



BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS

FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY

EXAMINATION OF SUPPORTED CATALYSTS IN ORGANIC CHEMICAL REACTIONS

Ph.D. thesis

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1. INTRODUCTION

Nowadays an important target in the organic chemistry is the development of new catalysts and reagents which are more active and selective than the traditional ones, which are easy to handle, often reusable and are very important from environmental point of view, too. Considering that most of the organic chemical reactions - according to statistical data about 80% - require catalyst, the research of catalysis acquire ever greater interest and significance. In the last decades a number of heterogeneous catalyst were developed. They are cheap, non-toxic, non-corrosive, and the use of these materials ensure high activity and often selectivity under mild reaction conditions. In several cases synthetic or mineral based materials are applied simply because of their acidic or basic character, at the same time together with the development of modern synthetic methods the significance of different supported metal catalyst also increases.

The supported heterogeneous catalysts have a large number of advantages, in the batch technologies of the fine-chemical industry after finishing the reactions the catalyst can be recovered by a simple filtration, which make the technology simpler, reduce the operating time and grows the energy efficiency. Filtered catalyst are often reusable, or easily regenerable. Finally, because of their ordered cavernous structure they sometimes induce significant regio- or stereoselectivity. All these advantages make a lot of important organic chemical reactions not only environmentally more benign, but more economical, too.

My research work was performed at the Budapest University of Technology and Economics, Department of Organic Chemistry and Technology, where research activity has been oriented for the examination of different mineral-based acidic and basic catalysts and supported metal catalysts and their applicability in organic chemical reactions, as well as for the development of catalytic methods, too, for many years. In our work we examined reactions which could be interesting mostly for the fine chemical or rather pharmaceutical industry. Earlier the research group elaborated methods for different carbon-carbon coupling reactions, for example for the Suzuki, Heck, or Sonogashira reaction¹⁻³.

Continuing this work during my PhD research I worked on the elaboration of different organic reactions catalysed by supported metal catalysts which were traditionally homogeneous catalytic processes.

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1. Cwik, A.; Hell, Z.; Figueras, F. *Org. Biomol. Chem.* **2005**, *3*, 4307.
 2. Cwik, A.; Hell, Z.; Figueras, F. *Adv. Synth. Catal.*, **2006**, *348*, 523.
 3. Cwik, A.; Hell, Z.; Figueras, F. *Tetrahedron Lett.* **2006**, *47*, 3023.
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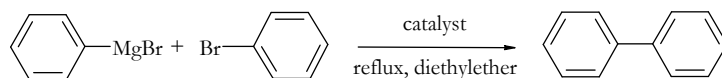
My aim was the developing of different organic chemical methods using catalysts which can be prepared easily, quickly and cost efficiently, which might be applicable even in the chemical industry and acceptable also from environmental point of view. The reactions examined were also chosen accordingly, especially from industrial point of view.

As support I have used 4 Å molecular sieve or Mg:Al 2:1 hydrotalcite and magnesium-lanthanum mixed oxide which were used frequently earlier by our research group.

During my research work I examined the following four reactions: the Kumada-Corriu coupling, the so called A³ coupling, the dehydration of aldoximes into nitriles and the hydration of nitriles to amides.

2. RESULTS

2.1. Catalysts containing different metals on different supports were tested in the Kumada-Corriu coupling. I have established that the best catalyst was nickel(II) on magnesium-lanthanum mixed oxide support (Ni^{2+} -MgLaO)⁴.



Using this catalyst I have developed a new and efficient method for the formation of carbon-carbon bond using Grignard compounds and aryl halogenides as starting materials. I have examined the reaction conditions, the effect of metal amount used, the reaction time, the effect of the halogene, the cross-coupling of different aryl-halogenides and the effect of the substituents (Table 1). I found that 0.16% nickel was enough to achieve the appropriate conversion which is unequivocally less than metal amounts described in literature. The reaction achieved the maximal conversion after 3 hours. The reactivity of halobenzenes increased to the chlorine-bromine-iodine direction. In the case of iodobenzene we obtained the product quantitatively. With the optimal reaction conditions we did not detected the formation of R_2 -homocoupled product.

