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FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY
GEORGE OLAH DOCTORAL SCHOOL

INVESTIGATION OF THE SELECTIVITY OF HETEROGENEOUS CATALYTIC ORGANIC SYNTHESSES

Summary of Ph.D. thesis

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1. Introduction

Nowadays more than 90% of chemical processes require some kind of catalyst to achieve the desired conversion.¹ A significant amount of these catalysts is some kind of mineral acid, base, metal salt or metal complex, which have lots of negative properties: they are toxic, corrosive and a large amount of waste is produced during their production and the workup of the reaction, which is harmful to the environment. In addition, these catalysts cannot be used for industrial syntheses, due to their high cost and the reaction conditions required for their operation. As a result the production of new heterogeneous catalysts, which are more selective, more active and easier to handle, has recently become important. Another crucial aspect is, that these catalysts should be reusable to reduce the environmental impact. Researchers have used a number of naturally occurring mineral-type substances as catalysts in organic syntheses. Their advantages are that they are non-toxic, non-corrosive and easily filtered out of the reaction mixture at the end of the reaction. Usually they can be reused immediately or after minimal treatment without significant loss of activity.

A further advantage of heterogeneous catalysts is that, due to their special chambered structure, some of them show significant regio- and stereoselectivity in certain reactions under relatively mild conditions. In case of synthetic clay minerals, these properties can even be tailored to the specific task.

At the Department of Organic Chemistry and Technology of the Budapest University of Technology and Economics researchers have been studying the applicability of solid acids and bases as catalysts or catalyst supports and have been developing catalytic synthetic methods for decades. In our research group molecular sieve supported copper and palladium catalysts, Mg-La mixed oxide supported palladium and nickel catalysts have been synthesized. These catalysts were successfully used in different carbon-carbon coupling reactions, such as *Suzuki*-,² *Heck*-³ and *Sonogashira*-reaction.⁴ The 4Å molecular sieve supported metal catalysts proved to be effective in the so called A³-reaction,⁵ different multicomponent reactions^{6,7} and the transfer hydrogenation of nitrobenzenes.⁸

¹ Armor, J. N. *Catal. Today* **2011**, 163 (1), 3-9.

² Cwik, A.; Hell, Z.; Figueras, F. *Org. Biomol. Chem.* **2005**, 3 (24), 4307-9.

³ Cwik, A.; Hell, Z.; Figueras, F. *Adv. Synth. Catal.* **2006**, 348 (4-5), 523-530.

⁴ Cwik, A.; Hell, Z.; Figueras, F. *Tetrahedron Lett.* **2006**, 47 (18), 3023-3026.

⁵ Fodor, A.; Kiss, A.; Debreczeni, N.; Hell, Z.; Gresits, I. *Org. Biomol. Chem.* **2010**, 8 (20), 4575-81.

⁶ Magyar, Á.; Hell, Z. *Catal. Lett.* **2016**, 146 (6), 1153-1162.

⁷ Magyar, Á.; Hell, Z. *Green Process. Synth.* **2018**, 7 (4), 316-322.

⁸ Németh, J.; Kiss, Á.; Hell, Z. *React. Kinet. Mech. Cat.* **2013**, 111 (1), 115-121.

During my PhD work I have joined this research and studied the applicability and selectivity of the 4Å molecular sieve supported metal catalysts synthesized earlier in organic syntheses. In addition, new MgO and Mg-Al mixed oxide supported metal catalysts have been prepared and tested in different organic reactions. My goal was to elaborate new, industrially and environmentally significant heterogeneous catalytic methods using the new catalysts and the ones prepared earlier in our research group. In the reactions the regio- and stereoselectivity of the catalysts was examined as well.

