macroporous structure, turned out to be inactive catalysts of the acylation reaction. This is explained by the fact that the above oxides are unable to form salts — Lewis acids, necessary for catalysis of this reaction. This explanation is supported by the fact that the reaction is activated by the CoO and CrO oxides forming *in situ* Lewis acids $CoCl_2$ and $CrCl_2$.

IV.6. Pechmann reaction

The Pechmann reaction is the acid-catalyzed condensation of phenol with ketoesters to give corresponding coumarins. As a rule, the catalysts of this reaction are Lewis acids and mineral and organic acids (H_2SO_4, P_2O_5, $FeCl_3$, HCl, $TiCl_4$, $ZnCl_2$, CF_3CO_2H).[108 – 112] The reaction is carried out in a solvent at 100 – 150 °C.

Mixed nano-oxide WO_3 (10 mol.%) – ZrO_2 (particle size 10 – 25 nm) is an efficient catalyst of the microwave-assisted condensation of phenols with ethyl acetoacetate and ethyl benzoylacetate (Scheme 28). Major advantages of using $WO_3 - ZrO_2$ as the catalyst are the simplicity of the experiment, the absence of a solvent, repeated use of the catalyst, the high yield (76% – 92% depending on the substituents) and the high purity of coumarins **38** at short reaction times.[113]

Scheme 28



38 (76% – 92%)

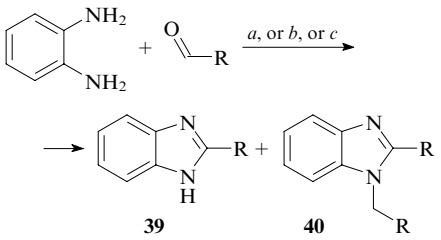
R^1_n = H, 2-OH, 3-OH, 4-OH, 2,3-$(OH)_2$, 3,5-$(OH)_2$, 2-Me;
R^2 = Me, Ph

IV.7. Condensation of amines with aldehydes

Metal oxides are efficient catalysts of the condensation of *o*-diaminobenzene with aldehydes. The reaction in the absence of a catalyst gives a mixture of 2- and 1,2-substituted benzimidazoles **39** and **40** (Scheme 29).[114]

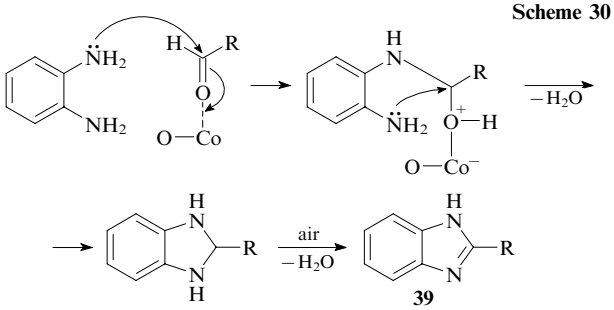
The condensation of diaminobenzene with aldehydes in the presence of bulk CoO and air oxygen in ethanol at room temperature occurs under mild conditions in short time to give target 2-substituted benzimidazoles **39** in 73% – 96% yield (depending on the initial aldehyde).[114] No traces of by-products **40** are observed. The authors suggest a reaction mechanism in which the key stage is coordination of the aldehyde carbonyl group to the catalyst surface (Scheme 30).

Scheme 29

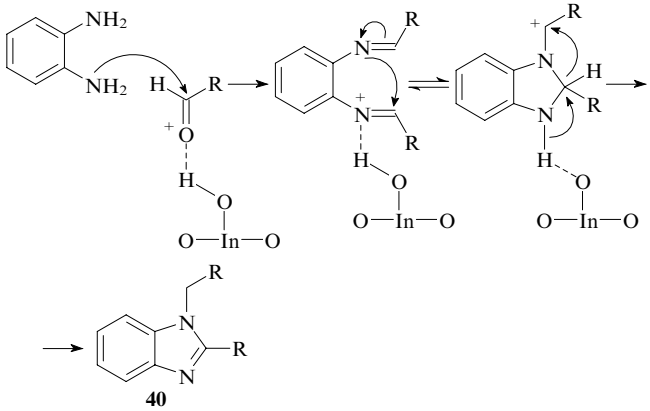


R = Ar, Alk, Het;
(*a*) CoO, EtOH, 25 °C (73% – 96% **39**, 0% **40**);
(*b*) In_2O_3, EtOH – H_2O, 60 °C (0% **39**, 84% – 92% **40**);
(*c*) Al_2O_3-Fe_2O_3, Al_2O_3-V_2O_5, Al_2O_3-CuO, neat, MW (0% **39**, 82% – 90% **40**)

Scheme 30



Scheme 31



The use of nano In_2O_3 (Ref. 115) or mixed nano-oxides Al_2O_3-Fe_2O_3, Al_2O_3-V_2O_5 and Al_2O_3-CuO (particle size 20 – 50 nm)[116] as the catalyst drives the reaction toward the formation of 1,2-disubstituted benzimidazole **40** (Scheme 31). Compound **39** in this case is not formed.

Under analogous conditions,[116] 2-substituted benzothiazoles are synthesized, using *o*-sulfanylaniline instead of diaminobenzene. In all cases, the high selectivity is observed for aliphatic (78% – 80%), aromatic (83% – 89%) and heteroaromatic aldehydes.

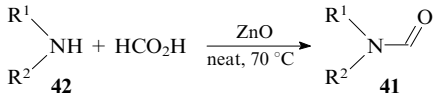
V. N-Formylation, N-acylation, N-alkylation and N-arylation reactions

N-Formylation is an important reaction in organic synthesis since it affords various formamides, which serve as intermediates in synthesis of pharmacologically active com-

pounds.[117] The classical reaction of an amine and formic acid is carried in a solvent under reflux for a rather long period of time. Metal oxides catalyze this reaction, acting as uncommon Lewis acids and facilitating the formation of a carbocation from a carbonyl-containing reactant. The catalysis efficiency increases with an increase in the specific surface area of the metal oxide.

Commercially available bulk ZnO catalyzes solvent-free synthesis of both aliphatic and aromatic substituted formamides **41** from amines **42** in high yields of 65%–99% (Scheme 32).[118]

Scheme 32

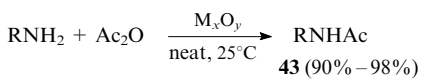


R^1 = Ar, Alk; R^2 = Ar, Alk, H

Study of the catalytic activity of ZnO separated from the reaction mixture has shown that the yield of product **41** after the first, second and third cycles of catalyst operation remains almost unaltered (90%, 86% and 84%, respectively). The use of macroporous transition metal oxides (CuO, NiO, CoO, Mn_2O_3, Cr_2O_3 and ZnO) makes it possible to increase the yields of both the aromatic and aliphatic formamides. This is caused by the increase in the active surface area of metal oxides due to their porous structure as compared with commercially available bulk metal oxides.[119, 120]

The use of macroporous transition metal oxides (CuO, NiO, CoO, Mn_2O_3, Cr_2O_3 and ZnO) in the N-acylation reaction (Scheme 33) also leads to target products **43** in high yields (90%–98%).[119]

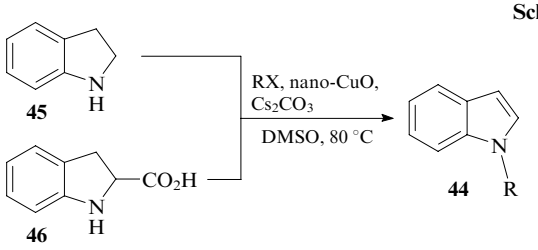
Scheme 33



R = Ar, Alk

N-Substituted indoles play an important role in organic chemistry, pharmaceutics and agricultural chemistry, as well as in materials science, and, therefore, are actively studied. In particular, Reddy *et al.*[121] have developed a protocol for the synthesis of N-substituted indoles **44** through aromatization of indoline (**45**) or 2-carboxyindoline (**46**) followed by the attack with aryl(alkyl) halide in the presence of nano CuO as a heterogeneous catalyst and Cs_2CO_3 as a base (Scheme 34). Unfortunately, the authors do not discuss the mechanism of action of metal oxides as catalysts.