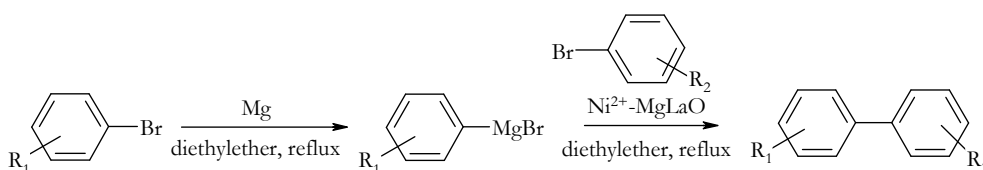


Table 1 Results of the cross-coupling^a

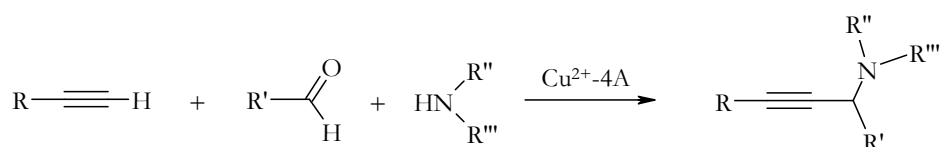
Entry	R ₁	R ₂	Yield ^b (%)
1	H	<i>p</i> -Me	86
2	H	<i>o</i> -OMe	73
3	H	<i>m</i> -OMe	81
4	H	<i>p</i> -OMe	83
5	H	<i>o</i> -CF ₃	23
6	H	<i>m</i> -CF ₃	78
7	H	<i>p</i> -CF ₃	84
8	<i>p</i> -Me	<i>o</i> -CF ₃	25
9	<i>p</i> -Me	<i>m</i> -CF ₃	69
10	<i>p</i> -Me	<i>p</i> -CF ₃	29
11	<i>p</i> -Me	<i>p</i> -OMe	55
12	<i>p</i> -OMe	<i>p</i> -Me	11

^a13 mmol R₁-aryl-bromide, 11.5 mmol magnesium, 10 mmol R₂-aryl-bromide, 0.2 g Ni^{2+} -MgLaO catalyst, 10 ml diethylether, 35 °C, 3 h. ^bIsolated yield, the product purity was checked by GC-MS. The crude product contains about 15% R₁-R₁ by-product.

4. Kiss, Á; Hell, Z.; Bálint, M.: Nickel/magnesium-lanthanum mixed oxide catalyst in the Kumada-coupling *Org. Biomol. Chem.* **2010**, *8*, 331-335.

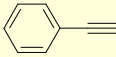
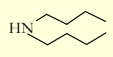
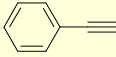
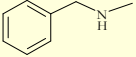
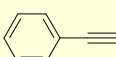

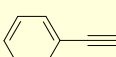

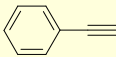
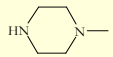
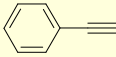

XRF examinations showed that in contrast of the frequently used homogeneous catalytic methods nickel did not contaminate the product.

2.2. 4 Å molecular sieve impregnated with copper(II) (Cu²⁺-4A) proved to be the best catalysts in the so called A³ (alkyne-aldehyde-amine) coupling⁵. Different supported metal catalysts were tested in the reactions.



Examination of other metals on the same support indicated that beside the best Cu(II) Fe(III) showed also significant activity. In the presence of Cu²⁺-4A catalyst the coupling of alkynes, aliphatic aldehydes and secondary amines at room temperature under solvent-free conditions gave the corresponding propargylamines with excellent yields (Table 2).

Table 2 A³ coupling in the presence of Cu²⁺-4A^a

Entry	Alkyne	Aldehyde	Amine	Yield ^b (%)
1		CH ₂ O		96
2		CH ₂ O		93
3		CH ₂ O		92
4		CH ₂ O		76
5		CH ₂ O		72
6		CH ₂ O		70

^a6 mmol alkyne, 5 mmol aldehyde, 5 mmol amine, 0.5 g Cu²⁺-4A catalyst, in substantia, RT, 24 h. ^bIsolated yields, the product purity was checked by GC-MS and ¹H NMR.

In the case of aromatic aldehydes the use of toluene solvent and reflux temperature was necessary to achieve good yield (Table 3). The catalyst could be easily separated from the reaction mixture and could be reused without significant loss of activity.

5. Fodor, A.; Kiss, Á.; Debreczeni, N.; Hell, Z.; Gresits, I.: A simple method for the preparation of propargylamines using molecular sieve modified with copper(II) *Org. Biomol. Chem.* **2010**, *8*, 4575-4581.

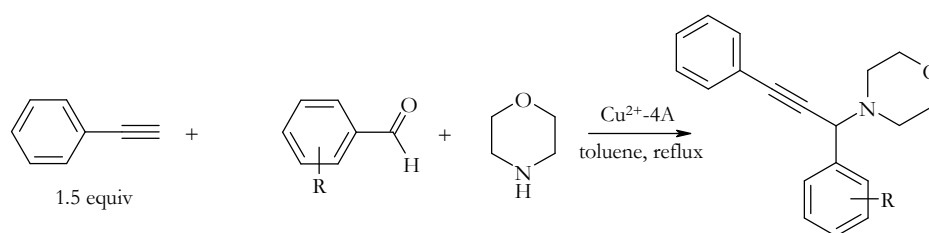


Table 3 The A³ coupling of aromatic aldehydes with phenylacetylene and morpholine^a

Entry	Aldehyde	Yield ^b (%)
1		99
2		96
3		90
4		89
5		70
6		70
7		54

^a7.5 mmol phenylacetylene, 5 mmol aromatic aldehyde, 5 mmol morpholine, 0.5 g Cu²⁺-4A catalyst, 2 ml toluene, 110 °C, 15 h.

^bIsolated yield, the product purity was checked by GC-MS and ¹H NMR.

