



Budapest University of Technology and Economics
Faculty of Chemical Technology and Biotechnology

The use of palladium or copper catalysts on mixed oxide and molecular sieve supports in organic synthesis

Thesis summary

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1. Introduction

In most of the organic chemical reactions it is necessary to use a compound having catalytic activity. Apart from the catalytic oxidation and reduction, most of these materials are acids or bases. Both the preparation of the traditional mineral acids, and their disposal after the reaction result the formation of environmentally harmful waste. The same can be stated about the conventional bases too. In consequence several heterogeneous catalysts were developed in the last decades, which are cheap, non-toxic, catalytically active, selective and stable even at mild reaction conditions. There is no need for their neutralization, therefore the salt and acid content of the industrial wastewaters decrease. The catalyst can be separated *via* filtration making the technology simpler, decreasing the time and the energy consumption of the downstream. Most of these catalysts are non-corrosive, but the solid materials can have an eroding effect. Some natural or synthetic minerals can be readily used as a heterogeneous catalyst due to their acido-basic and/or redox properties; others are applied as a support for very active transition metal catalysts. Often, the filtered catalyst can be reused several times. They are cheap because they are (partially modified) natural materials. High selectivity can be reached using them, under mild conditions. Synthetic clay minerals can possibly be optimized for their specific task. The hollow structure can help performing highly region- and stereoselective reactions.

At the Budapest University of Technology and Economics, in the research group of the Department of Organic Chemistry and Technology the application of heterogeneous catalysts in organic syntheses has been studied over decades. Coupling reactions were carried out in the presence of a Pd⁰/MgLaO catalyst as Heck¹, Sonogashira² and Suzuki-Miyaura³ reactions. Furthermore, Cu²⁺/4A catalyst proved to be efficient for the A3-coupling⁵.

In the framework of my thesis, based on earlier results of the group, I studied the use of different solid base supports (MgLaO and 4 Å molecular sieve) modified by different metals (Cu and Pd) as a catalyst in organic syntheses.

2. Literature

In the supported catalysts the support serves as the shell or the binder for the active component – often the catalyst metal. The support has usually little or no activity in the reaction, but its amount is significantly higher. Formerly, the support was used to spare the active component and to ensure the large dispersity of the active constituent. However, the quality and the physical chemistry attributions (*e.g.* the acidity or basicity) of the support can notably effect the catalytic activity, the selectivity, the lifespan, the regenerability and the sensibility to poisons; they can increase the surface and stabilise the large dispersity of the active component and can act as a promotor⁶.

¹ Cwik, A.; Hell, Z.; Figueras F. *Adv. Synth. Catal.* **2006**, *348*, 523.

² Cwik, A.; Hell, Z.; Figueras F. *Tetrahedron Lett.* **2006**, *44*, 3023.

³ Cwik, A.; Hell, Z.; Figueras F. *Org. Biomol. Chem.* **2005**, *3*, 4307.

⁴ Kiss, Á.; Hell, Z.; Bálint, M. *Org. Biomol. Chem.* **2010**, *8*, 331.

⁵ Fodor, A.; Kiss, A.; Debreczeni, N.; Hell, Z.; Gresits, I. *Org. Biomol. Chem.* **2010**, *8*, 4575.

⁶ Petró, J. *Kontakt katalízis* (szerk.: Szabó, Z.; Kalló, D.), Akadémiai Kiadó, **1966**, 498.

Many materials can serve as supports, basically, there are natural (*e.g.* diatomaceous earth, bauxite) and synthetic (different metal oxides, graphite, synthetic zeolites) options. During my PhD I had used magnesium-lanthanum mixed oxide and 4Å molecular sieve as a support.

Molecular sieves has widely been used in the chemical industry since years, mostly for the drying of gases, solvents and other liquid reagents, and the largest part of these materials are still manufactured for this purpose. However, the range of their use is wider – molecular sieves can be catalysts in organic syntheses due their acidic or basic properties, or water absorbing abilities. They can also serve as supports for metal catalysts.

Magnesium-lanthanum mixed oxide (MgLaO) was prepared by our research group in cooperation with a group of the Institut de Recherches sur la Catalyse (Lyon) using a co-precipitation method⁷. According to the adsorption microcalorimetry measurement the MgLaO is stronger base than the hydrotalcite and worked as a basic catalyst in the Michael-addition⁸ and the Wadsworth-Emmons⁹ reactions.