2. Literature survey

In supported catalysts the support is usually the skeleton or binder material for the active component, typically a catalyst metal. It was assumed that the appropriate support has a low activity or no activity at all. The amount of the support in a supported catalyst is usually much higher than that of the active component. Earlier the support has been used for economic considerations to reduce the amount of the active component. However, later on it was observed, that the properties of the support can affect the activity, the selectivity, the lifetime, the regenerability and the sensitivity to toxic compounds of the catalyst. In addition to increasing the surface area of the active component and stabilizing its dispersity, the support can in many cases act also as a promoter. Due to its acidic or basic properties, the support can replace the ligands generally required in homogeneous catalysis.⁹

Molecular sieves have been used for a long time in many fields of the chemical industry, usually for drying liquid reagents, solvents and gases. In addition, 4Å pore size molecular sieve is a widely used environmentally friendly catalyst with excellent stability and mechanical, thermal and osmotic resistance.¹⁰ Moreover, it is a cheap and readily available compound, which can be used both in an organic and an aqueous medium. Due to its water absorbing ability the 4Å molecular sieve is often used as a drying agent and in reactions where water is formed. The 4Å molecular sieve can also be effectively used for the enhancement of enantioselectivity, in decarboxylative Mannich and aldol reactions and in multicomponent reactions.¹¹

⁹ Petró, J., *Kontakt katalízis*. ed.; Akadémiai Kiadó: Budapest, **1966**.

¹⁰ Gujar, J. B.; Chaudhari, M. A.; Kawade, D. S.; Shingare, M. S. *Tetrahedron Lett.* **2014**, 55 (44), 6030-6033.

¹¹ Magyar, Á.; Juhász, K.; Hell, Z. *Synthesis* **2020**, 53 (02), 279-295.

3. Experimental methods

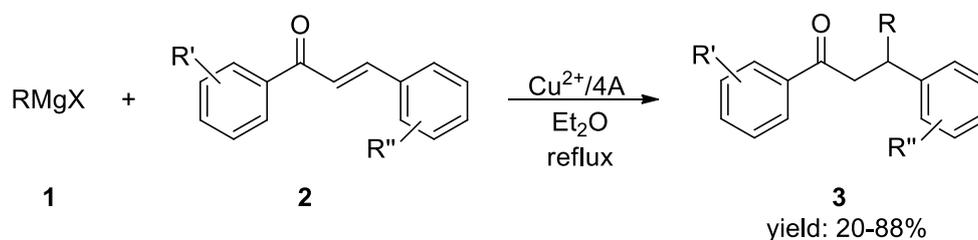
The physicochemical properties of the catalysts have been examined by SEM-EDS and BET methods, their metal content has been determined by ICP-OES. The synthesized compounds have been identified by mass spectrometry, ^1H , ^{13}C and ^{31}P NMR spectroscopy.

4. Results

4.1 Selective 1,4-addition of *Grignard* compounds to chalcone derivatives^{D1,D2}

Generally the reaction of α,β -unsaturated carbonyl compounds with organometallic reagents gives the corresponding 1,2-addition product. However, in combination with various salts of transition metals, organometallic reagents can be used in several organic chemical transformations. For example *Kharash* and *Tawney* found that the addition of a catalytic amount of a copper compound can lead to the conjugate addition of an organomagnesium compound (*Grignard* reagent) to an α,β -unsaturated ketone.¹²

During my work the $\text{Cu}^{2+}/4\text{A}$ catalyst synthesized earlier in our research group has been successfully used in the 1,4-addition of *Grignard* reagents (**1**) to chalcones (**2**) (**Scheme 1**). The effect of the catalyst on the selectivity of the reaction was also examined.



Scheme 1: Reaction of chalcone derivatives (**2**) with *Grignard* reagents (**1**) in the presence of a $\text{Cu}^{2+}/4\text{A}$ catalyst

Both aliphatic and aromatic *Grignard* reagents (**1**) were tested in the reaction, but no significant steric effect was observed. In accordance with the previous work of the research group the presence of a methoxy group on the aromatic halide inhibited the *Grignard* reaction. The effect of the substituents on the aromatic ring of the chalcone on the reaction was also tested, but there was no significant difference in the reactivity of the different derivatives. The desired products (**3**) were synthesized with excellent selectivity and in excellent yields and the catalyst could be reused multiple times after a mild treatment without significant loss of activity.

Based on literature data the effect of different previously synthesized metal catalysts on the yield of the reaction between ethylmagnesium iodide (**1a**) and chalcone (**2**) was examined. 4Å molecular sieve supported La^{3+} , Ti^{4+} , In^{3+} , Co^{2+} and Ni^{2+} catalysts were tested and the

^{D1} Juhász, K.; Hell, Z.: Heterogeneous catalytic 1,4-addition of arylmagnesium compounds to chalcones. *Tetrahedron Lett.*, **2018**, 59, 3136-3138; *Synfacts*, **2018**, 14 (10), 1103.