Scheme 34

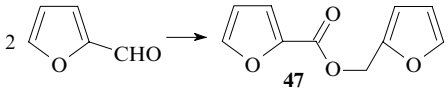


X = I, Br; for **45**: R = Ar, Het, Alk (69%–84% yield of **44**);
for **46**: R = Ar (73%–85% yield of **44**)

VI. Tishchenko reaction

The Tishchenko reaction is the dimerization of aldehydes to give the corresponding esters, for example, compound **47** (Scheme 35).

Scheme 35



When furfural is used as the initial aldehyde, traditional reaction catalysts — aluminium alkoxide and boric acid — do not lead to a desired product,[122, 123] and modern homogeneous catalysts $(\eta^5\text{-}C_5Me_5)_2LaCH(SiMe_3)_2$ and $La[N(SiMe_3)_2]_3$ require long reaction times and provide low yields of the product.[124] It turned out that, among alkaline earth metal oxides MgO (S_{sp} = 267 $m^2\ g^{-1}$), CaO, SrO and BaO (S_{sp} = 12–48 $m^2\ g^{-1}$), calcium and strontium oxides are efficient catalysts of furfural dimerization *via* the Tishchenko reaction.[125] In the presence of CaO or SrO, target product **47** is synthesized in 75%–95% yield at 80 °C in 4–6 h. Although bulk MgO was active in the Tishchenko reaction for pivalaldehyde (50% conversion),[126] the yield of the product of furfural dimerization in the presence of this oxide was <1%.

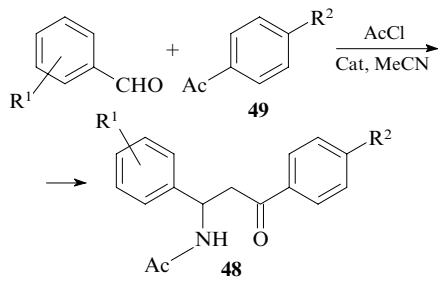
VII. Multicomponent reactions

Multicomponent reactions (MCRs) is an important subclass of tandem reactions in which at least three readily available components react in one reactor to give a product containing all atoms of the initial reactants. Such reactions make it possible to easily and quickly amass huge libraries of organic compounds and are also a perfect instrument for the creation of large organic molecules and complexes. Multicomponent reactions proceed in several stages and often require the presence of acidic or basic catalysts. Therefore, metal oxides with active sites of different nature are promising catalysts of MCRs. It should be noted that one of the reactants in the vast majority of the MCRs is an aldehyde and(or) a ketone with the carbonyl group capable of being coordinated to the oxide surface. This can have a positive effect on the reactivity of the aldehyde (ketone).

VII.1. Synthesis of acetamido- and aminoketones

The most common method of synthesis of acetamido- and aminoketone derivatives is the condensation of α-amino acids with acetic anhydride in the presence of a base by the Dakin–West reaction.[127] Recently, there has been developed an alternative multicomponent synthesis of β-acetamidoketones **48** through condensation of an aromatic aldehyde, a derivative of acetophenone **49** and acetyl chloride (Scheme 36) in acetonitrile in the presence of Lewis or Brønsted acids, such as $CoCl_2$,[128] $ZrOCl_2 \cdot 8\,H_2O$,[129] $CeCl_3 \cdot 7\,H_2O$,[130] $Sc(OTf)_3$ (Tf = CF_3SO_2), heteropoly acids, $FeCl_3 \cdot 6\,H_2O$,[131] $SiCl_4$–$ZnCl_2$,[132] $Zr(HSO_4)_4$ and $Mg(HSO_4)_2$.[133]

Scheme 36

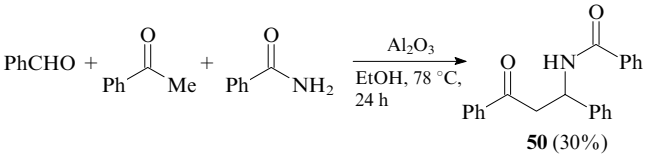


R^1 = H, Cl, Me, NO_2; R^2 = H, Cl, Me

An attempt to carry out this synthesis [for the synthesis of *N*-(3-oxo-1,3-diphenylpropyl)acetamide (**48a**; $R^1 = R^2 = H$) as an example] under heterogeneous catalysis conditions showed that, among bulk oxides CuO, Fe_2O_3, CdO, TiO_2, Th_2O_3, Al_2O_3 and ZnO, the last one was most efficient: it afforded a target product in 90% yield in 6 h.[134] When nano ZnO (particle size 30 nm) was used, 88% yield of products was achieved in 1 h.[135]

The synthesis of β-amidoketones through direct condensation of aldehyde, enol and amide turned out to be impossible in the presence of Lewis acids ($ZnCl_2$, $CuCl_2$, $MgCl_2$, $FeCl_3$, *etc.*), but in the presence of Al_2O_3, a target product, for example, amidoketone **50**, was obtained in moderate yield (Scheme 37).[136]

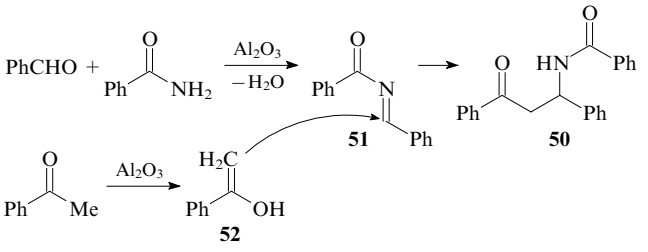
Scheme 37



50 (30%)

It is assumed that the condensation of the aldehyde and amide gives intermediate **51**, which is then attacked by the enol form of ketone **52** to give target product **50** (Scheme 38).

Scheme 38

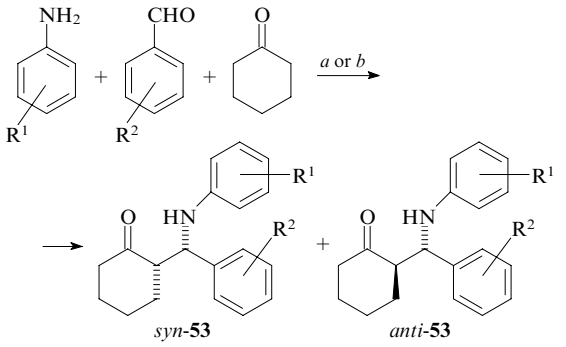


It should be noted that good yields in the reaction are achieved only when aromatic aldehydes with electron-donating substituents are used. If aldehydes contain strong electron-withdrawing substituents, a desired product does not form, which is likely due to the difficulty of formation of key intermediate **51**.

VII.2. Mannich reaction

The Mannich reaction is a classical method of synthesis of β-aminoketones. A highly efficient method of condensation of aldehydes, ketones and amines in the presence of ZnO nanoparticles has been reported [137] (Scheme 39, path *a*).