3. Experimental methods

Organic compounds were identified by ¹H-NMR and ¹³C-NMR spectroscopy and/or GC-MS measure. The melting point of the solid materials was measured and was compared with the literature.

⁶ Petró, J. *Kontakt katalízis* (szerk.: Szabó, Z.; Kalló, D.), Akadémiai Kiadó, **1966**, 498.

⁷ Lopez, J. *Synthèse et caractérisation de catalyseurs hétérogènes basiques et leur application aux réactions de condensation aldolique*, PhD értekezés, **1999**.

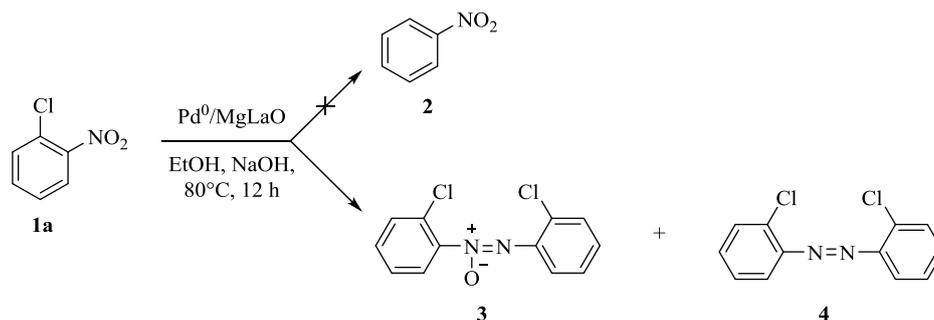
⁸ Veldurthy, B.; Clacens, J.-M.; Figueras, F. *Adv. Synth. Catal.* **2005**, 347, 767.

⁹ Kantam, M. L.; Kochkar, H.; Clacens, J.-M.; Veldurthy, B.; Garcia-Ruiz, A.; Figueras, F. *Appl. Catal. B* **2005**, 55, 177.

4. Results and Discussion

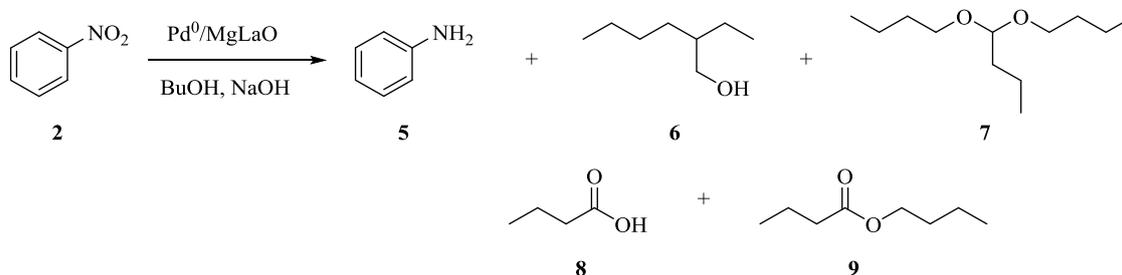
4.1. Palladium-catalyzed transfer hydrogenation of nitrobenzenes: investigation of the selectivity [P1]

Earlier we examined the dehalogenation of different aryl halides using our supported palladium catalyst (Pd⁰/MgLaO) in the presence of NaOH. When 2-chloronitrobenzene (**1a**) was used as a substrate, surprisingly, instead of nitrobenzene (**2**) the mixture of 2,2'-dichloro-azoxybenzene (**3**) and 2,2'-dichloroazobenzene (**4**) was obtained.

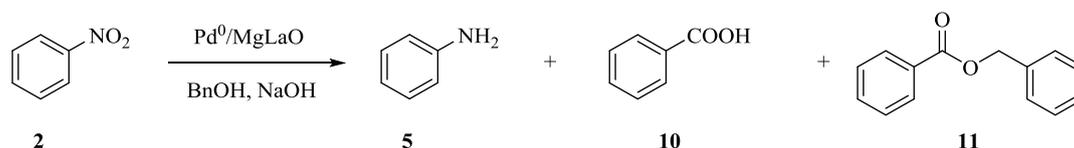


We also investigated the reaction of nitrobenzene under these conditions. After 8.5 hours with 1.5 equivalent NaOH the product was a 90:10 mixture of azobenzene and aniline; after 11 hours and using 3 equivalent NaOH the ratio of these two products changed to 38:62.

