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Applying Heterogeneous Catalytic Reactions for Organic Chemical Syntheses

László Hegedűs[1*], Zoltán Hell[1]

[1] Department of Organic Chemistry and Technology, Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics, Műegyetem rkp. 3, H-1111 Budapest, Hungary
[*] Corresponding author, e-mail: hegedus.laszlo@vbk.bme.hu

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Abstract

In this review the most important results achieved in the recent 12–15 years are summarized focusing on the heterogenous catalytic hydrogenations over transition metals (Pd, Pt, Ru, Rh, La), as well as the application of palladium, copper and other metals on a molecular sieve (4A) support in several organic chemical syntheses in liquid phase.

Keywords

heterogeneous catalysis, hydrogenations, supported metal catalysts, palladium, copper, lanthanum, titanium, iron, zinc

1 Introduction

Heterogeneous catalysis is essential to both the economy and the science, allowing us to convert raw materials into valuable chemicals in an economical, efficient and environmentally benign manner. As estimated, 80–90% of all chemical processes apply heterogeneous catalysts. However, the principles of heterogeneous catalysis are based on the results of scientific studies which advance and guide the researchers and developers of new catalysts and catalytic processes.

It has been dealing with heterogeneous catalysis for decades at the Department of Organic Chemistry and Technology of the Faculty of Chemical Technology and Biotechnology (VBK) at the Budapest University of Technology and Economics (BME). These investigations were initiated by *Zoltán Csűrös* and *József Petró* in the 1950's [1], which have been pursuing by their co-workers, such as *Zsigmond Dusza*, *József Heiszmann*, *Éva Polyánszky*, *Tamás Mallát*, *Tibor Máthé*, *Antal Tungler*, *Sándor Békássy*, as well as Zoltán Hell and László Hegedűs (authors). In this review the most important results achieved in the recent 12–15 years are summarized focusing on the heterogenous catalytic hydrogenations over transition metals (Pd, Pt, Ru, Rh, La), as well as the application of palladium, copper and other metals on a molecular sieve (4A) support in several organic chemical syntheses in liquid phase.

2 Heterogeneous catalytic hydrogenations over transition metals (Pd, Pt, Ru, Rh, La)

In the synthesis of pharmaceutical intermediates, the liquid-phase heterogeneous catalytic hydrogenation is a frequently applied process. Since biologically active materials often contain nitrogen, sulphur or phosphorus, the hydrogenation of these compounds requires special methods, such as increased amounts of catalyst or auxiliary materials (e.g., acids), which convert these substrates to a "shielded" form. However, these methods cannot always be applied (e.g., a catalyst is very expensive, or a reactant is sensitive to acids) and, therefore, other solutions must be found.

2.1 Hydrogenation of *N*-containing compounds

Heterogeneous catalytic hydrogenation of several substrates containing nitrogen (e.g., nitriles, nitro compounds, Schiff bases, pyridines, pyrroles) was investigated during our research work.

Primary amines obtained from nitriles by hydrogenation are valuable intermediates in the pharmaceutical, herbicide and plastic industries [2]. As well-known [3–5], conversion of the nitrile group to a primary amine takes place relatively easily over precious metal catalysts, but typically a mixture of primary, secondary and tertiary amines is formed in various consecutive and parallel reactions, due to the high reactivity of the imine intermediate (Scheme 1). A new process was developed by us for

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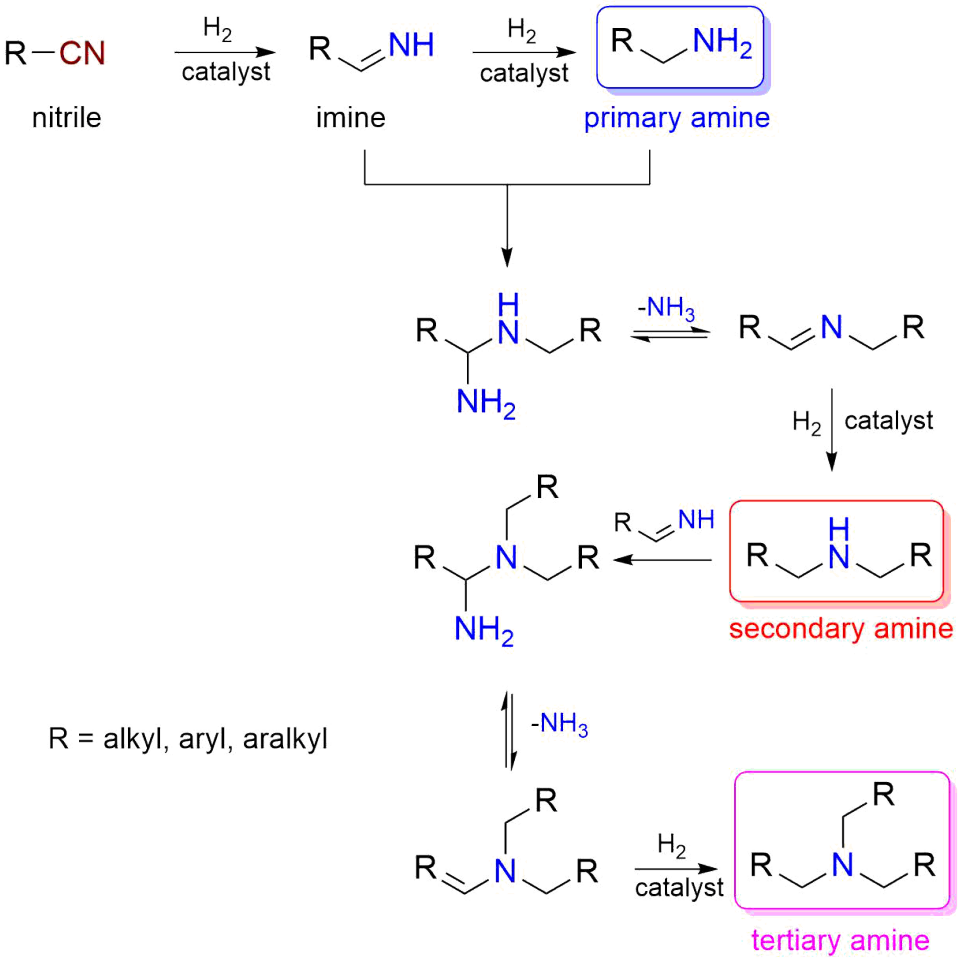
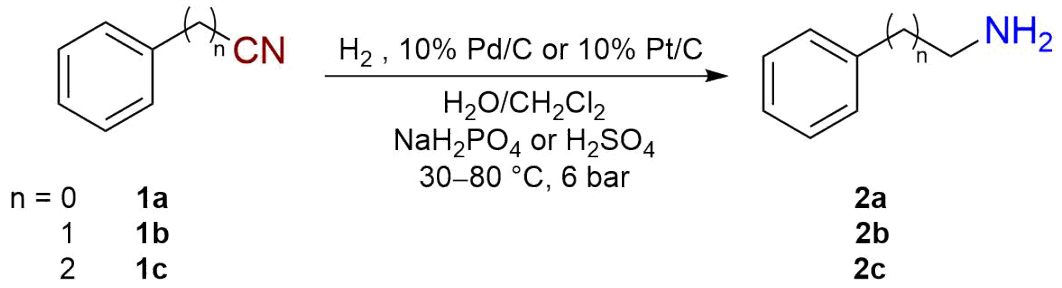