Scheme 39



R^1 = H, 3-NO_2, 4-Cl, 4-NO_2, 4-Me;
R^2 = H, 3-NO_2, 3-F, 4-Cl, 4-NO_2, 4-Me, 4-OMe;
(*a*) ZnO (particle size 105 nm), H_2O, 60 °C (74%–93% yield);
(*b*) WO_x-ZrO_2 (particle size 12–16 nm, S_{sp} = 35 $m^2\ g^{-1}$, neat, 23°C, N_2 (79%–92% yield)

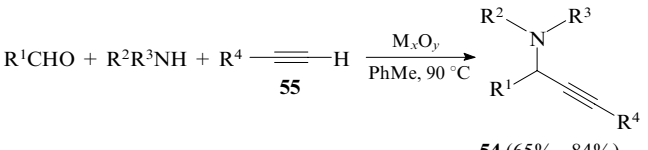
For the condensation of 4-chlorobenzaldehyde, aniline and cyclohexanone as an example, it has been shown that target product **53** is not formed in the presence of classical Lewis acids ($ZnCl_2$, $ZnSO_4$ and $CuCl_2$). At the same time, nano ZnO efficiently catalyzes this reaction, and the best solvent for it is water. The procedure is applicable for aromatic aldehydes and amines with both electron-donating and electron-withdrawing substituents. The authors have isolated the *syn* and *anti* isomers of compounds **53**; however, they have not discussed the effect of the catalyst on the formation of a certain isomer.

The Mannich reaction also occurs in high yield in the presence of the WO_x-ZrO_2 catalyst at room temperature under solvent-free conditions (Scheme 39, path *b*).[138] ZrO_2 itself did not show the catalytic activity; however, its doping with WO_x led to a significant increase in the porosity of the catalyst surface, as well in the strength and number of active acid sites.

VII.3. Synthesis of propargylamines

Metal oxides are widely used as catalysts of the condensation of an aldehyde, an amine and an alkyne. Propargylamines **54** obtained by this reaction (Scheme 40) are intermediates in synthesis of biologically active compounds, such as β-lactams, conformationally hindered peptides, *etc.*

Scheme 40



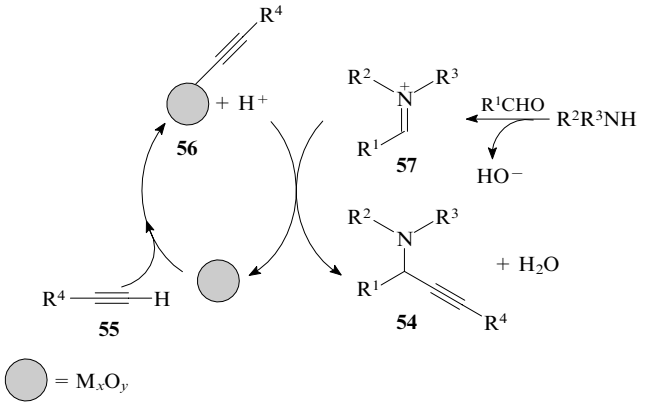
54 (65%–84%)

R^1 = Ar, cyclo-C_6H_{11}; R^2, R^3, R^4 = Alk, Ph

Almost all researchers carry out the reaction in toluene at 90–100 °C. As heterogeneous catalysts, both readily available nano CuO,[139] Fe_3O_4 [140, 141] and ZnO (particle size 10–50 nm; S_{sp} = 100–200 $m^2\ g^{-1}$),[142] and less common nano In_2O_3 [143] and Co_3O_4 (particle size 45 –90 nm; S_{sp} = 27–50 $m^2\ g^{-1}$) [144] and MgO with supported gold nanoparticles [145] (S_{sp} = 143 $m^2\ g^{-1}$; gold particle size 10–12 nm) are used. The reactants are aromatic and aliphatic aldehydes and amines.

A putative mechanism of formation of propargylamines **54** catalyzed by nano metal oxides is shown in Scheme 41.[139]

Scheme 41

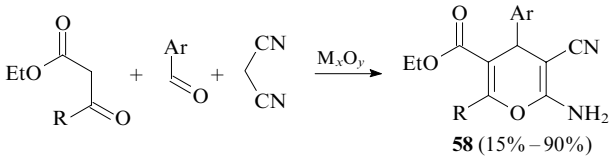


The authors of Refs 139–145 believe that the role of the nano oxide is to activate the terminal C–H bond of acetylene substrate **55** through interaction with basic sites. Then, metal acetylenide intermediate **56** reacts with ionic iminium intermediate **57**, produced *in situ* from aldehyde and amine, to give corresponding propargylamine **54**.

VII.4. Synthesis of 4*H*-pyrans

Multicomponent reactions are an efficient tool for constructing various heterocyclic systems. The effect of heterogeneous catalysts (MgO, $MgO\text{-}La_2O_3$, $MgO\text{-}SnO_2$, $MgO\text{-}Al_2O_3$, Al_2O_3, CaO, SnO_2) on the reaction of substituted benzaldehydes, malononitrile and active methylene components as a model system for synthesis of corresponding 4*H*-pyrans **58** (Scheme 42) has been described.[146–148] It has been noted that aldehydes with electron-withdrawing substituents more readily react with the other components than aldehydes bearing an electron-donating substituent (Table 5).

Scheme 42

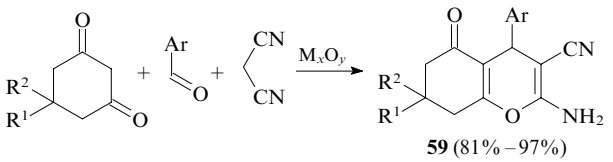


R = Me, CH_2CO_2Et, OEt; Ar = Ph, $4\text{-}MeC_6H_4$, $4\text{-}MeOC_6H_4$, $4\text{-}ClC_6H_4$, $4\text{-}HOC_6H_4$, $4\text{-}O_2NC_6H_4$, $4\text{-}NCC_6H_4$

In this reaction, basic sites of the catalyst presumably play an important role. It has been reported[146, 148–150] that mixed oxides $MgO\text{-}La_2O_3$ and $MgO\text{-}SnO_2$, exhibiting the highest regioselectivity, contain the largest number of strong basic sites on the surface as compared with the other catalysts under consideration.

ZnO, MgO and $MgO\text{-}SnO_2$ oxides also efficiently catalyze the reaction when ethyl acetoacetate is replaced by more complex diketones, including cyclic; products **59** are obtained in high yield (Scheme 43).[147, 151]

Scheme 43



R^1, R^2 = H, Me

Other 4*H*-pyran derivatives, namely, pyranopyrazoles **60** (Scheme 44), have also been synthesized in the course of

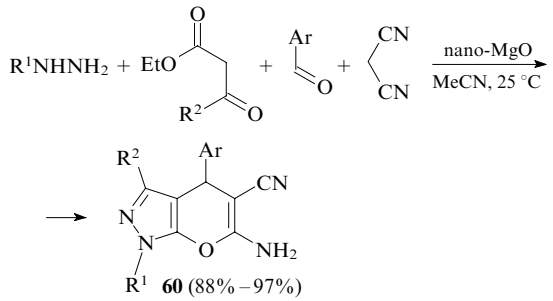
Table 5. Different heterogeneous catalysts in synthesis of 4*H*-pyrans **58** (see Scheme 42).