Examining the reaction pathway the solvent was changed for *n*-BuOH and benzyl alcohol.



In butanol different aldol-products (**6**, **7**), butyric acid (**8**) and butyl butyrate (**9**) were found in the reaction mixture, proving that the reaction was a transfer hydrogenation, where the reducing agent was the alcohol, used as solvent,



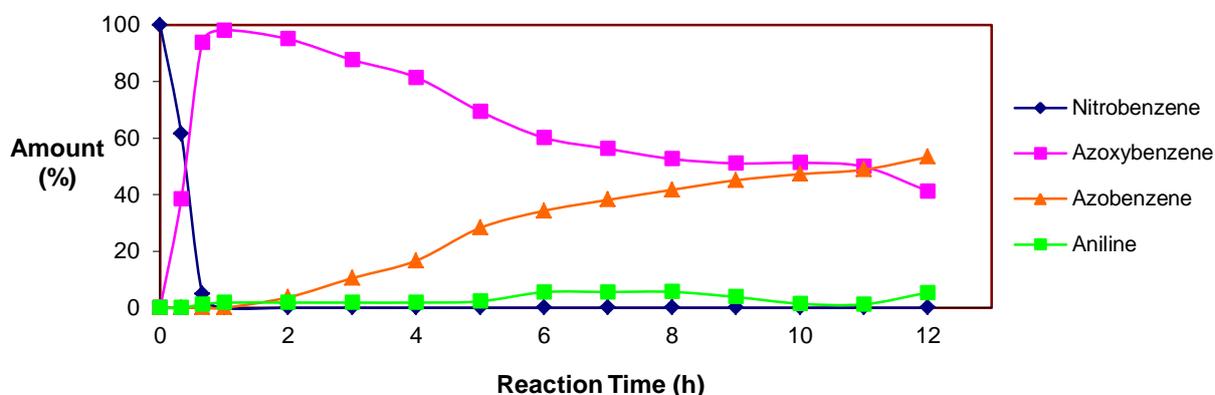
Using benzyl alcohol, the results also confirmed the reaction path – benzoic acid (**10**) and benzyl benzoate (**11**) were present in significant amount. Thus in this case Tishchenko reaction occurred instead of aldol reactions.

The progress of the reaction

I investigated the progress of the reaction. Two different catalysts (Pd^0/MgLaO , $\text{Pd}^0/4\text{A}$) and three different amounts of base were used (1.5, 3 and 4.5 equivalents) in ethanol, and samples were taken from the mixture in every hour. Based on the analytical results, the next statements can be made regarding the selective synthesis of the products and intermediates:

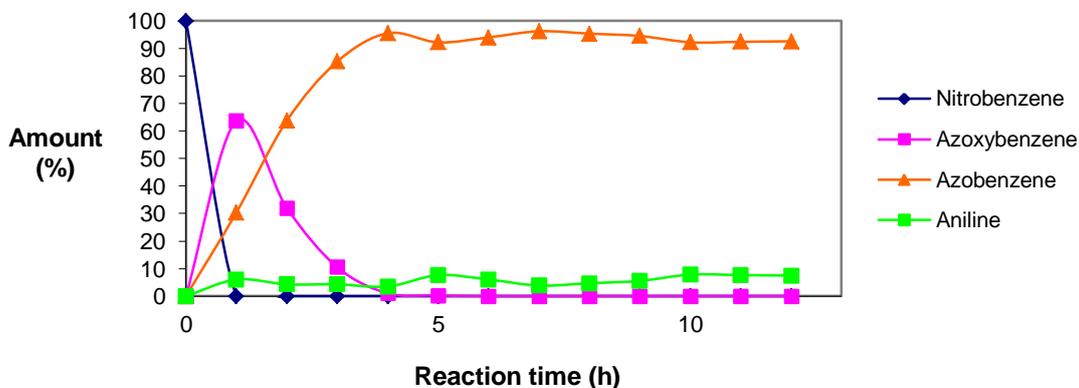
- **Azoxybenzene** can be synthesized with excellent purity by both catalysts, using 1.5 equivalent NaOH with 1 hour reaction time. By $\text{Pd}^0/4\text{A}$ a slightly better purity can be reached, and economical reasons also support the use of this material, because the mixed oxide has to be prepared, while the molecular sieve is commercially available, and requires only an impregnation with the metal salt.