Scheme 1 General scheme for the catalytic hydrogenation of nitriles

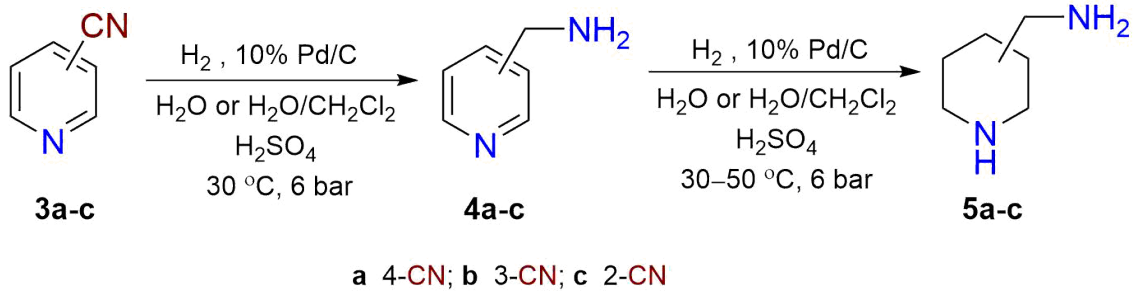
the selective liquid-phase heterogeneous catalytic hydrogenation of nitriles to primary amines [6], in which complete conversion of benzonitrile (**1a**), excellent selectivity (95%) and isolated yield (85–90%) of benzylamine (**2a**) could be achieved under mild reaction conditions (30 °C, 6 bar), over a 10% Pd/C catalyst (Selcat [7]), in a mixture of two immiscible solvents (e.g., water/dichloromethane) and in the presence of a medium acidic additive (NaH_2PO_4) (Scheme 2). This method was extended to the Pd-catalyzed hydrogenations of benzyl cyanide (**1b**) to 2-phenylethylamine (**2b**) [8] and 3-phenylpropionitrile (**1c**) to 3-phenylpropylamine (**2c**) [9], but lower isolated yields (40 and 20%, respectively) and primary amine selectivities (45 and 26%, respectively) were achieved (Scheme 2). It was made the diverse primary amine selectivities probable by high-level quantum chemical calculations using a density functional theory (DFT) approach, which were decisively due to the different adsorption interactions between the imine



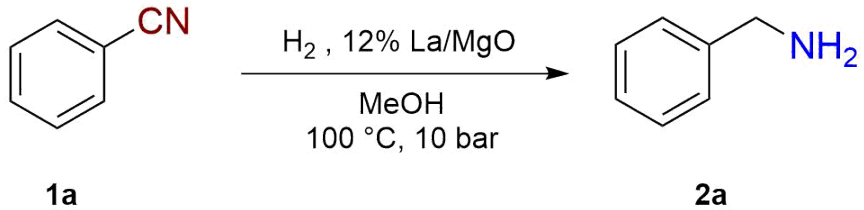
Scheme 2 Hydrogenation of benzonitrile and its homologues (**1a-c**) to the corresponding primary amines (**2a-c**) over Pd or Pt catalyst

intermediates and palladium [9]. Later, various supported precious metal (Pt, Rh, Ru, Ir) catalysts were screened in the hydrogenations of **1a-c**, and a readily available platinum on carbon catalyst (10% Pt/C) afforded the best results [10]. Complete conversion of nitriles, as well as comparatively high isolated yields (58–70%) and selectivities to primary amines (57–68%) under mild and optimized conditions [6 bar, 30 °C, two immiscible solvents (water/dichloromethane or water/toluene), acidic additives (NaH_2PO_4, $(NH_4)H_2PO_4$ or H_2SO_4)] were obtained. Contrary to the typical high secondary amine selectivity of platinum, surprisingly, this Pt/C catalyst proved to be much more effective and selective in the formation of **2b** and **2c** than a Pd/C one applied earlier. The observed divergences in the primary amine selectivity were also clarified by DFT calculations related to the adsorption interactions between the imine intermediates and platinum [10]. Based on our experience, an effective method for the chemoselective, catalytic hydrogenation of some pyridinecarbonitriles to the corresponding (aminomethyl)pyridines or -piperidines over a 10% Pd/C catalyst (Selcat Q) was also developed [11]. Using our process, not only an adequate primary amine selectivity to the wanted 4-, 3- or 2-(aminomethyl)pyridine (**4a-c**) can be achieved, but it has also been proved to be effective for the selective preparation of 4-, 3- or 2-(aminomethyl)piperidine (**5a-c**) by further hydrogenation of the pyridine ring in addition to the nitrile group (Scheme 3). The essence of this method is that the synthesis can be fine-tuned by simply adjusting the amount of acidic additive (H_2SO_4) based on whether the products to be prepared are compounds **4a-c** or **5a-c**. Complete conversions were obtained under mild conditions (30–50 °C, 6 bar), in all cases, but the very high selectivity to **5a** or **4a** (98 and 93%, respectively) decreased to 76% (**5b**) and 72% (**4b**), as well as 10% (**5c**) and 57% (**4c**) by changing the position of nitrile group in the pyridine ring. The possible reasons for the diverse primary amine selectivities observed in the hydrogenation of the constitutional isomers of pyridinecarbonitriles were also confirmed by DFT calculations. Adsorption energy profiles regarding the interactions between the nitrile starting materials, imine intermediates or amine products and palladium were computed to clear the selectivity changes [11]. In addition, a 12% La/MgO catalyst prepared by us was also found to be very effective in the hydrogenation of benzonitrile (**1a**) [12], which is unprecedented in the literature. Although lanthanum was already applied as a promoter of nickel in the reduction of adiponitrile [13], there are no examples concerning the hydrogenation activity of La itself, according to our best knowledge. Thus, benzylamine (**2a**) was achieved with 47% selectivity accompanied by 98% conversion of **1a** (Scheme 4), but the reaction conditions (methanol, 10 bar, 5 h) were not optimized.

During the stereoselective synthesis of (±)-*trans*-dihydronarciclasine and its derivatives having significant cytostatic activity [14], cyclic aliphatic nitro compounds were hydrogenated to the corresponding



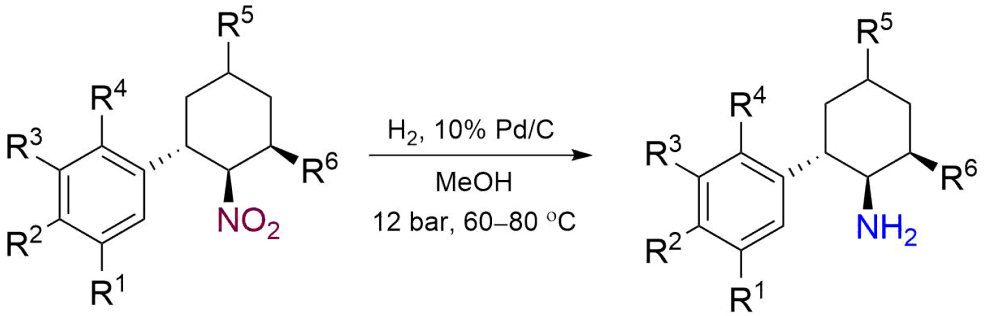
Scheme 3 Selective, Pd-catalyzed hydrogenation of 4-, 3- and 2-pyridinecarbonitriles (**3a-c**) to 4-, 3- and 2-(aminomethyl)pyridines (**4a-c**) or 4-, 3- and 2-(aminomethyl)piperidines (**5a-c**)



Scheme 4 Hydrogenation of benzonitrile (**1a**) to benzylamine (**2a**) over a 12% La/MgO catalyst

cyclohexylamines [15–21]. It was found that the conversions of (±)-*trans*-4-nitro-5-phenylcyclohexane-1,3-diol and its derivatives (**6a-j**) over 10% Pd/C (Selcat Q) were complete only at 12 bar and 60–80 °C (Scheme 5), namely the hydrogen uptake ceased at lower temperature and pressure, presumably due to the poisoning effect of strongly basic nitrogen of the cyclohexylamines (**7a-j**) formed [15].

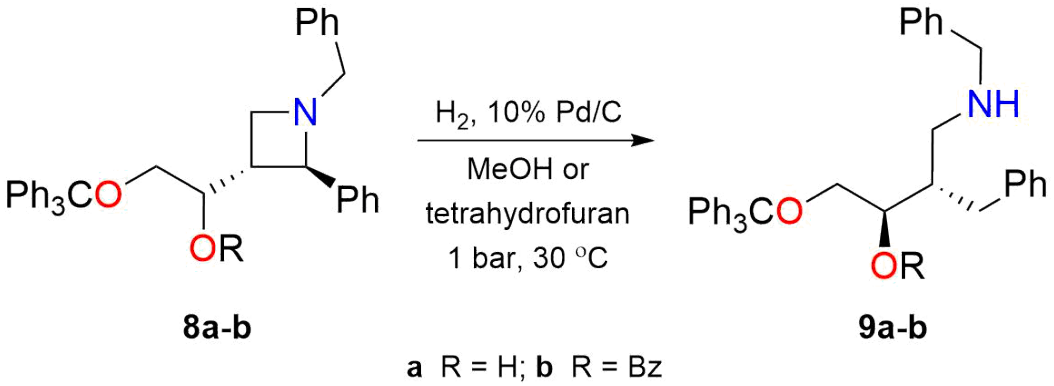
Optically active, five-membered heterocycles, such as pyrrolidines and tetrahydrofurans, can be used as valuable new chiral ligands or organocatalysts and can serve as building blocks of practically important, biologically active compounds [22]. To synthesize some of these compounds, ring opening and *N*-debenzylation or *O*-detritylation of protected amino- and hydroxyoxetanes, as well as azetidines were also carried out over a 10% Pd/C catalyst (Selcat Q), in a 4:1 or 7:3 methanol/dichloromethane solvent mixture, at 10 bar and 30 °C [23–25]. However, the selective, Pd-catalyzed ring opening of *trans*-*N*-benzylazetidines (**8a-b**) resulted in the corresponding *anti*-*N*-benzylamino derivatives (**9a-b**) under very mild conditions (30 °C, atmospheric pressure), in methanol or tetrahydrofuran (Scheme 6), which can