Catalyst [a]	Ar	R	Solvent [b]	T/°C	Yields **58** (%)	Ref.
MgO	$4\text{-}ClC_6H_4$	Me	MeOH	65	67	146
MgO	Ph	Me	–	24	49	147
SnO_2	Ph	Me	–	24	12	147
CaO	Ph	Me	–	24	50	147
$MgO\text{-}Al_2O_3$	Ph	Me	–	24	53	147
$MgO\text{-}La_2O_3$	$4\text{-}ClC_6H_4$	Me	MeOH	65	92	146
$MgO\text{-}La_2O_3$	Ph	Me	MeOH	65	83	146
$MgO\text{-}La_2O_3$	$4\text{-}O_2NC_6H_4$	Me	MeOH	65	88	146
$MgO\text{-}La_2O_3$	$3\text{-}O_2NC_6H_4$	Me	MeOH	65	86	146
$MgO\text{-}La_2O_3$	$4\text{-}NCC_6H_4$	Me	MeOH	65	90	146
$MgO\text{-}La_2O_3$	$4\text{-}HOC_6H_4$	Me	MeOH	65	79	146
$MgO\text{-}La_2O_3$	$4\text{-}MeC_6H_4$	Me	MeOH	65	87	146
$MgO\text{-}La_2O_3$	$4\text{-}MeOC_6H_4$	Me	MeOH	65	82	146
$MgO\text{-}La_2O_3$	$4\text{-}ClC_6H_4$	CH_2CO_2Et	MeOH	65	87	146
$MgO\text{-}La_2O_3$	$4\text{-}MeC_6H_4$	CH_2CO_2Et	MeOH	65	76	146
$MgO\text{-}La_2O_3$	$4\text{-}HOC_6H_4$	CH_2CO_2Et	MeOH	65	15	146
$MgO\text{-}SnO_2$ (particle size 150 nm, $S_{sp} = 115\ m^2\ g^{-1}$)	$4\text{-}ClC_6H_4$	Me	–	24	93	147
$MgO\text{-}SnO_2$	$4\text{-}MeC_6H_4$	Me	–	24	72	147
$MgO\text{-}SnO_2$	$4\text{-}MeOC_6H_4$	Me	–	24	59	147
$MgO\text{-}SnO_2$	$4\text{-}F_3CC_6H_4$	Me	–	24	97	147

[a] Characteristics are given only for $MgO\text{-}SnO_2$; [b] a dash means solvent-free conditions.

a multicomponent reaction, but in the presence of nano MgO (particle size 100–200 nm) as a catalyst.[152]

Scheme 44



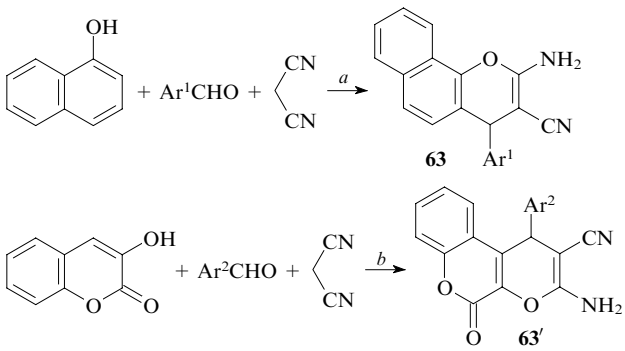
R^1 = H, Ph; R^2 = Me, Pr^n, Pr^i; Ar = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 2-ClC_6H_4, 4-$O_2NC_6H_4$, 4-BrC_6H_4, 3-BrC_6H_4

Comparison of the catalytic activity of commercially available MgO (yield of the product of 83% in 90 min) with the activity of nano MgO (97% in 10 min) is reliable evidence that the latter is more efficient. The mechanism of this reaction involves formation of arylidenemalononitrile **61** in quantitative yield from aldehyde and malononitrile by the Knoevenagel reaction with subsequent loss of a water molecule (Scheme 45).

This stage is very fast since metal oxides are efficient catalysts of the Knoevenagel reaction.[82–84] On the whole, the formation of target product **60** involves the following sequence of reactions: the formation of pyrazolone **62**, the Knoevenagel condensation of aldehyde with malononitrile, the Michael addition of pyrazolone **62** to arylidenemalononitrile **61** followed by cyclization and tautomeric transformation. Nano oxides analogously activate the initial reactants and intermediates in the above synthesis of pyrans **58** and **59**.

Nano ZnO and MgO (particle size 100–200 nm) are also efficient catalysts of the multicomponent synthesis of 2-amino-4*H*-chromenes **63** and dihydropyrano[2,3-*c*]chromen-2-ones **63′** (Scheme 46),[151,153–155] which are widely used in cosmetic and agrochemical industry.[156,157] As in synthesis of pyranopyrazoles **60**,[152] nano MgO exhibits a higher catalytic activity (yield of 70% in 50 min) than bulk MgO (53% in 60 min). Although the specific role of MgO in the reaction mechanism has not been revealed, the authors note that the reaction product is not formed in the absence of the oxide.

Scheme 46



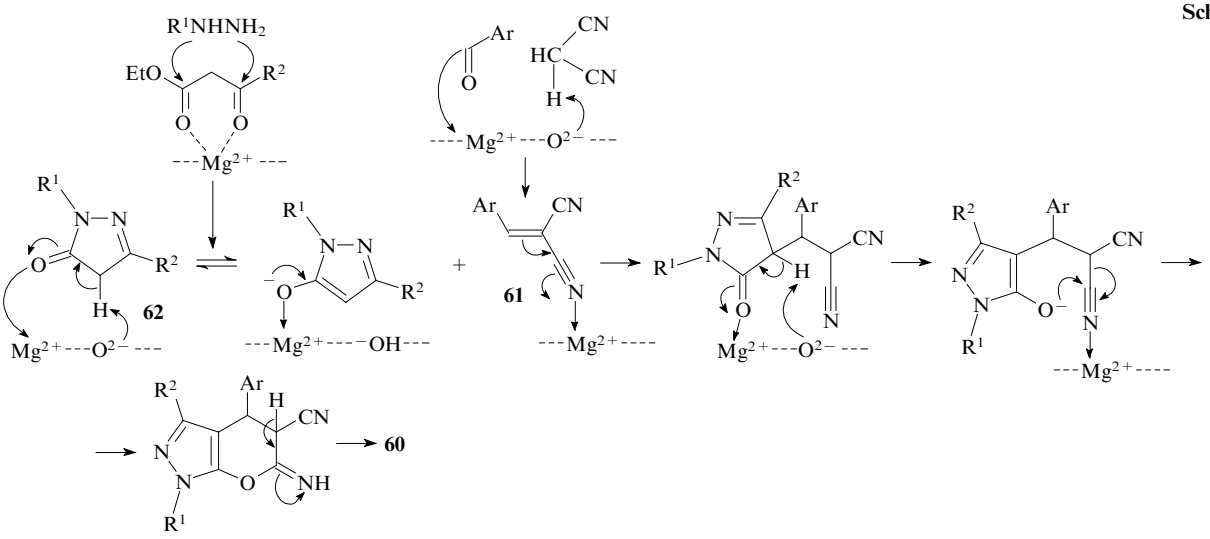
Ar^1 = Ph (96% yield), 4-$MeOC_6H_4$ (95%), 3-$O_2NC_6H_4$ (96%), 4-$O_2NC_6H_4$ (97%), 4-ClC_6H_4 (89%), 2-Fu (87%);
Ar^2 = Ph (87%), 4-$O_2NC_6H_4$ (91%), 4-$MeOC_6H_4$ (78%), 4-BrC_6H_4 (89%), 4-MeC_6H_4 (83%), 4-NCC_6H_4 (90%), 4-FC_6H_4 (90%);
(*a*) nano-MgO, MeOH, 40 °C, 1 h; (*b*) nano-ZnO, H_2O, 70 °C, ~3 h

The activity of nano ZnO in this reaction is explained by its amphoteric properties. In particular, at the first stage, it catalyzes the Knoevenagel reaction as a base, and then, as a weak acid, it activates the nitrile group for the reaction with the hydroxyl group.[154] We believe that MgO, like ZnO, catalyzes this reaction due to the presence of both basic and acid sites on its surface.