Pd-4A, 1,5x NaOH

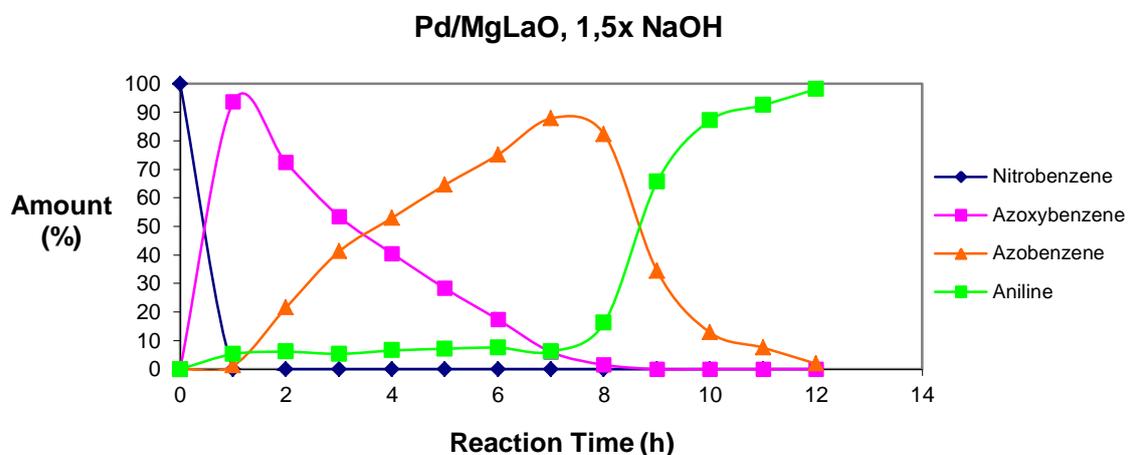


- **Azobenzene** could be prepared by $\text{Pd}^0/4\text{A}$ with 3 and 4.5 equivalents NaOH, too, with excellent purity (95%). In case of $\text{Pd}^0/4\text{A}$ azobenzene is the final product. Pd/MgLaO is also suitable when 3 or 4.5 equivalents base were used, but this reaction is less robust, because when the reaction time is shorter or longer, the main product will be either the azoxybenzene or the aniline.

Pd-4A, 3x NaOH



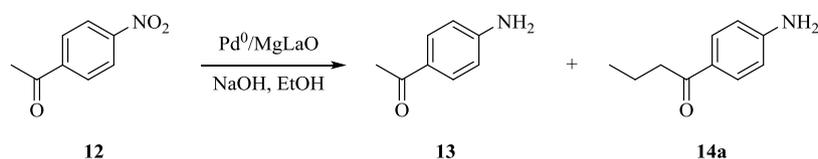
- **Aniline** can only be obtained using MgLaO support catalyst. After 12 hours with 1.5 equivalent base 98 % pure aniline can be isolated, it is not necessary and uneconomic to use more NaOH. More bases should be added when reaction time should be shortened.



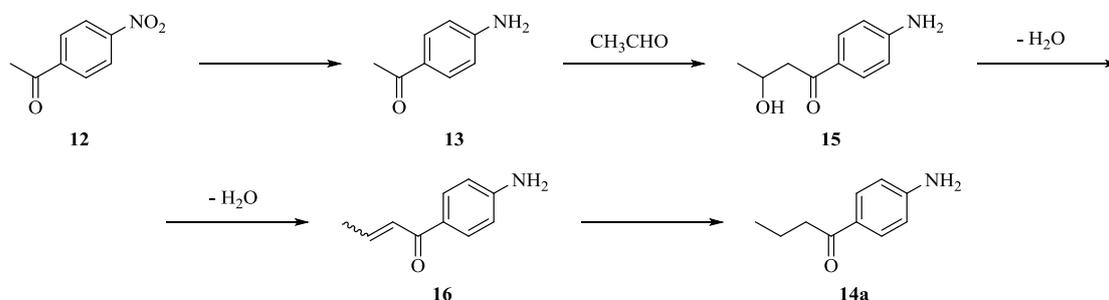
4.2. Transfer hydrogenation of nitrobenzenes [P2]