6a-j **7a-j**

a R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = OH, R^6 = OH
b R^1 = H, R^2 and R^3 = OCH_2O, R^4 = H, R^5 = OCH_2CH_2O, R^6 = OH
c R^1 = H, R^2 = OMe, R^3 = H, R^4 = H, R^5 = OCH_2CH_2O, R^6 = OH
d R^1 = OMe, R^2 = OMe, R^3 = OMe, R^4 = H, R^5 = OCH_2CH_2O, R^6 = OH
e R^1 = OMe, R^2 = OEt, R^3 = OEt, R^4 = H, R^5 = OCH_2CH_2O, R^6 = OH
f R^1 = OEt, R^2 = OEt, R^3 = OEt, R^4 = H, R^5 = OCH_2CH_2O, R^6 = OH
g R^1 = OMe, R^2 and R^3 = OCH_2O, R^4 = H, R^5 = OCH_2CH_2O, R^6 = OH
h R^1 = H, R^2 and R^3 = OCH_2CH_2O, R^4 = H, R^5 = OCH_2CH_2O, R^6 = OH
i R^1 = OMe, R^2 and R^3 = OCH_2CH_2O, R^4 = H, R^5 = OCH_2CH_2O, R^6 = OH
j R^1 = OMe, R^2 and R^3 = OCH_2O, R^4 = OMe, R^5 = OCH_2CH_2O, R^6 = OH

Scheme 5 Hydrogenation of (±)-*trans*-4-nitro-5-phenylcyclohexane-1,3-diol and its derivatives (**6a-j**) to the corresponding cyclohexylamines (**7a-j**) over palladium



8a-b **9a-b**

a R = H; **b** R = Bz

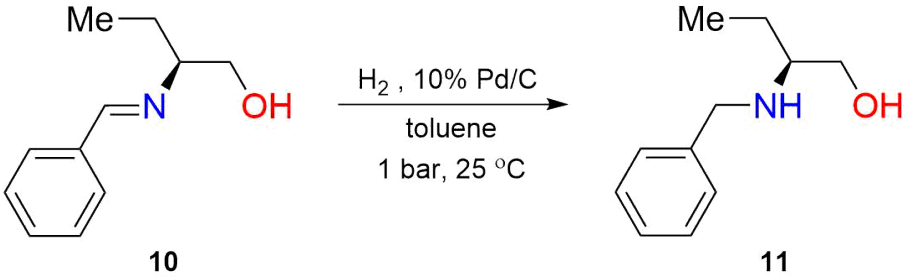
Scheme 6 Selective ring opening of *trans*-*N*-benzylazetidines (**8a-b**) to *anti*-*N*-benzylamino derivatives (**9a-b**) over Pd/C

be promising intermediates for the synthesis of valuable and important chiral pyrrolidine derivatives, like the *trans*-3-benzoyloxy-1,4-dibenzylpyrrolidine [25].

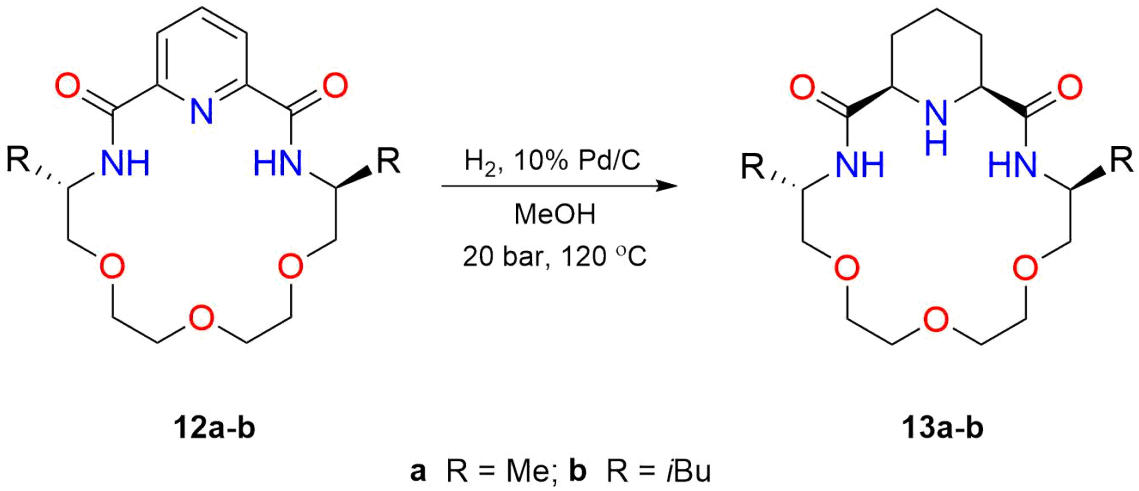
Using also 10% Pd/C (Selcat Q) in the hydrogenation of a Schiff base [(*S*)-(+)-2-(*N*-benzylideneamino)butan-1-ol, **10**] to a 1,2-amino alcohol derivative [(*S*)-(+)-2-(*N*-benzylamino)butan-1-ol, **11**], which was a key step in a facile and efficient synthesis of compound **11**, at a very low catalyst/substrate ratio (0.02 $g \cdot g^{-1}$), in toluene, at atmospheric pressure and 25 °C (Scheme 7), the optically active product was isolated with very high purity (97%), yield (93%) and selectivity (90%) [26]. This industrially relevant resolving agent can be applied for the resolution of *cis*- or *trans*-permethric acid (*cis*- or *trans*-3-(2',2'-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid) based on diastereomeric salt formation under conventional [27] or supercritical [28] conditions.

Enantiopure pyridino-18-crown-6 ethers (**12a-b**) were converted to the corresponding *cis*-piperidino-18-crown-6 ethers (**13a-b)** by Pd-catalyzed hydrogenations (10% Pd/C) in methanol, at 20 bar and 120 °C, in good yields (48–57%) and with complete conversion (Scheme 8). Based on their pK_a measurements, these crown ethers containing *N*-heterocyclic moiety can be applied as bifunctional organocatalysts, for instance, in *Michael* addition reactions [29]. Later, a piperidine-based camphorsulfonamide derivative was also prepared from the corresponding pyridine derivative in 78% yield by using our aforementioned catalytic hydrogenation method [30]. It was also used for some *Michael* addition reactions as an organocatalyst.

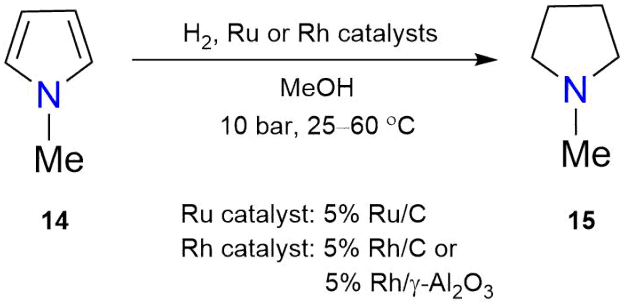
Poisoning and reuse of supported precious metal catalysts, such as 5% Ru/C [31] and 5% Rh/C or 5% Rh/γ-Al_2O_3 [32], were also investigated in the saturation of pyrrole ring, in a non-acidic medium (methanol), at 10 bar and 25–60 °C. In the hydrogenation of 1-methylpyrrole (**14**) to 1-methylpyrrolidine (**15**), as a model reaction (Scheme 9), it was found that reusing the spent, unregenerated 5% ruthenium on carbon and 5% rhodium on carbon or γ-alumina catalysts, the conversion of this model substrate and the activity of the catalysts were strongly dependent on the amount of catalyst, the type of support, the catalyst pre- or aftertreatment, the temperature, and the number of recycling, respectively. Interestingly, the prehydrogenation of this Ru/C catalyst improved its activity during its