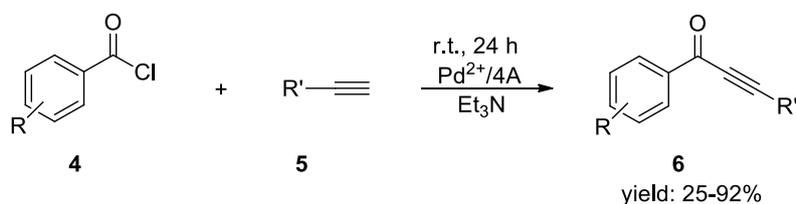
^{D2} Juhász, K.; Hell, Z.: The effect of the catalyst on the selectivity of the heterogeneous catalytic 1,4-addition of organomagnesium compounds to chalcone. *Period. Polytech. Chem. Eng.*, **2019**, 63 (4), 636-639.

¹² Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, 63 (9), 2308-2316.

Ti⁴⁺/4A catalyst was found to be the most effective. Thus, the applicability of this catalyst was extended to the 1,4-addition of aromatic *Grignard* reagents. In this case, the desired products were synthesized in excellent yields, but the catalyst could not be reused after the reaction due to a significant loss of activity in the second run.

4.2 Preparation of ynones in the presence of a 4Å molecular sieve supported palladium(II) catalyst^{D3}

Ynones (**6**) can be key intermediates to numerous biologically active compounds, thus, several synthesis routes were elaborated for their preparation. The most common and most significant method is the so called acyl *Sonogashira* reaction. In this reaction terminal alkynes (**5**) are reacted with carboxylic acid derivatives (**4**) in the presence of a palladium catalyst, a ligand (mainly phosphorous compounds) and copper iodide.^{13,14,15}



Scheme 2: Reaction of acyl-chlorides (**4**) and terminal alkynes (**5**) in the presence of a Pd²⁺/4A catalyst

During my work different ynones were successfully synthesized in the reaction of acyl-chlorides (**4**) and terminal alkynes (**5**) in the presence of a Pd²⁺/4A catalyst (**Scheme 2**). If there was a halide substituent on the aromatic ring of the acyl-chloride (**4**), the yield of the reaction was significantly lower due to the reactivity of the halide substituents. In case of *ortho*-substituents a steric hindrance was observed in the reaction. Replacing the aromatic phenylacetylene with aliphatic terminal alkynes (hept-1-yne, 3-methylpent-1-yne-3-ol) the yield of the reaction was significantly lower and there was a considerable amount of the 3-benzoyl-benzoic acid by-product in the reaction mixture. The reason for the formation of this by-product is the low reactivity of the aliphatic terminal alkynes.

^{D3} **Juhász, K.**; Hell, Z.: Palladium(II) on 4Å molecular sieves: A simple and reusable catalyst for the preparation of ynones *Catal. Lett.*, **2020**, 150 (11), 3335-3341.

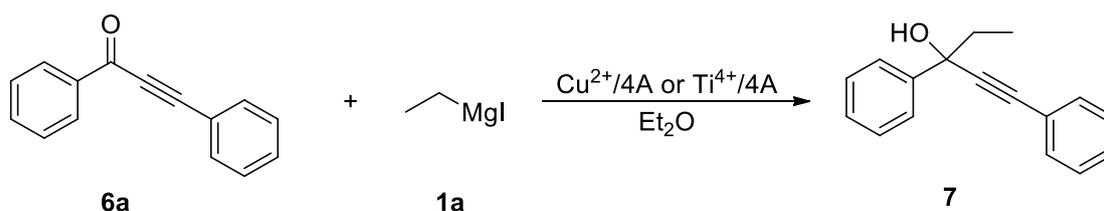
¹³ Cox, R. J.; Ritson, D. J.; Dane, T. A.; Berge, J.; Charmant, J. P.; Kantacha, A. *Chem. Commun. (Camb)* **2005**, (8), 1037-9.