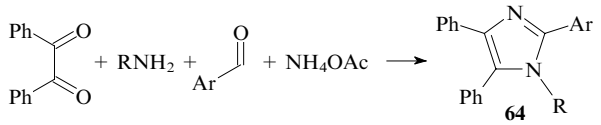
VII.5. Synthesis of imidazoles

Biologically active substituted imidazoles **64** are synthesized through condensation of a 1,2-diketone, an aromatic aldehyde and an amine (Scheme 47). The effect of bulk MgO, CaO, BaO[158] and ZnO,[159,160] as well as of nano MgO (particle size 12 nm; S_{sp} = 116 $m^2\ g^{-1}$)[158], on the chemoselectivity of the multicomponent reaction of synthesis of 1,2,4,5-tetrasubstituted and 2,4,5-trisubstituted imidazoles (the latter are formed in the absence of RNH_2) has been studied.

Scheme 45



Scheme 47



R = Ph, 4-MeC_6H_4, 4-ClC_6H_4, Bn; Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 2-HOC_6H_4, 4-HOC_6H_4, 2-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$

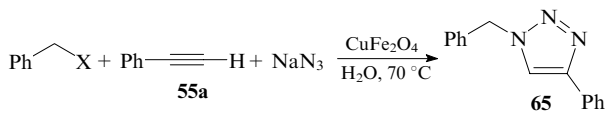
Under solvent-free conditions at 100 °C, bulk ZnO (95%–99% yield) and nano MgO (92%–95%) turned out to be more efficient;[158] at room temperature, high yields (93%) were achieved only in the presence of zinc oxide in acetonitrile.[160]

Bahrami *et al.*[159] have suggested that sorption onto metal oxides increases the electrophilicity of the aldehyde carbonyl group, which facilitates the electrophilic attack of the nitrogen atoms of ammonia, formed from NH_4OAc, and amine. The resulting intermediate reacts with dibenzoyl to give 1,2,4,5-tetrasubstituted imidazole.

VII.6. Synthesis of triazoles

Nano copper ferrite $CuFe_2O_4$ has been suggested as a new catalyst of the classical synthesis of 1,2,3-triazoles **65** with the use of phenylacetylene (**55a**) and metal azide (Scheme 48).[161] Using this catalyst, it was possible to decrease the reaction temperature from 125 to 70 °C and exclude the use of organic solvents. This approach has been extended to a wide range of substrates. An evident advantage of $CuFe_2O_4$ is the ease of separating it by magnetic decantation.

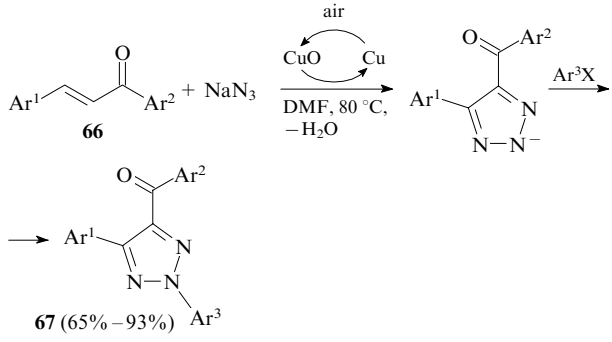
Scheme 48



X = Br, Cl

The use of chalcone **66** instead of alkyne **55a** leads to N(2)-substituted 1,2,3-triazoles **67** (Scheme 49).[162]

Scheme 49



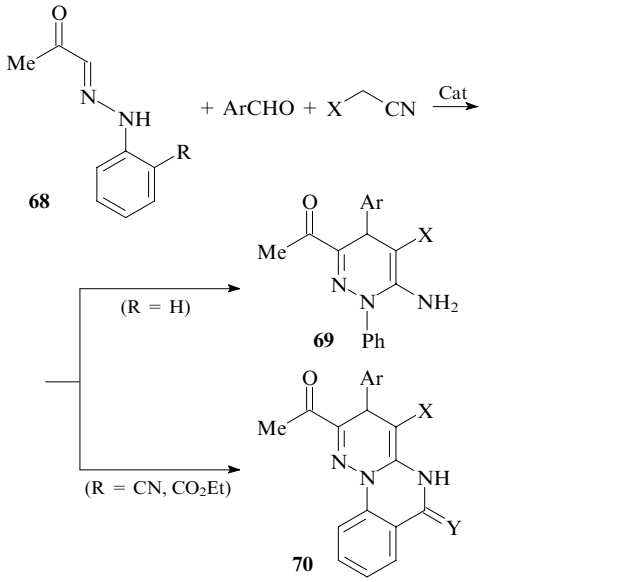
Ar^1 = Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-FC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$;
Ar^2 = Ph, 4-ClC_6H_4, 4-$O_2NC_6H_4$, 4-BrC_6H_4, 4-$MeOC_6H_4$;
Ar^3X = 2-$O_2NC_6H_4F$, 2-$O_2NC_6H_4Cl$, 2,4-$(NO_2)_2C_6H_3Cl$, 2,5-$F_2C_6H_3NO_2$, 3,4-$F_2C_6H_3NO_2$, 2-MeC_6H_4Cl

Bulk CuO, like in the above example, acts as the copper source. In the course of reaction, copper is again oxidized to oxide with air oxygen. It is worth noting that, in the absence of the catalyst, the reaction with alkynes as initial compounds becomes slower, and the reaction with chalcone **66** does not occur at all.

VII.7. Synthesis of pyridazines

The multicomponent reaction of arylhydrazones **68** with an aldehyde and malononitrile (or ethyl cyanoacetate) in the presence of bulk MgO afforded a series of 3-amino-2,5-dihydropyridazines **69** and fused pyridazinoquinazolines **70** (Scheme 50).[163]

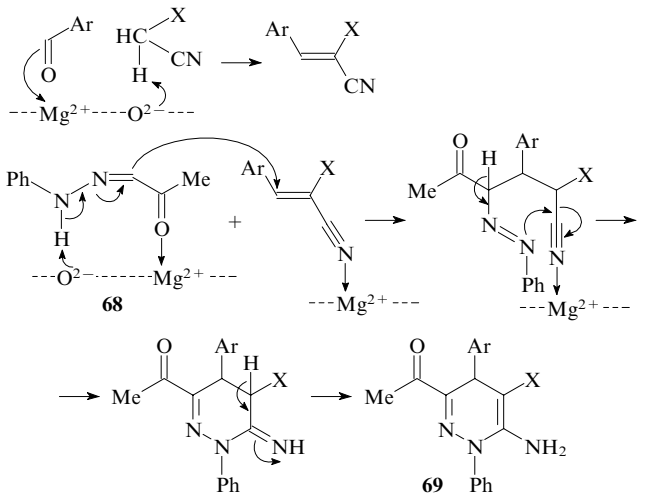
Scheme 50



R = H, CN, CO_2Et; X = CN, CO_2Et; Ar = Ph, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 4-MeC_6H_4, 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$; Y = O, NH