Scheme 7 Hydrogenation of a Schiff base, (*S*)-(+)-2-(*N*-benzylideneamino)butan-1-ol (**10**), to (*S*)-(+)-2-(*N*-benzylamino)butan-1-ol (**11**) over Pd/C



Scheme 8 Synthesis of enantiopure *cis*-piperidino-18-crown-6-ethers (**13a-b**) by Pd-catalyzed hydrogenation of pyridino-18-crown-6-ethers (**12a-b**)



Scheme 9 Saturation of 1-methylpyrrole (**14**) to 1-methylpyrrolidine (**15**) over supported Ru or Rh catalyst

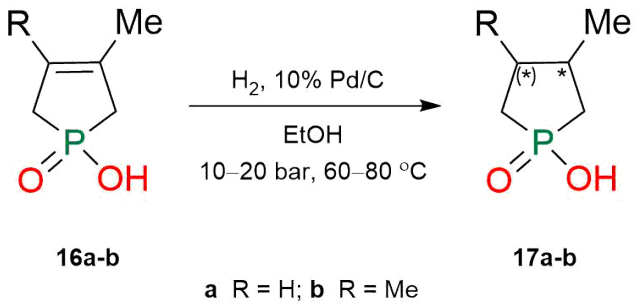
recycling [31], while this pretreatment caused a significant activity decrease of these rhodium catalysts (5% Rh/C and 5% Rh/γ-Al_2O_3) during their reuse [32].

2.2 Hydrogenation of *P*-containing substrates

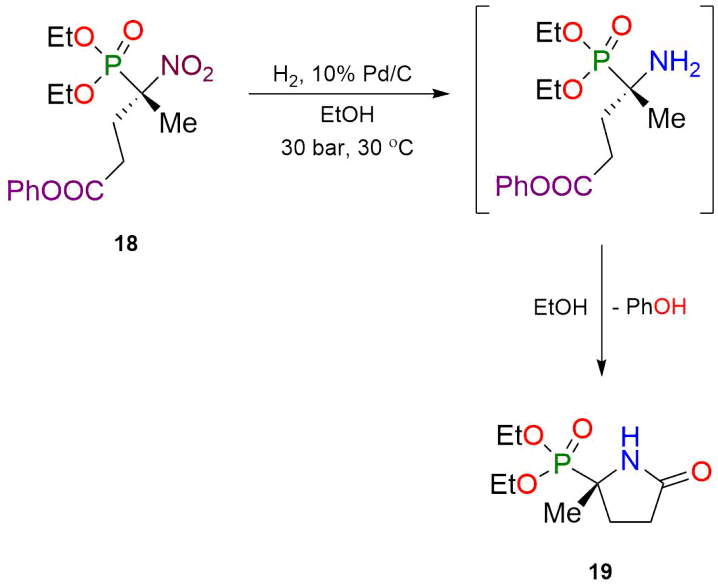
Cyclic phosphinic acids were afforded by a new, one-step hydrogenation method (10% Pd/C, 10–20 bar, 60–80 °C, ethanol) starting from 1-hydroxy-3-phospholene 1-oxides (**16a-b**) (Scheme 10) to use them for their direct esterification by alcohols under microwave (MW) conditions [33]. The products, 1-hydroxy-3-methylphospholane 1-oxide (**17a**) or 1-hydroxy-3,4-dimethylphospholene 1-oxide (**17b**), were obtained in 90% isolated yield. Thus, these phosphinic acid derivatives can be prepared much easier and in an environmentally benign way than applying the previous multistep synthesis.

Enantioselective *Michael* addition of α-nitrophosphonates to aryl acrylates resulted in adducts (96% *ee*) whose aliphatic nitro groups were hydrogenated to the corresponding optically active, quaternary α-aminophosphonates over 10% Pd/C (Selcat Q), in ethanol, at 10–30 bar and 30 °C [34]. For example, the Pd-catalyzed reduction of phenyl (*S*)-4-(diethoxyphosphoryl)-4-nitropentanoate (**18**) gave diethyl (*S*)-(2-methyl-5-oxopyrrolidin-2-yl)-phosphonate (**19**) in 51% isolated yield, at 30 bar and 30 °C, after an *in situ* intramolecular ring closure reaction (Scheme 11).

A novel approach for the synthesis of several *N*,*N*-bis- and *N*,*N*,*N*-tris(phosphinoylmethyl)amines bearing different substituents on the phosphorus atoms was developed applying MW-assisted and catalyst-free Kabachnik–Fields



Scheme 10 Hydrogenation of 1-hydroxy-3-phospholene 1-oxides (**16a-b**) to the corresponding 1-hydroxy-3-phospholane 1-oxides (**17a-b**) with Pd/C



Scheme 11 Pd-catalyzed hydrogenation of an α-nitrophosphonate *Michael* adduct (**18**) to a cyclic α-aminophosphonate derivative (**19**)

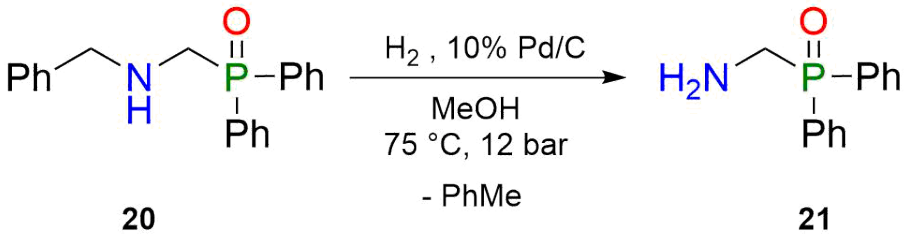
reaction of (aminomethyl)phosphine oxides with paraformaldehyde and diphenylphosphine oxide [35]. To obtain the key intermediate for these syntheses, (*N*-benzylaminomethyl)diphenylphosphine oxide (**20**) was debenzylated over a 10% Pd/C catalyst (Selcat Q), in methanol, at 12 bar and 75 °C to afford (aminomethyl)diphenylphosphine oxide (**21**) in 47% isolated yield (Scheme 12). Later, a similar Pd-catalyzed *N*-debenzylation was accomplished to obtain a diethyl (aminomethyl)phosphonate derivative [36].

During the synthesis of some *P*-stereogenic compounds [37], enantiopure (*R*)-(2-methoxyphenyl)(methyl)(phenyl)phosphine oxide (**22**) was completely converted to (*R*)-cyclohexyl(2-methoxyphenyl)(methyl)phosphine oxide (**23**) by selective saturation of the phenyl ring over a 5% Rh/C catalyst, in methanol, at 20 bar and 95 °C, in 80% isolated yield with an *ee* of 96% (Scheme 13).

2.3 Development and implement of a hydrogenation process on an industrial scale

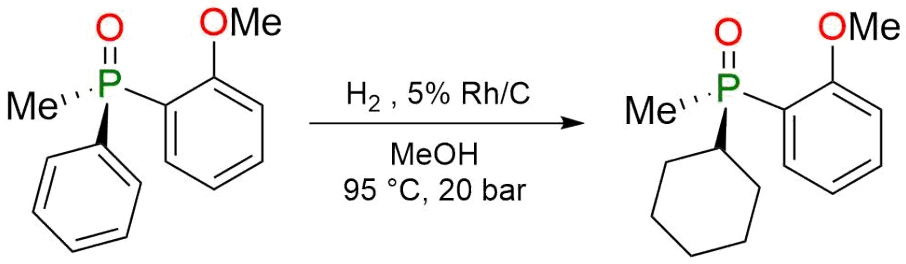
Cariprazine (**24**) is a new, original drug against schizophrenia (Scheme 14) discovered by the researchers of Gedeon Richter Plc. [38, 39], and it was marketed, under the brand name Vraylar® (USA) and Reagila® (EU), in 2016 and 2018, respectively.

trans-4-Aminocyclohexylacetic acid ethyl ester hydrochloride (*trans*-**25**) is a key intermediate in the synthesis of **24**, which serves as a spacer group between the head and tail ones (Scheme 14). To prepare compound **25**, the first step is the hydrogenation of 4-nitrophenylacetic acid (**26**) to *cis*- and *trans*-4-aminocyclohexylacetic acid (*cis*/*trans*-**28**) through 4-aminophenylacetic acid (**27**) over a Pd/C catalyst, in water, at 0.5–4 bar and 25–50 °C (Scheme 15). Esterification of *cis*/*trans*-**28** with ethanol, in the presence