¹⁴ Kumar, B.; Maity, J.; Kumar, A.; Khatri, V.; Shankar, B.; Prasad, A. K. *Chem. Heterocyc. Comp.* **2018**, 54 (3), 362-368.

¹⁵ Müller, T.; Breuer, N. *Synthesis* **2018**, 50 (14), 2741-2752.

The reusability of the catalyst was also investigated in the acyl *Sonogashira* reaction. After an initial decrease of the activity the catalyst could be used multiple times effectively after being washed with ethanol and dried at 120 °C for 1 hour.

Then the reaction of the ynones (**6a**) with ethylmagnesium iodide (**1a**) was investigated in the presence of Cu²⁺- and Ti⁴⁺-catalysts on the analogy of the 1,4-addition to chalcones (**Scheme 3**). In this case, however, in contrast to the conjugate addition the *Grignard* reagent reacted with the carbonyl group. The carbon-carbon triple bond remained intact.



Scheme 3: Investigation of the reaction of ynone (**6a**) and ethylmagnesium iodide (**1a**)

4.3 Cu²⁺/4A catalysed addition of *H*-phosphinates and secondary phosphine oxides to phenylacetylene^{D4}

Alkenylphosphine oxides represent a group of important compounds in organic, medicinal and agricultural chemistry. They can be synthesized with the so called hydrophoshylation, where secondary phosphine oxides are added to an alkyne, usually in the presence of a transition metal.¹⁶⁻²²

Our research group found the idea of elaborating a heterogeneous catalytic P-C coupling for the preparation of alkenylphosphine oxides (**11**) and alkenyl phosphinates (**9**) appealing. During my work the reaction of different *H*-phosphinates (**8**) and secondary phosphine oxides (**10**) has been examined in the presence of molecular sieve supported metal catalyst (**Scheme 4**). The starting materials of the reactions were mostly synthesized by *Dr. Péter Bagi* and *Bence Varga*.

^{D4} Juhász, K.; Varga, B.; Bagi, P.; Hell, Z. *Catal. Lett.*, **2021**, DOI: 10.1007/s10562-021-03694-6.

¹⁶ Xu, Q.; Han, L.-B. *J. Organomet. Chem.* **2011**, 696 (1), 130-140.

¹⁷ Gaumont, A. C.; Gulea, M. *Sci. Synth.* **2007**, 33, 701.

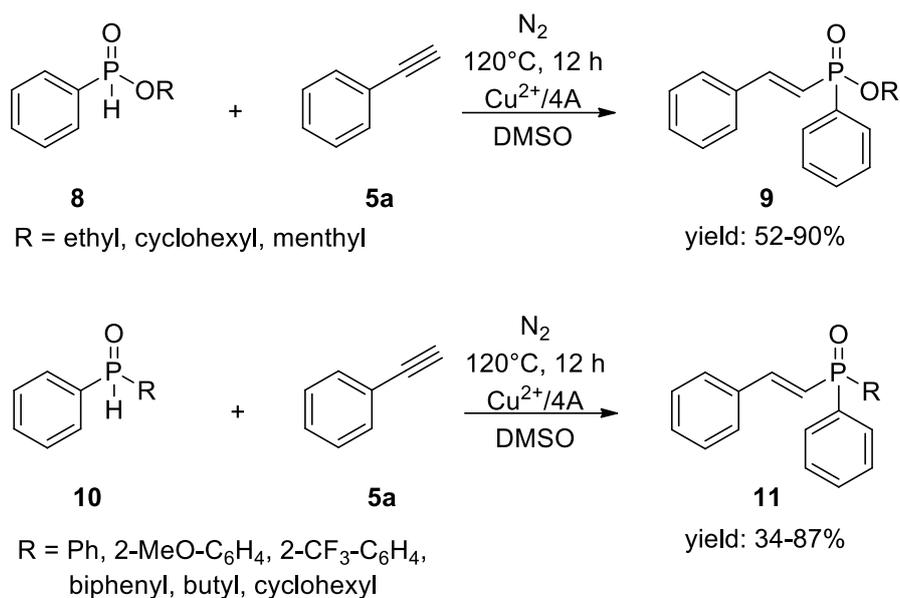
¹⁸ Huang, Y.; Hao, W.; Ding, G.; Cai, M.-Z. *J. Organomet. Chem.* **2012**, 715, 141-146.