Reduction of substituted nitrobenzenes

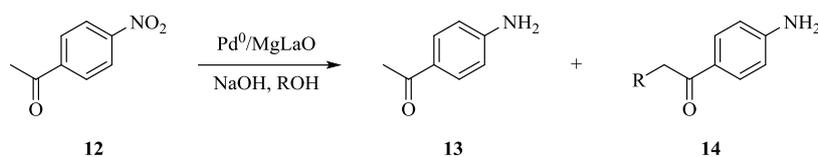
Using the method described in the previous section, we examined the reduction of other nitrobenzene derivatives. From 2-chloronitrobenzene the expected azoxy-, azo- and aminocompounds were formed, but in case of 4-nitroacetophenone an unexpected side-product appeared – the acetyl side chain of the molecule elongated with an ethyl group.



The following pathway is proposed for this reaction. After the reduction of the nitro group, an aldol-type reaction of the **13** acetophenone and the acetaldehyde derived from the alcohol occurs. This is followed by the dehydration of intermediate β -keto-alcohol (**15**), and the final product (**14a**) is formed by reduction of the olefinic double bond of **16**.



On examining other alcohols in this reaction, we obtained the following results.



Entry	ROH	Reaction time (h)	Yield ^a
1	MeOH	24	13 (84), 14b (16)
2	<i>n</i> -PrOH	24	13 (20), 14c (42), 17 (33)
3	<i>i</i> -PrOH	12	13 (~ 100)
4	<i>n</i> -BuOH	24	13 (25), 14d (73)
5	<i>i</i> -BuOH	24	13 (16), 14e (75)

Conditions: 5 mmol **38**, 0.2 g catalyst, 0.6 g NaOH, 10 ml alcohol, reflux.

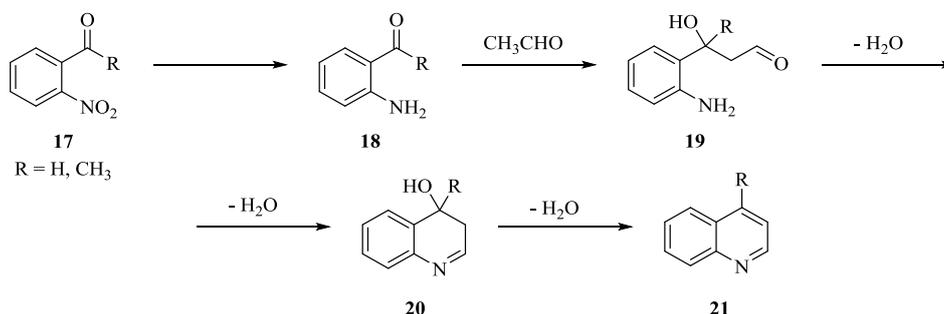
^aBased on GC-MS analysis of the product.

In *n*-propanol, a significant amount of 1-(4-aminophenyl)-2-propylpentan-1-one (**17**) was formed via the addition of two propyl groups onto 4-aminoacetophenone.

Reactions of other acetophenone and benzaldehyde derivatives

We also investigated the reactions of other acetophenones as well as benzaldehyde derivatives in ethanol under the conditions used above. In almost every case the chain-elongation occurred, but only with low conversions. In the reaction of acetophenone, mainly 1-phenyl-1-butanol, 1-phenylethanol and the acetophenone dimer, 1,3-diphenylbutan-1-ol were obtained, the oxo group did not remain intact. 4-Chloroacetophenone gave mainly acetophenone, so dehalogenation occurred. 2-Nitroacetophenone gave the appropriate aniline as main product, but 4-methylquinoline was also obtained in significant amount.

Benzaldehydes did not give the desired chain-elongated products, but interesting side products appeared, for example when 2-nitrobenzene was used, the quinoline derivative was obtained again. The formation of the quinoline derivatives can be explained by the reaction of the intermediate amino-carbonyl compound (**18**) with acetaldehyde, to give an aldehyde (**19**) which undergoes intramolecular cyclisation.