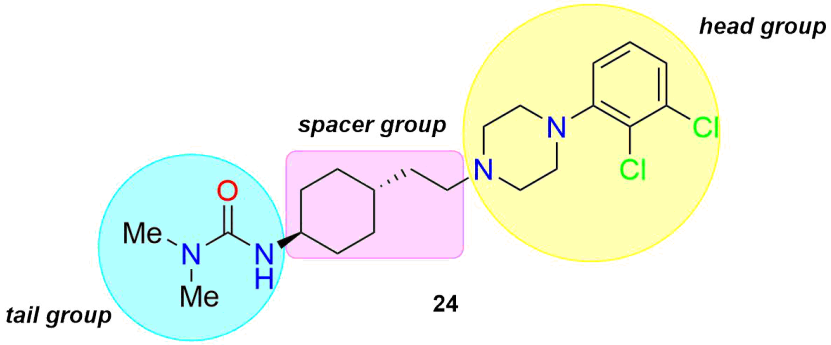
20 **21**

Scheme 12 Hydrogenolysis of (*N*-benzylaminomethyl)diphenylphosphine oxide (**20**) to (aminomethyl)diphenylphosphine oxide (**21**) over Pd/C



22 **23**

Scheme 13 Selective, Rh-catalyzed hydrogenation of a phenylphosphine oxide derivative (**22**) to the corresponding cyclohexyl one (**23**)



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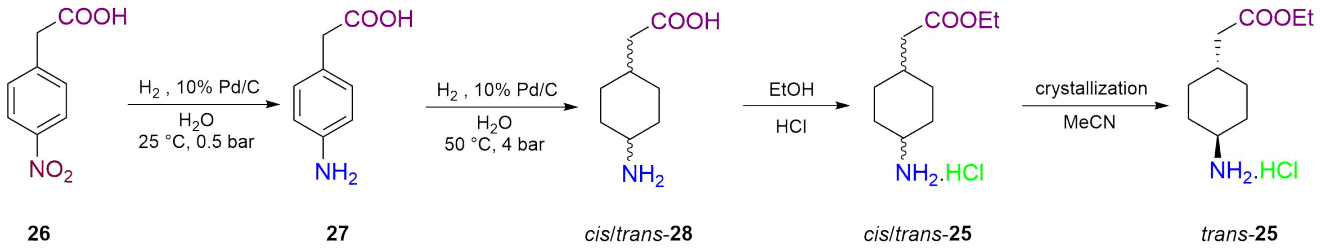
Scheme 14 Structure of cariprazine (**24**)



Scheme 15 Synthesis of *trans*-4-aminocyclohexylacetic acid ethyl ester.HCl (*trans*-**25**)

of HCl, afforded the mixture of *cis*- and *trans*-4-aminocyclohexylacetic acid ethyl ester.HCl (*cis*/*trans*-**25**). Separation of these stereomers was carried out by crystallization from acetonitrile. Our new, patented process [40] provides several technological advantages (low pressure and temperature, glass-lined autoclave) compared to the previous methods (Raney® nickel, 150 bar and 130 °C, stainless steel reactor) [41].

3 Application of molecular sieve-supported metal catalysts in organic syntheses

During the development of a supported metal catalyst the selection of the appropriate support is a determinant factor. Earlier the most important requirement was the inertness of the support in a given chemical reaction. But later it was recognized, that besides the high specific surface area, and the high dispersity of the metal on the surface of support, the acidic or basic properties of the support may also influence the catalytic effect adversely. Moreover, in some cases the use of a heterogeneous catalyst may even change the mechanism of the reaction. It was found, that in the Friedel-Crafts alkylation of toluene with benzyl chloride, in the presence of K10 montmorillonite modified with different heavy metal ions (Fe^{3+}, Sn^{2+}, Cu^{2+}, Mn^{2+}) a radical intermediate (benzyl radical) was detected [42].

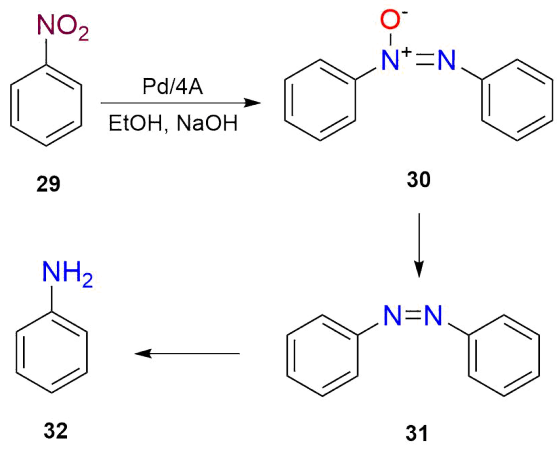
In a heterogeneous catalytic reaction, the addition of an organic ligand is generally not required, in these cases the role of the ligand is played by the support. This makes the workup of the reaction easier and increases the atom efficiency of the process.

In our experiments the 4Å molecular sieve (MS-4A) was generally used as a support. 4Å molecular sieves are artificial zeolites, the Na form of type A one, which are crystalline microporous aluminosilicates. They possess pores with uniform size and shape that are of a specific size and are located in a three-dimensional framework consisting of AlO_4 and SiO_4 tetrahedra linked together through oxygen bridges [43, 44]. The pH value of their aqueous suspension is basic (typically around 10.40).

MS-4A was impregnated with different metal salts using a standardized method [45]. Samples of 1 mmol metal/1 g support were prepared. During the impregnation the metal ions replaced the sodium ions being present in the zeolite structure, but the SEM analysis of the catalysts showed that the original cubooctahedral structure of MS-4A did not change. EDS measurements showed that the new metal ions took place on the surface of the zeolite structure. This was also verified by the measurement of the specific surface, which significantly decreased from the original ca. 800 m^2/g to about 50–80 m^2/g.

3.1 Palladium-catalyzed reactions

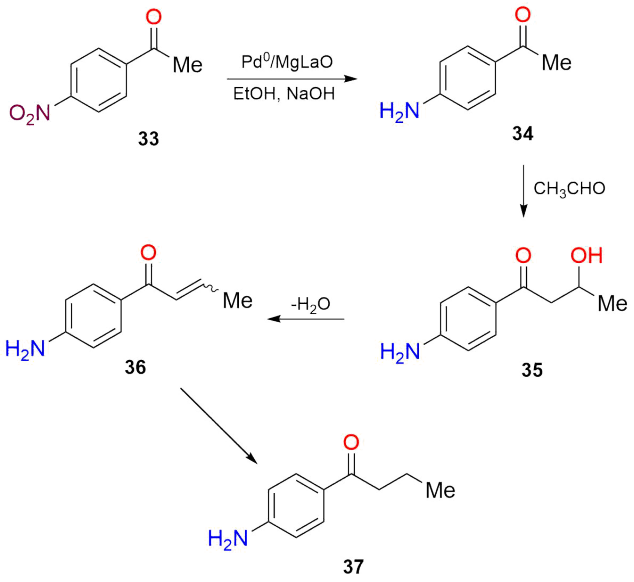
During the examination of the palladium-catalyzed cross-coupling reactions it was found that when nitroaryl halides were reacted organosilicon compounds in ethanol, in the presence of sodium hydroxide and Pd^0 on MS-4A, instead of the Hiyama coupling the reduction of the nitro group to amine was observed. It was shown that in this transfer hydrogenation process the alcohol served as hydrogen source. Depending on the amount of the sodium hydroxide added, the known intermediates of the reduction of the aromatic nitrobenzene (**29**), such as azoxybenzene (**30**) (1.5 equiv. NaOH, 1.5 h) and azobenzene (**31**) (3 equiv. NaOH) could be produced in good yield and selectivity (Scheme 16) [46].



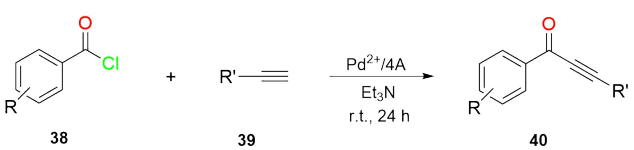
Scheme 16 Selective transfer hydrogenation of nitrobenzene (**29**)

The support had a determinant factor on this reaction. Using Pd on Mg-La mixed oxide catalyst in the reaction of 4-nitroacetophenone (**33**), an unexpected chain elongation reaction was observed (Scheme 17), yielding 4-aminobutyrophenone (**37**). The other C_1-C_4 aliphatic alcohols gave the appropriate aminoketones with different yields. Examination of the mechanism showed that an aldol condensation occurred between the 4-aminoacetophenone (**35**) and the oxo compound obtained from the alcohol, then the formed C=C bond was reduced under the reaction conditions [47].