¹⁹ Chen, T.; Zhou, Y.; Guo, C.; Han, L.-B. *Chem. Lett.* **2013**, 42 (9), 1065-1067.

²⁰ Yao, F.; Peng, J.; Hao, W.; Cai, M. *Catal. Lett.* **2012**, 142 (6), 803-808.

²¹ Julienne, D.; Delacroix, O.; Gaumont, A.-C. *Curr. Org. Chem.* **2010**, 14, 457-482.

²² Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, 104, 3079-3159.



Scheme 4: Reaction of different *H*-phosphinates (**8**) and secondary phosphine oxides (**10**) with phenylacetylene

The desired products (**9** and **11**) were synthesized in good to excellent yields using a regio- and stereoselective method. Seven of the prepared alkenyl phosphinates (**9**) and alkenylphosphine oxides (**11**) are new compounds, which were not described in the literature before. The applied Cu²⁺/4A could be reused multiple times in the reaction after a minimal treatment.

The addition of different alkyl phosphites (diethyl, diisopropyl, dibutyl and diphenyl phosphite) to phenylacetylene was also attempted under the same reaction conditions. In these cases, the formation of the desired dialkyl-vinyl phosphinates could not be detected by the applied spectroscopic methods.

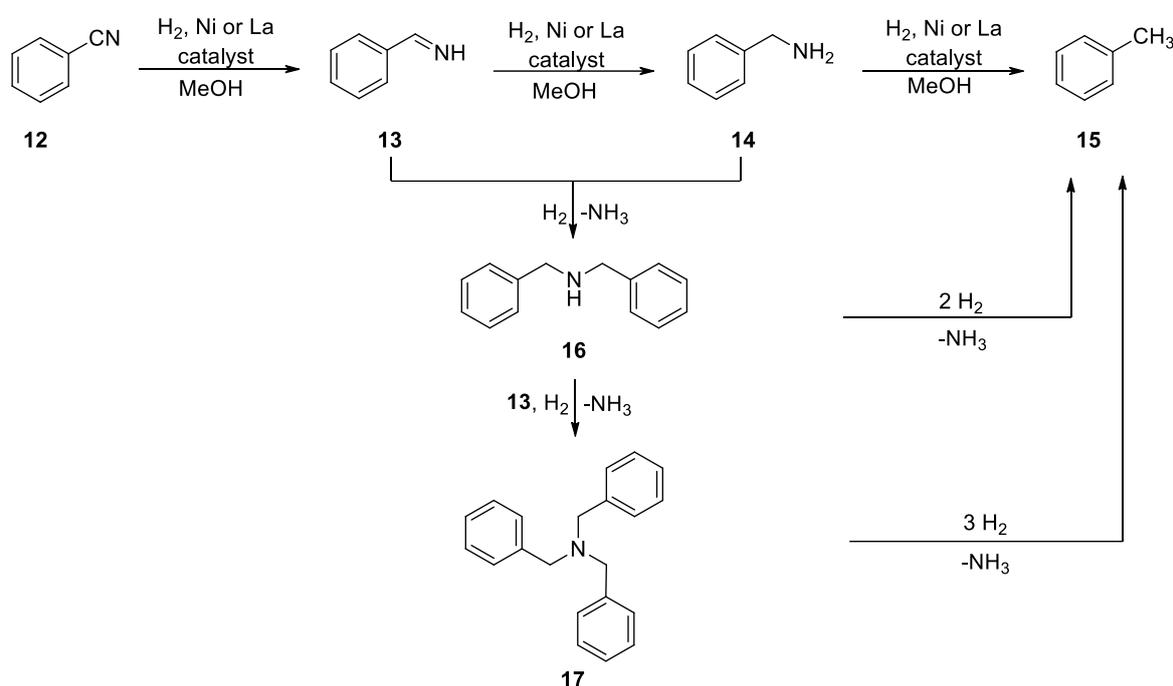
4.4 Preparation of supported nickel and lanthanum catalysts and the investigation of their applicability^{D5}

In collaboration with the University of Poitiers within the framework of the Hungarian-French Intergovernmental Cooperation Programme various supported basic catalysts were synthesized. The physicochemical properties of these catalysts were examined, and they were tested in different reactions. First, the catalysts were tested in cross-coupling reactions, but no significant results were achieved. Thus, the hydrogenation of nitriles was chosen to be the next model reaction due to wide application of primary amines in the pharmaceutical and pesticide industry.