The mechanism of this reaction in the presence of a heterogeneous catalyst is shown in Scheme 51.[163]

Scheme 51

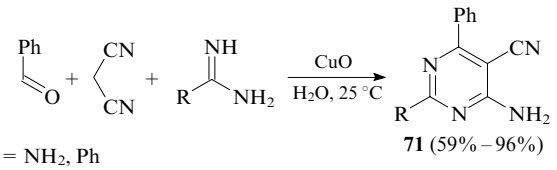


VII.8. Synthesis of substituted dihydropyrimidines

An efficient route to 4-aminopyrimidine-5-carbonitriles **71** *via* three-component condensation of malononitrile, an aldehyde and an N-substituted amine (Scheme 52) in an

aqueous solution in the presence of copper oxide microspheres has been suggested by Ahmadi *et al.*[164]

Scheme 52



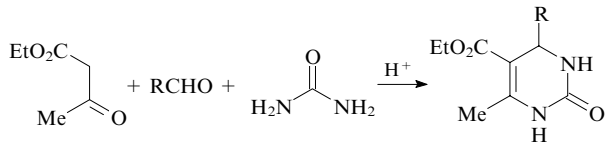
R = NH_2, Ph

71 (59% – 96%)

Among copper oxides with different particle size — nano (5 nm), microspheric (300 – 500 nm) and bulk (0.1 mm) — the authors prefer microspheric CuO as the most available, easily separable and efficiently recyclable catalyst.

The Biginelli reaction — an important three-component reaction in which the dihydropyrimidine ring is formed — is the three-component condensation of urea, ethyl acetoacetate and an aldehyde (Scheme 53).

Scheme 53



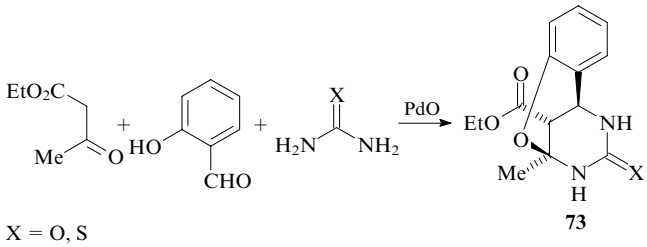
R = Ar, Het, Alk

72

Unfortunately, the classical Biginelli synthesis (in ethanol, catalytic amounts of HCl, under reflux) to give target 3,4-dihydropyrimidin-2(1*H*)-one **72** often occurs in low yield (20% – 30%), in particular, for substituted heteroaromatic and aliphatic aldehydes or thioureas. Catalytic amounts of metal oxides successfully solve this problem, and an increase in the specific surface area of the oxide has a positive effect on the reaction result.

To synthesize dihydropyrimidines **72** under solvent-free conditions, MoO_3/Al_2O_3 (S_{sp} = 248 $m^2\ g^{-1}$; pore size 20 – 100 Å) is efficiently used.[165] High yields of the product (80% – 98%) are achieved in 30 min even with different substituted heteroaromatic aldehydes. The solvent-free MW-assisted Biginelli reaction is catalyzed by nano ZrO_2 (particle size 53 – 57 nm; S_{sp} = 275 $m^2\ g^{-1}$). Compounds **72** are formed in 85% – 96% yield in 10 – 20 min depending on the aldehyde nature.[166] In the presence of catalytic amounts of PdO, the reaction of salicylaldehyde, ethyl acetoacetate and (thio)urea occurs unusually to give tricyclic pyrimidine derivatives **73** in >90% yield (Scheme 54).[167]

Scheme 54

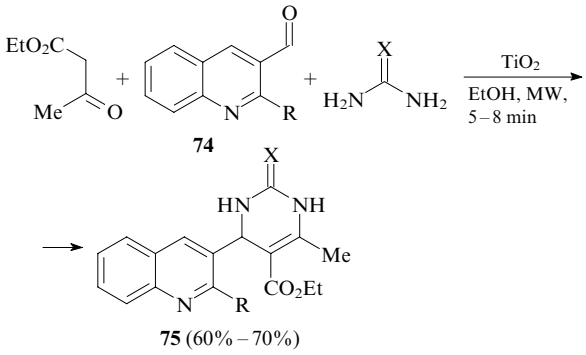


X = O, S

73

When formylquinolines **74** are used as substrates in this reaction, nano TiO_2 (particle size 10 – 20 nm) efficiently catalyzes the formation of product **75** under microwave irradiation in ethanol (Scheme 55).[168]

Scheme 55



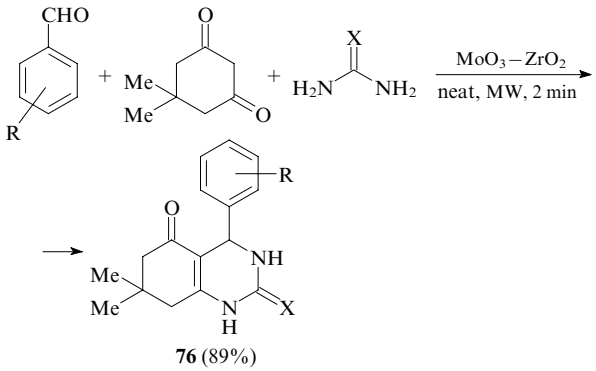
74

75 (60% – 70%)

R = Cl, SH, SeH; X = O, S

Nanocomposite $MoO_3 - ZrO_2$ (particle size 10 – 25 nm) turned out to be an efficient catalyst in the solvent-free synthesis of octahydroquinazolinones (and thiones) **76** under microwave irradiation (Scheme 56).[169]

Scheme 56

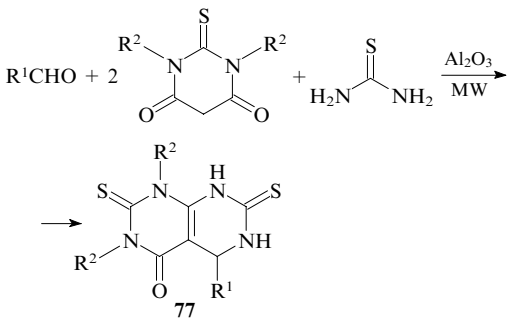


76 (89%)

X = O, S; R = H, 2-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-NO_2, 4-OMe, 2-OH, 4-OH

An interesting protocol for synthesis of Biginelli products has been suggested by Kidwai *et al.*[170] It involves sorption of the reactants onto the acidic alumina surface with subsequent microwave activation of the support in the absence of a solvent (3 – 9 min). Washing Al_2O_3 with ethyl acetate gives product **77** (Scheme 57) in 80% – 87% yield depending on the nature of the initial aldehyde.[170]

Scheme 57



77

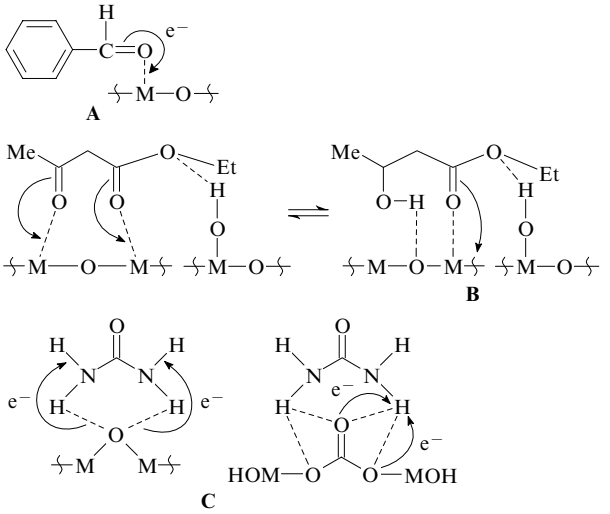
R^1 = Ph, 2-Fu, 3,4-methylenedioxyphenyl; R^2 = H, Ph

The use of activated fly ash rather than Al_2O_3 as a sorbent for the reactants affords substituted 3,4-dihydropyrimidin-2(1*H*)-ones **77** by the above procedure in 85%

yield in 2 min.[171] The authors assume that it is precisely the presence of SiO_2 (64%) and Al_2O_3 (16%) in activated fly ash that is responsible for this result; however, they do not discuss the role of microwave irradiation (as in the previous two papers).