Pd^{2+} on MS-4A was successfully applied in the preparation of ynones from acid chlorides and alkynes (acyl Sonogashira reaction) in the presence of triethylamine at room temperature without solvent (Scheme 18). Depending on the structure of the alkynes the ynones were formed with 25–92% yield. Aliphatic alkynes gave the poorer yield. In these cases, when benzoyl chloride (**38**) was used as acyl component, significant amount of 3-benzoylbenzoic acid was formed as by-product, indicating a Friedel-Crafts acylation-type concurrent reaction. The catalyst could be easily separated from the reaction mixture and reused without significant decrease in the activity at least in 4 cycles [48].



Scheme 17 Mechanism of the chain elongation reaction of 4-nitroacetophenone (**33**)



R = alkyl, alkoxy, Cl, Br, I, NO_2
R' = Ph, C_5H_{11}, 2-hydroxybut-2-yl

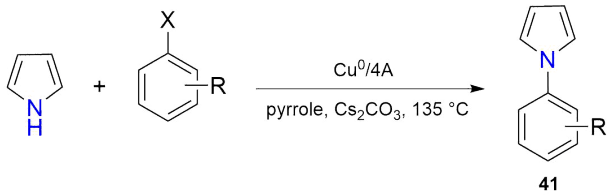
Scheme 18 Acyl Sonogashira reaction of benzoyl chloride derivatives (**38**) and acetylenes

3.2 Copper-mediated reactions

Copper and copper salts are widely used as efficient catalysts in different organic syntheses. The first syntheses elaborated were generally homogeneous methods, but the well-known advantages of the heterogeneous catalytic processes led us to develop heterogeneous copper catalytic processes.

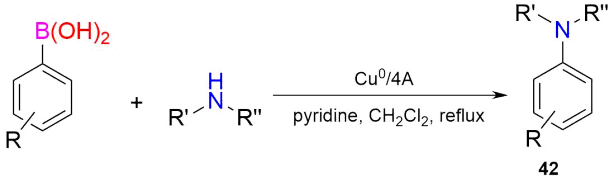
It was found [49] that copper(0) on MS-4A efficiently catalyzed the arylation of pyrrole with different aryl iodides and bromides in the presence of cesium carbonate, using excess of pyrrole as a solvent (Scheme 19). Chloro derivatives (e.g., chlorobenzene) did not react. Nitro substituted aryl halides gave the appropriate amino derivatives, while in case of a formyl substituted aryl halide no product was observed. In case of aryl iodides, Cu^{2+}/4A catalyst also gave the expected result, but it was not reusable with good result. Cu^0/4A was reusable 3 times with excellent activity. This difference in the activity may be explained by the result of the XRF examination of the product, which showed that in case of Cu^{2+}/4A significant amount of copper ions dissolved into the reaction mixture. Other aromatics amines, such as pyrazole, imidazole and indole could also be arylated efficiently with both catalysts.

Cu^0/4A was also used successfully in the coupling of boronic acids with amines (Chan-Lam reaction) in dichloromethane, in the presence of pyridine as base, under Ar atmosphere (Scheme 20). Both aromatic and aliphatic boronic acids gave the respective substituted amines **42** with moderate to good (50–75%) yield, which were comparable to the yields generally published for the Chan-Lam reaction. Phenols instead the amines also gave



R = H, CN, Et, 2-OH, 3-Me, 4-Me, 2-OMe, 4-OMe, 3-NO_2, 4-NO_2, 4-Ac;
X = Br, I

Scheme 19 Arylation of pyrrole in the presence of a Cu^0/4A catalyst



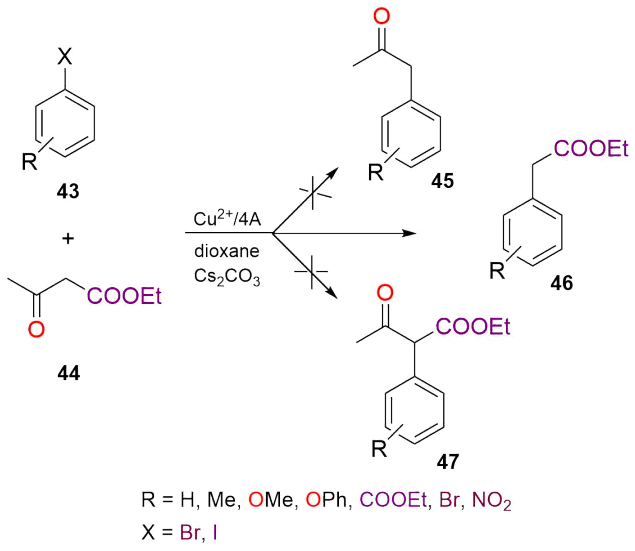
R = H, 4-CF_3, 2-Me, 3-Me, 4-Me; R' = Bu; R" = Bu;
R' and R" = $CH_2CH_2OCH_2CH_2$, $CH_2CH_2N(CH_3)CH_2CH_2$

Scheme 20 Chan-Lam reaction of boronic acids and amines in the presence of a Cu^0/4A catalyst

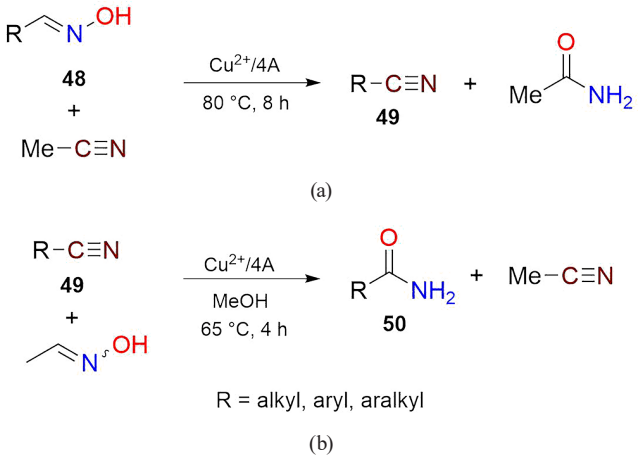
similar results. In these reactions the catalyst could not be reused with good results, probably because the pyridine salts precipitated to the surface of the catalyst, and thus covered the metal particles [50].

Arylacetic acid derivatives were formed selectively in the reaction of ethyl acetoacetate with aryl iodides, in the presence of cesium carbonate and Cu^{2+}/4A in refluxing dioxane. From the possible 3 products (arylacetic acid ethyl ester **46**, arylmethyl methyl ketone **45** and aryl substituted acetoacetic ester **47**) only the arylacetic acid ethyl ester derivatives were formed, with satisfactory to excellent yield, depending on the R substituent (Scheme 21) [51].

Cu^{2+}/4A efficiently catalyzed the oxime–nitrile conversion in acetonitrile. Investigation of the reaction mixture showed that a complex is formed between the oxime **48**, the copper(II) ion and the acetonitrile, and the transfer of the elements of the eliminated water is running in a concerted reaction, yielding acetamide as by-product [Scheme 22 (a)] [52]. Similarly, a non-hydrolytic nitrile–amide conversion process catalyzed by Cu^{2+}/4A were elaborated [Scheme 22 (b)]. Acetaldoxime addition assured the required "H-O-H" in a concerted reaction analogous with the oxime–nitrile conversion [53]. Both aromatic and aliphatic nitriles (**49**) gave the appropriate amide with good conversion and yield. Appreciable amount of copper leaching did not occur in the reactions, as the results of the XRF examination of the products showed. In both cases the catalyst could be reused several times without significant loss of activity.



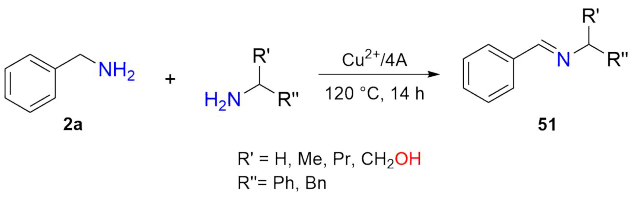
Scheme 21 Selective synthesis of arylacetic acid ethyl esters (**46**) in the presence of a Cu^{2+}/4A catalyst



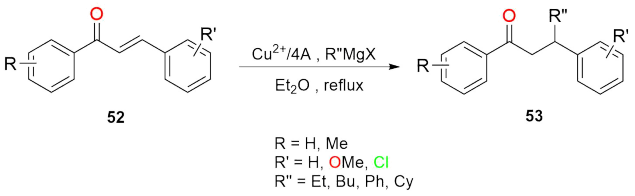
Scheme 22 Cu-catalyzed oxime–nitrile (a) and nitrile–amide (b) transformation

Cu^{2+}/4A proved to be an efficient catalyst for the preparation of imines **51** from benzylamine (**2a**) without oxidizing agents or oxidative atmosphere, under simple reaction conditions (Scheme 23). With aralkylamines, the yield dropped slightly with increasing number of carbon atoms between the amine function and the aromatic ring, while the reactivity of aliphatic amines depended on the length of the alkyl chain, probably due the boiling point of these amines. The absence of the aldehyde intermediate was verified by preparative experiments, excluding the oxidative mechanism of the coupling [54].