^{D5} Juhász, K.; Lévy, K.; Hegedűs, L.; Balogh-Weiser D.; Pirault-Roy, L.; Hell Z. *Reaction Kinetics, Mechanisms and Catalysis*, **2021**, 133 (2), 687-698.

The physicochemical properties of the four synthesized catalysts (Ni/MgO, La/MgO, Ni/MgO-Al₂O₃ and Ni-La/MgO-Al₂O₃) were examined by SEM-EDS and BET methods, the metal content was determined by ICP-OES. According to the measurements the metal content of the catalysts showed good correspondence with the theoretical values and the metal particles were typically located on the surface of the catalyst.

The applicability of the catalysts was tested in the hydrogenation of benzonitrile (**12**) at different temperatures, in methanol, without any additives, in cooperation with *Dr. László Hegedűs* and *Krisztina Lévy* (**Scheme 5**).



Scheme 5: Nickel and lanthanum catalyzed hydrogenation of benzonitrile (**12**)

It was found that lanthanum has an outstanding hydrogenation activity, which was not published, yet. Thus, this reaction was extended to other nitriles (benzyl cyanide, cinnamionitrile, adiponitrile). It was observed, that with increasing number of the aliphatic carbon atoms in the starting material, the conversion and selectivity decrease significantly. In these cases, the desired amines were formed only in small amounts. During the hydrogenation of cinnamionitrile 3-phenylpropionitrile was the main product instead of 3-phenylpropylamine.

5. Thesis statements

1. The selective 1,4-addition of alkyl and aryl *Grignard* reagents can be realized in good yields in the presence of a $\text{Cu}^{2+}/4\text{A}$ catalyst. In the reaction the formation of the 1,2-adduct could not be detected in any of the cases. Herewith, a selective method was elaborated, where the catalyst can be easily recovered and reused multiple times without significant loss of activity. [1]
2. In addition to the $\text{Cu}^{2+}/4\text{A}$ catalyst the 1,4-addition reaction of ethylmagnesium iodide and phenylmagnesium iodide to chalcone can be realized with good yields and selectivity in the presence of the $\text{Ti}^{4+}/4\text{A}$ catalyst. [2]
3. Different ynones were synthesized with good yields in the $\text{Pd}^{2+}/4\text{A}$ catalysed acyl *Sonogashira* reaction of acyl chlorides and terminal alkynes. At the end of the reaction the catalyst can be easily regenerated and reused multiple times with good results. [3]
4. A heterogeneous catalytic method was elaborated for the hydrophosphinylation of phenylacetylene with different *H*-phosphinates and secondary phosphine oxides in the presence of a $\text{Cu}^{2+}/4\text{A}$ catalyst. The desired alkenylphosphinates and alkenylphosphine oxides were prepared in good to excellent yields in a regio- and stereoselective reaction. Seven of the synthesized products are new, which were not described in the literature before. At the end of the reaction the catalyst could be reused multiple times after a minimal treatment. [4]
5. Four new metal oxide and mixed oxide supported metal catalysts were prepared. Their physicochemical properties (SEM-EDS, BET) and metal contents (ICP-OES) were determined. [5]
6. The prepared La/MgO catalyst showed a particularly high activity in the heterogeneous catalytic hydrogenation of benzonitrile. The desired benzilamine was formed with 43-52% selectivity in the reaction without the addition of ammonia. Lanthanum was not used earlier as an individually active catalyst in the hydrogenation of nitriles. [5]

6. Possible application of the scientific results

In organic chemical reactions the replacement of homogenous catalysts and ligands with heterogeneous catalysts is bearing numerous advantages. The catalysts synthesized and the reactions elaborated in our research group are primarily on laboratory scale of great importance, although some methods could be adapted to industrial processes. The preparation of the

catalysts is simple, the catalyst support is cheap and commercially available. The applied catalysts can usually be reused multiple times after a simple treatment without significant loss of activity. Thus, they offer a more environmentally friendly alternative to homogeneous catalysts.