The synthesis of substituted dihydropyrimidines **72** in the presence of metal oxides (Al_2O_3, CuO, TiO_2, ZnO, MgO), but without microwave irradiation, has been described.[172] The best results are achieved when nano Al_2O_3 (particle size 20–60 nm) is used. Its catalytic activity in the Biginelli reaction is explained by activation of the reactants [benzaldehyde (**A**), ethyl acetoacetate (**B**) and urea (**C**)] when they are sorbed onto the catalyst surface (Scheme 58).[172, 173]

Scheme 58



Significant differences in efficiency between bulk and nano oxide catalysts are attributed by the authors to the increase in the number of active sites with an increase in the specific surface area of the oxide (Table 6).

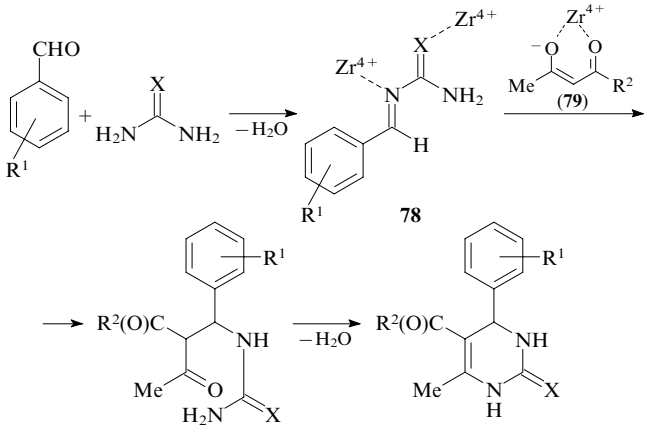
Table 6. Catalysis efficiency in the Biginelli reaction.[172]

Catalyst (10 mol.%)	Time /h	Yield of **72** (R = Ph) (%)
–	10	32
nano-Al_2O_3	20	87
Bulk Al_2O_3	20	50

Classical catalysts of the Biginelli reaction are acids; therefore, metal oxides modified with acidic reagents have been used in some studies: $TfOH/Al_2O_3$,[174] SO_4^{2-}/ZrO_2,[175] SO_4^{2-}/SnO_2,[176] $SbCl_3/Al_2O_3$ (Ref. 177) *etc*. Inasmuch as the efficiency of most of these catalysts is considered by the authors in the context of simple acid catalysis and the role of oxides is not considered, we do not dwell in detail on them. Among these catalysts, sulfated zirconia (SO_4^{2-}/ZrO_2) should be distinguished from the other catalysts. As already mentioned in Section IV.1, the introduction of sulfate groups into the catalyst structure leads to a considerable increase in the specific surface area and in the number of acid sites of ZrO_2. The strength of acid sites on the surface of SO_4^{2-}/ZrO_2 exceeds that in conventional solid acidic catalysts, such as zeolites.

Although Kumar *et al*.,[175] as distinct from Fedorova *et al*.,[172] have focused on the promotion of formation of iminium intermediate **78**, rather than on the activation of the reactants, in the presence of Brønsted acid sites of sulfated zirconia and on the facilitation of its nucleophilic attack by coordinated β-dicarbonyl compound **79** (Scheme 59), it is evident that the principle of action of the oxide catalyst considered in these studies is the same and that the reactants are also activated on the SO_4^{2-}/ZrO_2 surface.

Scheme 59



R^1 = H, 3-NO_2, 4-NO_2, 4-Cl, 4-OMe, 2-OH; R^2 = OEt, Me, Ph; X = O, S

Fedorova *et al*.[172] were the first who described the ability of metal oxides to enhance the stereocatalytic activity of chiral inductors in the Biginelli reaction (see Scheme 53). It has been shown that metal oxides, including nano oxides (MgO, Al_2O_3, NiO; particle size 20–80 nm), can improve not only the chemoselectivity but also the stereoselectivity of the Biginelli reaction. In the presence of chiral inductors, such a s quinine sulfate, L-proline and their simplest derivatives, the enantiomeric excess of compound **72** (see Scheme 53) increases from 0% to 23%.[172, 173]

The same authors enhanced the catalytic activity of the known chiral inductor[178] of the Biginelli reaction — (2*S*,4*R*)-hydroxypropyl-(*S*)-1-phenylethylamine trifluoroacetate (**80**) — from 39% to 72% by the mere introduction of ZrO_2-SiO_2 (particle size 20–60 nm) into the reaction mixture.[173, 179] The best simultaneous effect on the chemo- and stereoselectivity of the synthesis of compound **72** is exhibited by the double nano oxide TiO_2-SiO_2 (particle size 20–80 nm) (92% yield; 66% *ee*).

When estimating the effect of oxide particle size on the reaction result, the authors noted an interesting fact. Bulk oxides improve the chemoselectivity of the reaction to a smaller degree as compared with nano oxides; however, these catalysts can be comparable in their effect on stereoselectivity (Table 7).

Structure 80

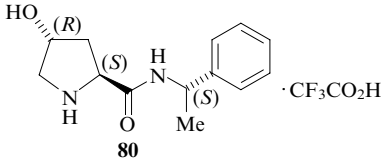


Table 7. Result of the Biginelli reaction [a] in the presence of different oxides and compound **80**.[173]

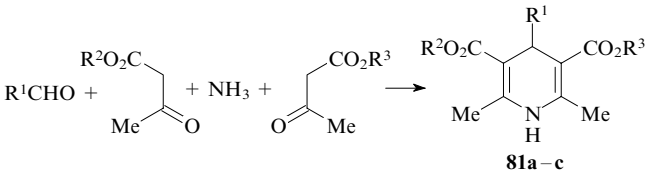
Catalyst (10 mol.%)	Yield of **72** (R = Ph) (%)	*ee* (%)
–	29	39(*R*)
Nano-Al_2O_3	44	60(*R*)
Bulk Al_2O_3	33	59(*R*)
Nano-TiO_2	37	54(*R*)
Nano-SiO_2	59	64(*R*)
Bulk SiO_2	45	60(*R*)
Nano-ZrO_2	5	–
Nano-TiO_2-SiO_2 (40 mass % TiO_2)	92	66(*R*)
Nano-ZrO_2-SiO_2 (50 mass % ZrO_2)	44	72(*R*)

Reaction conditions: 10 mol.% **80**, THF, 20 °C, 45 h.

VII.9. Synthesis of dihydropyridines (the Hantzsch reaction)

The first 1,4-dihydropyridine **81a** was synthesized *via* the Hantzsch reaction more than a century ago (Scheme 60).[180] This reaction is the one-pot condensation of aldehyde with ethyl acetoacetate and ammonia in acetic acid or in ethanol.