Cu^{2+}/4A efficiently catalyzed the selective 1,4-addition of Grignard compounds to chalcones **52** [55]. Both aromatic and aliphatic halides gave good yield, and no significant steric or electronic effects were found (Scheme 24).



Scheme 23 Transformation of benzylamine (**2a**) into imines (**51**) with a Cu^{2+}/4A catalyst



Scheme 24 Cu-catalyzed 1,4-addition of Grignard compounds to chalcones (**52**)

The 1,2-addition products were not detected. The catalyst could be recycled without significant loss of activity multiple times. The effect of other metals was also examined. It was found that titanium on MS-4A (Ti^{4+}/4A) was also efficient, but it could not be reused in the reaction due to loss of selectivity towards the 1,4-addition product **53** [45].

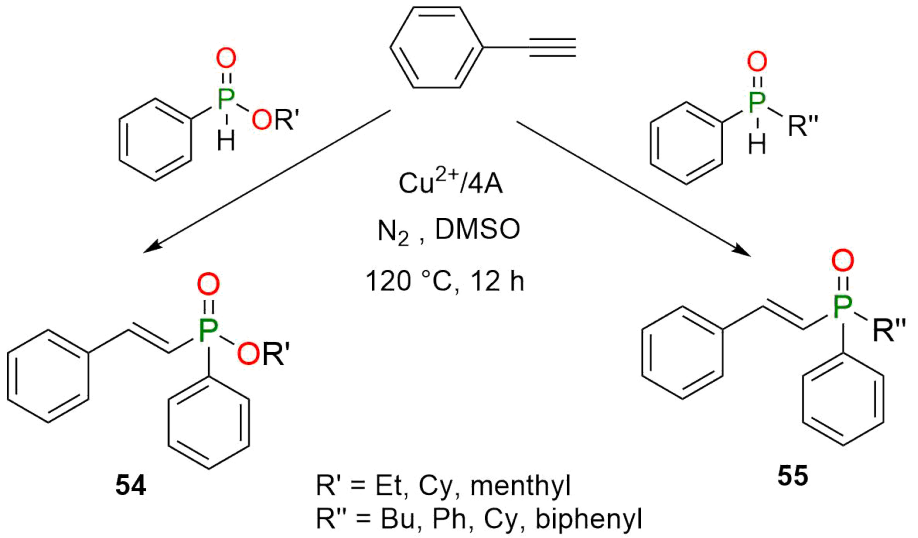
The Cu^{2+}/4A catalyst showed also good activity in the addition of *H*-phosphinates and secondary phosphine oxides to phenylacetylene (Scheme 25) [56]. Both reactions were completely regioselective, only the *β*-isomers were formed. The (*E*)-alkenylphosphinates (**54**) and (*E*)-alkenylphosphine oxides (**55**) were synthesized in moderate to excellent yields (52–90 and 34–87%, respectively). The catalyst could be reused at least twice more without significant decrease in the yield.

3.3 MS-4A supported heterogeneous metal catalysts in multicomponent reactions

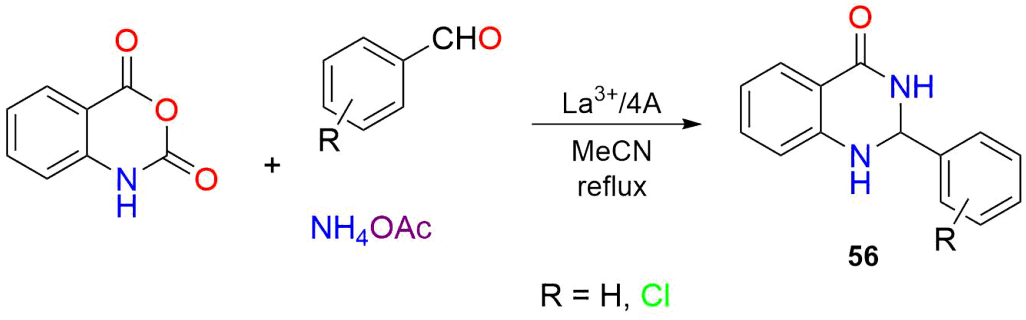
Multicomponent reactions (MCRs) have emerged as valuable and efficient tools in the hands of synthetic organic chemists, as they have several advantages over the classical synthetic strategies. They can provide complex organic compounds in a single step from three or more readily available substrates without the isolation of any intermediates. The further advantages of the MCRs are the shorter reaction time and the less side products together with lower energy consumption and waste production, thus they can provide environmentally more friendly processes.

We have successfully applied our MS-4A supported metal catalysts in several MCRs, yielding different heterocycles having pharmaceutical interest. The examined reactions are acid-catalyzed processes, and the pH of the catalysts are basic, the results were nevertheless generally very good. This can be explained as follows; the metal particles are settled on the surface of the support, forming acidic centers. The reactions take place on these metal seats.

Isatoic anhydride, aldehydes, and ammonium acetate in the presence of lanthanum on MS-4A (La^{3+}/4A) in refluxing acetonitrile gave 2-substituted 2,3-dihydroquinazolin-4(1*H*)-ones **56** in good to excellent (65–93%) yield (Scheme 26) [57]. Benzaldehyde dimethylacetal instead of benzaldehyde, as well as benzylamine instead



Scheme 25 Conversion of *H*-phosphinates and phosphine oxides to (*E*)-alkenylphosphinates (**54**) and (*E*)-alkenylphosphine oxides (**55**)



Scheme 26 Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones (**56**) using a La^{3+}/4A catalyst

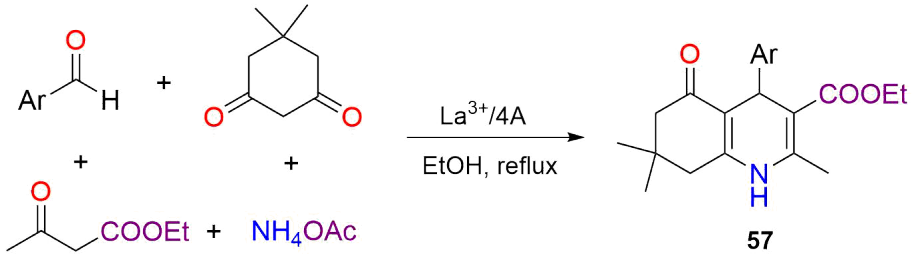
of ammonium acetate gave the appropriate derivatives with also good yield. The catalyst could be reused with the same result after stirring in boiling acetone for 5 h, then drying at 150 °C for 1 h.

La^{3+}/4A also efficiently catalyzed the reaction of dimedone, ethyl acetoacetate, ammonium acetate and aromatic aldehydes in refluxing ethanol yielding polyhydroquinoline derivatives **57** in high yields (Scheme 27) [58]. No electronic or steric effect of the substituents on the aromatic ring has been observed. The catalyst could be reused in at least two more runs without change in the yield.

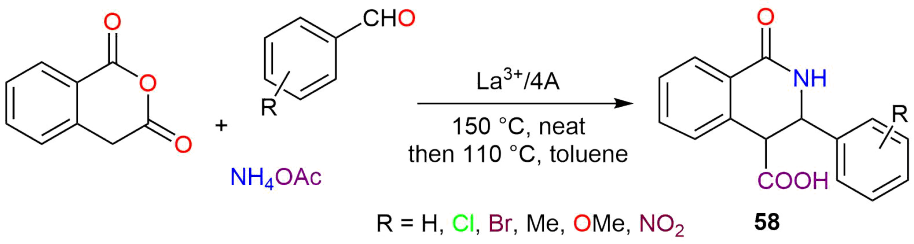
Tetrahydroisoquinolonic acid derivatives **58** were prepared in the reaction of homophthalic anhydride, ammonium acetate and aldehydes catalyzed by La^{3+}/4A (Scheme 28) [59]. Indium and zinc were also efficient, but they gave lower yields. The catalyst could be reused without significant loss of activity. This multicomponent reaction is also described as an acid-catalyzed one in the literature, using a slightly basic catalyst (pH = 8.40) is exceedingly rare.