7. Publications

7.1 Scientific publications related to the PhD thesis

- [1] **Juhász, K.**; Hell, Z. *Tetrahedron Lett.*, **2018**, 59, 3136-3138; *Synfacts*, **2018**, 14 (10), 1103.
DOI: 10.1016/j.tetlet.2018.07.016. IF: 2,259 (2018), FI: 1.
- [2] **Juhász, K.**; Hell, Z. *Period. Polytech. Chem. Eng.*, **2019**, 63 (4), 636-639.
DOI: 10.3311/PPch.13914. IF: 1,257 (2019).
- [3] **Juhász, K.**; Hell, Z. *Catal. Lett.*, **2020**, 150 (11), 3335-3341.
DOI: 10.1007/s10562-020-03235-7. IF: 3,186 (2020), FI:1.
- [4] **Juhász, K.**; Varga, B.; Bagi, P.; Hell, Z. *Catal. Lett.*, **2021**.
DOI: 10.1007/s10562-021-03694-6. IF: 3,186 (2020).
- [5] **Juhász, K.**; Lévy, K.; Hegedűs, L.; Balogh-Weiser, D.; Pirault-Roy, L.; Hell, Z. *React. Kinet. Mech. Cat.*, **2021**, 133 (2), 687-698.
DOI: 10.1007/s11144-021-02028-2. IF: 2,081 (2020).

7.2 Further scientific publications related to the PhD thesis

- [6] Magyar, Á.; **Juhász, K.**; Hell, Z. *Synthesis*, **2021**, 53 (02), 279-295.
DOI: 10.1055/s-0040-1706535. IF: 3,157 (2020), FI: 3.
- [7] **Juhász, K.**; Magyar, Á.; Hell, Z. *Synthesis*, **2021**; 53 (06), 983-1002.
DOI: 10.1055/s-0040-1705986. IF: 3,157 (2020), FI: 2.

7.3 Further scientific publications

- [8] Bagi, P.; **Juhász, K.**; Timári, I.; Kövér, E. K.; Mester, D.; Kállay, M.; Kubinyi, M.; Szilvási, T.; Pongrácz, P.; Kollár, L.; Karaghiosoff, K.; Czugler, M.; Drahos, L.; Fogassy, E.; Keglevich, G. *J. Organomet. Chem.*, **2015**, 797, 140-152.
DOI: 10.1016/j.jorganchem.2015.08.013. IF: 2,336 (2015).

- [9] Bagi, P.; Herbay, R.; **Juhász, K.**; Varga, B.; Fogassy, E.; Keglevich, G. *Phosphorus Sulfur Silicon Relat. Elem.*, **2016**, 191 (11-12), 1459-1461.
DOI: 10.1080/10426507.2016.1212039. IF: 0,723 (2016), FI: 1.
- [10] Bagi, P.; **Juhász, K.**; Kállay, M.; Hessz, D.; Kubinyi, M.; Fogassy, E.; Keglevich, G. *Heteroat. Chem.*, **2018**, 21411.
DOI: 10.1002/hc.21411. IF: 1,137 (2018).

7.4 Oral presentations

- [11] **Juhász, K.**; Hell, Z. Heterogeneous catalytic 1,4-addition of *Grignard* reagents to chalcone derivatives. 24-27 October 2018. XXIV. International Conference on Chemistry, Szovátafürdő, Romania.
- [12] **Juhász, K.**; Hell, Z.; Bagi, P. Investigation of the effect of chiral additives in reactions catalysed by supported transition metal catalysts. 23 February 2018. ÚNKP Conference, Budapest.
- [13] **Juhász, K.**; Hell, Z.; Bagi, P. Investigation of the effect of chiral additives in reactions catalysed by supported transition metal catalysts. 16-18 October 2017. XL. Chemistry Lectures, Szeged.

7.5 Poster presentations

- [14] Juhász K.; Hell Z. Heterogeneous catalytic 1,4-addition reaction in the presence of supported metal catalysts. 23 September 2019. 1st George Olah Conference