Scheme 60



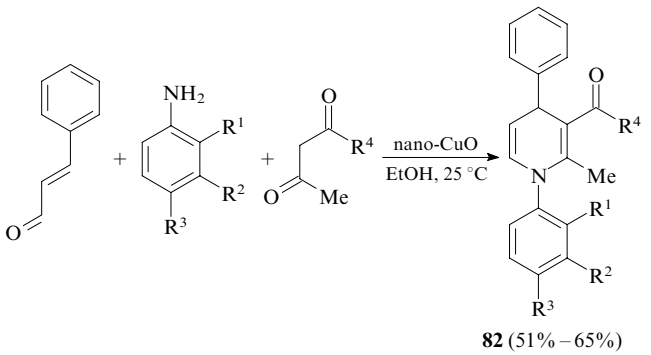
81a–c

$R^2 = R^3 = Et$: R^1 = H (**a**), Ph (**b**);
R^1 = 3-$O_2NC_6H_4$, R^2 = Me, R^3 = Et (**c**)

When Hantzsch reaction substrates with a more complex molecular structure, especially substituted aromatic aldehydes, are used, the reaction is accompanied by different side processes and requires laborious purification of the target products; the purification methods have been patented.[181,182] Hence, it is necessary to search for special reaction conditions, in particular, for new catalysts.

There has been described the three-component condensation of aromatic amines, β-ketoesters and cinnamaldehyde catalyzed by nano CuO to give corresponding 1,4-dihydropyridines **82** in good yield under mild conditions [183] (Scheme 61).

Scheme 61



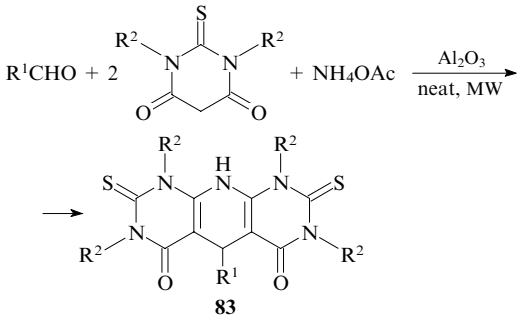
82 (51%–65%)

R^1, R^2 = H, Me; R^3 = H, Me, Cl, Br, F; R^4 = OEt, OBu^t, SBu^t

As compared with the commercially available bulk CuO (S_{sp} = 1.9 $m^2\ g^{-1}$; yield of 40% in 12 h), nano CuO exhibited a high catalytic activity (S_{sp} = 136 $m^2\ g^{-1}$, 60% in 6 h).

By analogy with bicyclic 1,4-dihydropyrimidines **77** (see Scheme 57), tricyclic 1,4-dihydropyridines **83** are synthesized in 80%–86% yield in a few minutes under solvent-free conditions using microwave-assisted activation of the reactants sorbed on the solid Al_2O_3 support (Scheme 62).[170]

Scheme 62



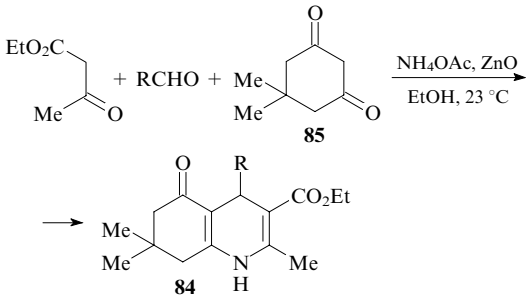
83

R^1 = Ph, 2-Fu, 3,4-methylenedioxyphenyl; R^2 = H, Ph

When benzaldehyde, ethyl acetoacetate and ammonium acetate are used as the starting compounds, their sorption on activated fly ash and subsequent microwave irradiation afford target product **81b** in 98% yield (see Scheme 60).[171]

Hydrogenated quinolines **84** can also be produced through the Hantzsch reaction from dimedone (**85**), aldehydes and ethyl acetoacetate as the active methylene component (Scheme 63).

Scheme 63



84

R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-ClC_6H_4, *etc.*

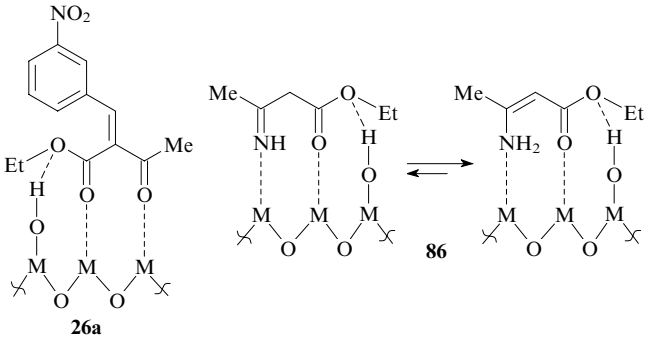
There have been described two efficient procedures for synthesis of compounds **84**. Katkar *et al.*[184] have suggested using ZnO supported on zeolite (particle size < 10 m, S_{sp} = 137 $\mu m^2\ g^{-1}$) as the catalyst. Target products **84** have been obtained in 86%–95% yield in ethanol at room temperature.

The second procedure [185] implies using ZnO nanoparticles (particle size, 20–40 nm) under solvent-free conditions without heating (83%–98% yield of products **84**). Both procedures have been studied for a wide range of aldehydes with both electron-withdrawing and electron-donating substituents.

The use of nano Al_2O_3 and CuO (particle size, 20–40 nm) enables the selective Hantzsch reaction. These oxides promote the four-component synthesis of nitrendipine (**81c**) in 61% yield (see Scheme 60).[186] The increase in the reaction selectivity is attributed by the authors to the activation of both the reactants (analogously to the Biginelli

synthesis, see Scheme 58), and the key intermediates of the Hantzsch reaction — ketoester **26a** and enamine **86** (Scheme 64).

Scheme 64



The same authors have studied the effect of nano magnesium and aluminium oxides (particle size 20–60 nm) on the ratio between the enantiomers of nitrendipine (**81c**). In the presence of quinine, cinchonidine and their simplest derivatives, the *ee* increases from 0% to 14%–37% in favour of the *S*-isomer.[173]

Based on the currently available data, the conclusion can be drawn that the efficiency of oxide catalysts in multicomponent reactions is due to their versatility — the ability to act as a catalyst at all stages of the process because of the existence of both the basic and acid active sites on the surface. It should be noted that carbonyl compounds are used in the vast majority of multicomponent reactions. The authors believe that, in these cases, it is precisely the sorption of the formyl or keto group of the reactants onto the active sites of the oxide surface that leads to the activation of molecules and subsequent promotion of the reaction.

* * *

The data covered in this review demonstrate that metal oxides and silica are versatile catalysts capable of being efficient in both basic and acid catalysis. Moreover, the possibility of regeneration enables the repeated use of metal oxides and silica, which makes them more economically attractive. Unfortunately, the mechanism of action of metal oxides in some reactions has not been completely understood. A possible reason is that most of researchers have not properly focused on the properties of the oxide surface, namely, on studying the nature (acidity or basicity) and strength of the surface active sites. However, it can be stated even now that the sorption and activation of the reaction reagents and(or) intermediates are the key stages of the catalytic processes over oxide catalysts.

We believe that catalysis of multicomponent reactions, which is very incompletely understood, is the most promising way to use bulk and nanoscale metal oxides. It is worth noting that stereoselective synthesis in the presence of metal oxides is a new and original field of research. Although relevant publications are sparse and not covered in available reviews, the reported results seem to be of interest and promising for further studies.[172, 173, 178, 187–189] Nanoscale mixed oxides are worth of special attention since they are often more efficient than their single and bulk counterparts.

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