2,4,5-Triarylimidazoles **59** has been synthesized with good to excellent yields by one-pot condensation reaction benzaldehydes, benzil, and ammonium acetate in the presence of 4Å molecular sieves modified with titanium(IV) (Scheme 29) [60]. This catalyst is also slightly basic (pH = 7.35), but it worked excellently in this typically acid catalyzed reaction during several runs.

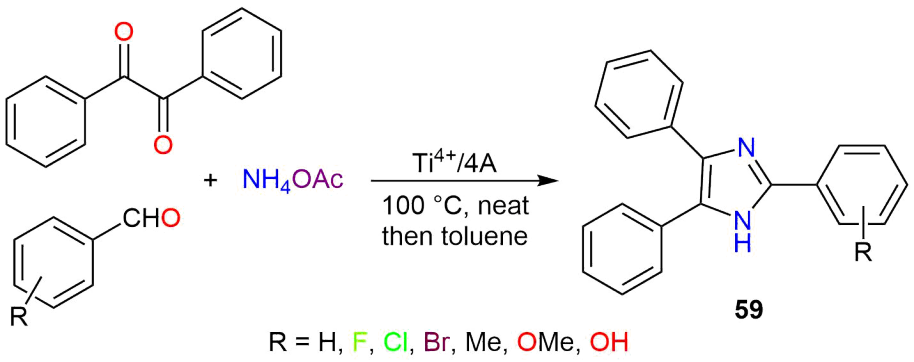
In the reaction of aldehydes, malononitrile and a compound with active methylene group, such as ethyl acetoacetate, in the presence of different acidic or basic catalysts 4*H*-pyran derivatives can be obtained. We found that using Zn^{2+}/4A (pH = 9.71) as a catalyst, 4*H*-pyrans **60** were



Scheme 27 Synthesis of polyhydroquinoline derivatives (**57**) over a La^{3+}/4A catalyst



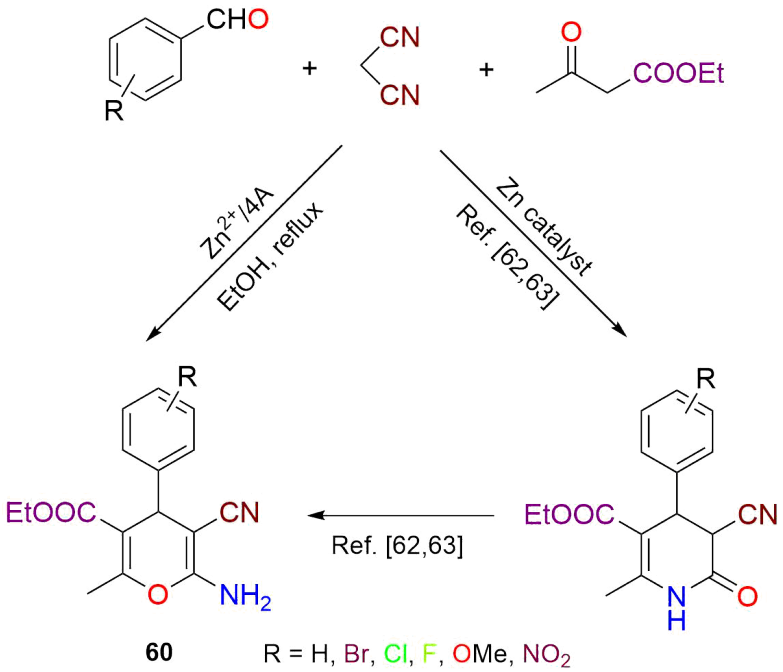
Scheme 28 La-catalyzed multicomponent reaction yielding tetrahydro-isoqunolonic acid derivatives (**58**)



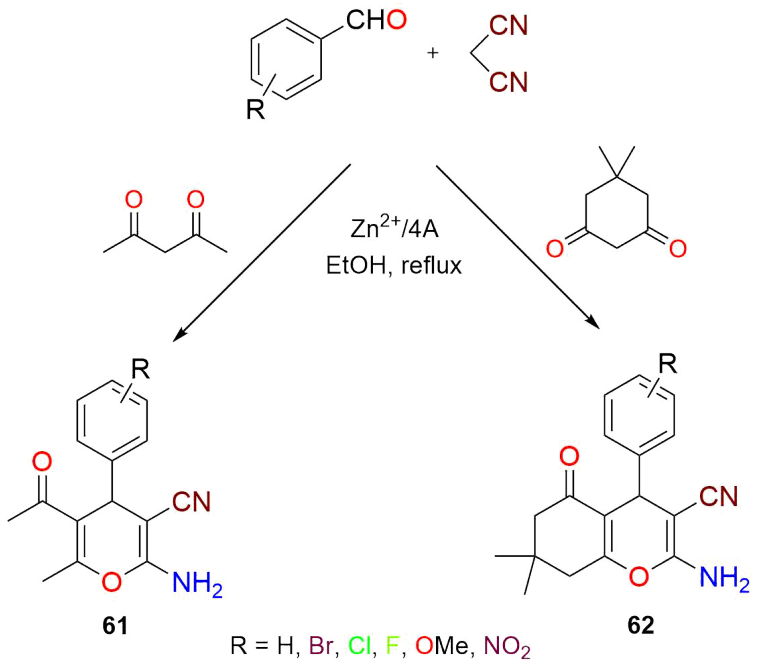
Scheme 29 Ti-catalyzed multicomponent synthesis of 2,4,5-triarylimidazole derivatives (**59**)

obtained with excellent yield (93–97%, Scheme 30) [61]. In the literature there were only few examples to the use of zinc or zinc derivatives in this reaction [62, 63]. Moreover, it was described in [62] that the reaction was not chemoselective, near the required 4*H*-pyran derivatives a respective 2-pyridinone by-product was always obtained. In our case no traces of such by-product were observed. Using acetylacetone or dimedone instead of ethyl acetoacetate the respective derivatives **61** and **62** were formed also in excellent yield (80–98 and 91–98%, respectively, Scheme 31).

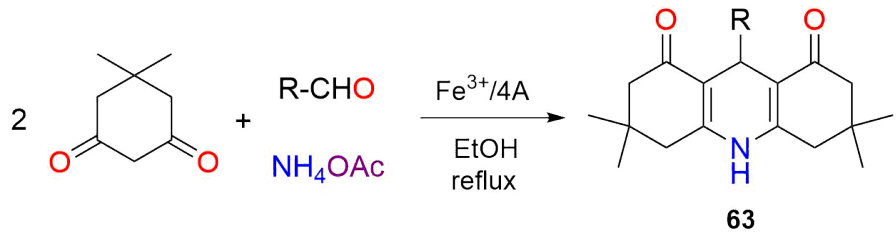
Dimedone, aldehydes and ammonium acetate in the presence of Fe^{3+}/4A (pH = 8.42), in boiling ethanol yielded acridindione derivatives **63** in a four-component reaction (50–98%, Scheme 32) [64]. Ti^{4+}/4A, Zr^{4+}/4A and Zn^{2+}/4A showed similar activity, but **63** was obtained with a slightly lower yield.



Scheme 30 Zn-catalyzed synthesis of 4*H*-pyran derivatives (**60**)



Scheme 31 Multicomponent reaction with acetylacetone or dimedone using a Zn^{2+}/4A catalyst



R = Ph, 4-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-MeOC$_6$H$_4$, 3-NO$_2$C$_6$H$_4$, Pr

Scheme 32 Fe-catalyzed synthesis of acridindione derivatives (**63**)

4 Conclusion

As a result of our R&D works, several heterogeneous catalytic hydrogenation methods were developed which proved to be very efficient in the syntheses of important and valuable pharmaceutical intermediates. These processes, however, can also be implemented on an industrial scale in an easier way, because the reaction conditions (pressure, temperature, catalysts) and the reactors (autoclaves) are very similar to those applied in the fine chemical industry.

In addition, our MS-4A supported transition metal (Pd, Cu, La, Ti, Zn) catalysts were successfully applied in several arylations, multicomponent reactions yielding different heterocycles having also pharmaceutical interest. Moreover, these heterogeneous catalysts induced more selective reactions than the homogeneous ones published previously. In some cases, interesting side-reactions were observed.

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