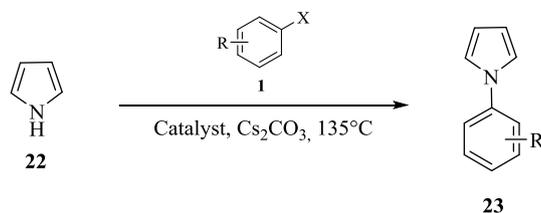


4.3. A heterogeneous catalytic method for the *N*-arylation of pyrrole and other *N*-heterocycles [P3]

Continuing my work, I examined the Ullmann reaction of aryl halides and pyrrole. Cu²⁺/4A and Cu⁰/4A catalysts were used.

I started with the optimization choosing the coupling of pyrrole and iodobenzene as a model reaction. I observed, that the best yield with the shortest reaction time can be reached, using Cs₂CO₃ as base, and pyrrole itself as solvent. This way after just 4 hours full or nearly full conversion could be obtained with both catalysts.

Under the optimal conditions we examined the reaction of pyrrole with other aryl halides.



Entry	Reagent	Time	Yield ^a (%)
1	Iodobenzene	4	100 (23a , 86 ^b)
2	Iodobenzene	4	86 ^c
3	4-Iodotoluene	4	100 (23b , 76 ^b)
4	4-Iodoanisole	4	100 (23c , 73 ^d)
5	4-Iodoanisole	4	100 (23c) ^c
6	3-Iodotoluene	4	100 (23d , 86 ^b)
7	2-Iodophenol	4	77 (23e), 2 (fenol)
8	4-Iodo-nitrobenzene	4	90 (23f , 74 ^d), 8 (23g , amino compound), 2 (2)
9	3-Iodo-nitrobenzene	4	42 (23h), 46 (23i , amino compound)
10	3-Iodo-nitrobenzene	15	25 (23h), 69 (23i)
11	3-Iodo-nitrobenzene	4	81 (23h), 10 (23i), 9 (2)
12	Bromobenzene	24	71 (23a)
13	4-Bromoanisole	24	100 (23c , 95 ^d)
14	4-Bromoanisole	24	4 ^c (23c)
15	2-Bromoanisole	24	100 (23j)
16	4-Bromo-ethylbenzene	24	90 (23k)
17	4-Bromoacetophenone	24	23l
18	2-Bromobenzaldehyde	24	0 ^f
19	4-Bromobenzaldehyde	24	0 ^f
20	4-Bromobenzonitrile	24	36 (23m)
21	Chlorobenzene	36	0 (23a)

Conditions: 3 mmol **1**, 0.3 g Cu⁰/4A, 6 mmol Cs₂CO₃, 3 ml pyrrole, 135°C.

^aBased on GC-MS analysis of the reaction mixture

^bIsolated yield

^cWith Cu²⁺/4A catalyst

^dIsolated yield after recrystallization.

^eat 115°C temperature

^fMixture of unidentified compounds, desired product did not occur.

Most iodo and bromo compounds gave good yields. For aryl iodides Cu²⁺/4A was also an effective catalyst, but aryl bromides only reacted in the presence of Cu⁰/4A. Chlorobenzene did not react, even after longer reaction time. Interestingly, starting from nitrobenzenes the product was a mixture of the appropriate nitro and amino compounds – probably via a transfer hydrogenation where the hydrogen source is the pyrrole, but we could not proof this theory so far.

The reusability of the catalysts was also tested. Cu⁰/4A could be used at least 4 times without a significant decrease in activity, but the catalytic effect of Cu²⁺/4A decreased largely after the second and third use (from 100% to almost 30%).

The arylations of other *N*-heterocycles were also successfully performed with iodobenzene as reagent and dimethylformamide as solvent. Both Cu²⁺/4A and Cu⁰/4A were effective catalysts.

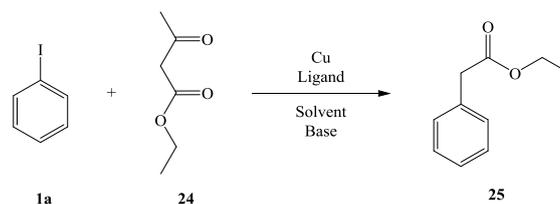
Entry	Catalyst	Reagent	Yield ^a
1	Cu ⁰ /4A	Imidazole	100
2	Cu ²⁺ /4A	Imidazole	100
3	Cu ⁰ /4A	Pyrazole	100
4	Cu ²⁺ /4A	Pyrazole	100
5	Cu ⁰ /4A	Indole	90
6	Cu ²⁺ /4A	Indole	96

Conditions: 6 mmol heterocycle, 3 mmol iodobenzene, 0.3 g catalyst, 6 mmol Cs₂CO₃, 5 mL DMF, 150°C, 24 h

^aBased on the GC-MS analysis of the reaction mixture.

4.4. Heterogeneous catalytic arylation of CH-acidic compounds [P4]

The applicability of Cu²⁺/4A catalyst in the reaction of aryl halides and CH-acidic compounds (ethyl acetoacetate, acetylacetone and malonic esters) was examined. First, on the model reaction of iodobenzene and ethyl acetoacetate I optimized the conditions.



The best result, almost full conversion was obtained in dioxane, with Cs₂CO₃ base, at 100°C under 24 hours. The product was **25** phenylacetic acid ester. By taking samples in every hour, the progress of the reaction was investigated, and I found that the conversion does not change significantly after 12 hours. Other CH-acidic chemicals were also examined (diethyl malonate, acetylacetone, Meldrum's acid), but no reaction occurred with iodobenzene.

Other aryl-iodides under the optimal conditions gave the following results.

Entry	Reagent	Yield ^a
1	2-Iodophenol	- ^b
2	3-Iodo-nitrobenzene	90
3	4-Iodo-nitrobenzene	90
4	3-Iodotoluene	75
5	4-Iodotoluene	75
6	4-Iodoanisole	33
7	4-Iodotoluene	84

Conditions: 5 mmol Reagent, 7.5 mmol ethyl acetoacetate, 0.5 g Cu²⁺/4A, 12.5 mmol Cs₂CO₃, 10 ml dioxane, 100°C, 12 h.

^aBased on GC-MS analysis.

^bProduct could not be isolated.

Beside aryl iodides, aryl bromides were also tested in this reaction, but the coupling did not occur under the optimal conditions, the bromides are probably not reactive enough for the heterogeneous catalytic reaction.

5. Thesis points

I summarize my work in the following thesis points:

1. Palladium (0) on magnesium-lanthanum mixed oxide (Pd^0/MgLaO) and on 4A molecular sieve support ($\text{Pd}^0/4\text{A}$) were used successfully as a catalysts in the reduction of nitrobenzene compounds via transfer hydrogenation. By changing the reaction conditions (catalyst, amount of base, reaction time) the intermediates of the reduction – azoxybenzene, azobenzene and aniline - were successfully, selectively synthesized. Using butanol and benzyl alcohol as solvents, the identified components confirmed the transfer hydrogenation pathway of the reaction, where the hydrogen source is the appropriate alcohol.

2. I found, that in the Pd^0/MgLaO catalyzed reaction of 4-nitroacetophenone in ethanol not just the reduction of the nitro group, but a chain-elongation of the acetyl group also occurred. I suggested a pathway, in which the acetaldehyde (formed during the transfer hydrogenation) reacts with the molecule, giving the isolated product after a dehydration step. The chain-elongation was performed with other alcohols too, but in cases of secondary and tertiary alcohols only the reduction of the nitro group occurred. Other acetophenones and nitroacetophenone gave the chain-elongated derivatives too, but it was a minor product in every examined case.

3. *N*-Arylation of pyrrole with aryl halides was successfully performed in the presence of $\text{Cu}^0/4\text{A}$ or $\text{Cu}^{2+}/4\text{A}$ catalyst, using the pyrrole itself as solvent. With iodobenzenes after 4 hours full conversion could be reached. $\text{Cu}^0/4\text{A}$ catalysed the coupling of bromo compounds too. From halides containing nitro group, the appropriate amines were also obtained, and after increasing the reaction time they became the main product. $\text{Cu}^0/4\text{A}$ could be reused at least three times without a decrease in activity. Other *N*-heterocycles (imidazole, pyrazole, indole) were also arylated successfully with excellent conversions.

4. The heterogeneous catalytic reaction of aryl iodides with ethyl acetoacetate was successfully performed using $\text{Cu}^{2+}/4\text{A}$ as catalyst. Good conversions were obtained in several cases, and I observed the effect of the substituents to the conversion.

6. Applicability

In organic chemistry, using heterogeneous catalysts instead of homogeneous ones has many advantages. According to our results, the catalysts prepared by us and the described reactions can offer significant help in laboratory work, and also industrial use can be discussed. The interesting reactions introduced earlier can help to widen the chemical space. The preparation of the applied catalysts is simple, the support is cheap, commercially available or can be synthesized from cheap starting materials by simple methods. The prepared catalysts can be reused directly, or after a simple pre-heating with good results.

7. Publications

Full scientific publications related to the PhD Thesis

[P1] Németh, J.; Kiss, Á.; Hell, Z. *Palladium-catalyzed transfer hydrogenation of nitrobenzenes; examination of the effect of the supports on the selectivity* Reaction Kinetics, Mechanism and Catalysis **2013**, *111*, 115-121. (IF: 0,983, (2013); NJ: 100%)

[P2] Németh, J.; Kiss, Á.; Hell, Z. *Palladium-catalysed transfer hydrogenation of aromatic nitro compounds – an unusual chain elongation* Tetrahedron Letters **2013**, *54*, 6094-6096. (IF: 2,391 (2013); NJ: 100%)

[P3] Németh, J.; Debreczeni, N.; Gresits, I.; Bálint, M.; Hell, Z. *An efficient heterogeneous catalytic method for the N-arylation of pyrrole and other heterocycles* Catalysis Letters, **2015**, *145*, 1113-1119. (IF: 2,307 (2014); NJ: 60%)

[P4] Zsolczai, D.; Németh, J.; Hell, Z. *Selective synthesis of arylacetic acid esters from ethyl acetoacetate and aryl halides in the presence of copper(II) on 4Å molecular sieve* Tetrahedron Letters, **2015**, *56*, 6389-6392. (IF: 2,379 (2014); NJ: 60%)

Further publications

[P5] Takács, A.; Fodor, A.; Németh, J.; Hell, Z. *Zeolite Catalysed Method for the Preparation of 2,3-dihydroquinazolin-4(1H)-ones* Synthetic Communications, **2014**, *44*, 2269-2275. (IF: 0,984 (2013); NJ: 20%)

[P6] Fodor, A., Németh, J.; Hell, Z. *Application of a clinoptylolite-type zeolite in the synthesis of different heterocycles* Current Green Chemistry, **2014**, *1*, 249-256. (IF: -; NJ: 50%)

[P7] Kiss, Á.; Németh, J.; Fodor, A.; Hell, Z. *Supported metal catalysts in organic syntheses* Periodica Polytechnica, **2015**, *59*, 72-81. ((IF: 0,296 (2014); NJ: 50%)

Oral and poster presentations

[P8] Németh, J.; Molnár, L.; Kiss, Á.; Hell, Z. *Hordozós fémkatalizátorok alkalmazása szerves kémiai reakciókban* Oláh György Doktori Iskola X. Konferenciája **2013**, Budapest – oral presentation

[P9] Németh, J.; Kiss, Á.; Hell, Z. *Investigation of Different Organic Reactions Catalysed by Metals on Heterogeneous Supports* 4th EuCheMS Chemistry Congress **2012**, Prága – poster presentation

[P10] Németh, J.; Kiss, Á.; Hell, Z. *Investigation of Heterogeneous Palladium-Catalysed Reactions* YoungChem2011 International Congress of Young Chemists **2011**, Krakkó – poster presentation

[P11] Németh, J.; Kiss, Á.; Hell, Z. *Heterogén palládiumkatalizált reakciók vizsgálata* Oláh György Doktori Iskola IX. Konferenciája **2012**, Budapest – poster presentation

[P12] Németh, J., Kiss, Á.; Hell, Z. *Hordozós fémkatalizátorok alkalmazása szerves kémiai reakciókban* MKE Vegyészkonferencia **2013**, Hajdúszoboszló – poster presentation