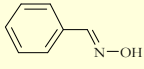
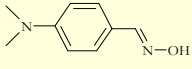
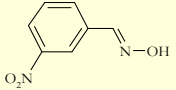
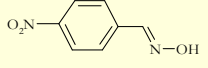
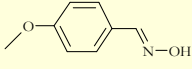
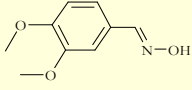
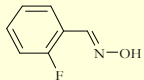
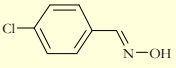
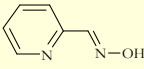
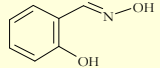
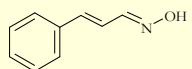
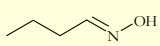
2.3. I have successfully converted aldoximes into nitriles using Cu²⁺-4A catalyst in acetonitrile solvent⁶.

Examining different metals on the same support I was led to the conclusion that 4 Å molecular sieve modified with palladium(II) was similarly active catalyst in the benzaldoxime - benzonitrile model reaction. The reaction conditions, the amount of the metal and solvent was optimized.

Under the optimal reaction conditions (8.5 mol% Cu, 2 mL acetonitrile / mmol aldoxime, 8 h reaction time) the following nitrile derivatives were synthesized (Table 4).

6. Kiss, Á.; Hell, Z.: A heterogeneous catalytic method for the conversion of aldoximes into nitriles using molecular sieve modified with copper(II) *Synth. Commun.* **2011**, közlésre elfogadva.

Table 4 Dehydration of aldoximes using Cu²⁺-4A catalyst^a

Entry	Aldoxime	Conversion ^b (%)	Nitrile ^{b,c} (%)	Amide ^b (%)
1		100	99	0
2		100	98(91)	1
3		100	96(90)	4
4		100	96(87)	4
5		100	95(88)	4
6		100	86(78)	14
7		100	90(82)	10
8		100	83(76)	17
9		87	25	62
10		15 ^d	6	0
11		100	96(87)	4
12		100	100	0

^a5 mmol substituted aldoxime, 0.5 g Cu²⁺-4A catalyst, 10 ml acetonitrile, 82 °C, 8 h. ^bGC-MS conversion. ^cIsolated yields are in parenthesis, the product purity was checked using GC-MS and ¹H NMR. ^d9 % Benzisoxazole was obtained.

In the case of salicylaldehyde I did not obtained the desired salicylonitrile with good yield, but using triethylamine as additive to the reaction mixture I achieved good result in this case also (Table 5).

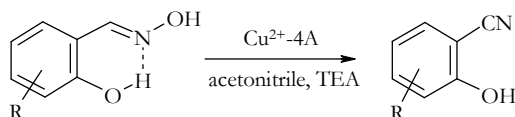
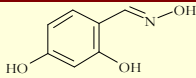
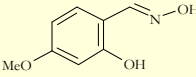
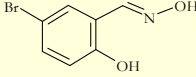
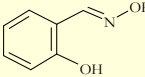
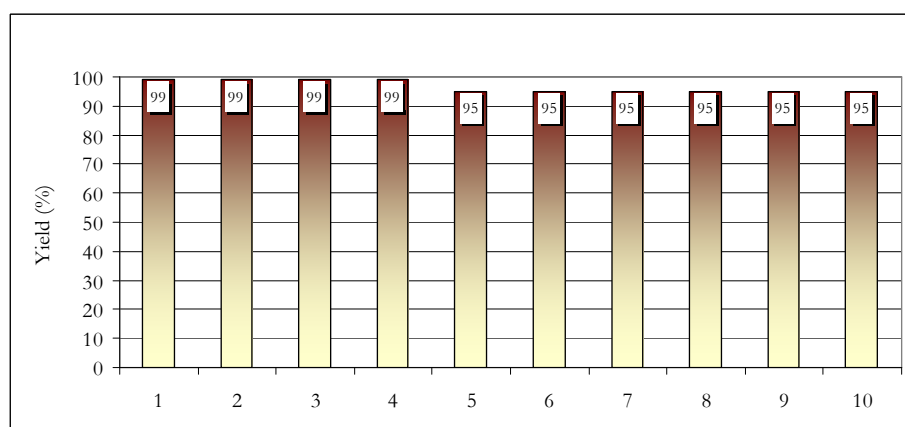


Table 5 Dehydration of different salicylaldoximes using Cu²⁺-4A catalyst in the presence of triethyl-amine^a

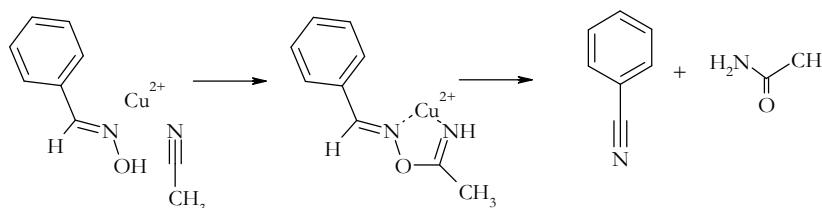
Entry	Salicylaldoxime	Conversion ^b (%)	Nitrile ^{b,c} (%)	Amide ^b (%)
1		100	100 (98)	0
2		100	99 (91)	1
3		100	99 (90)	1
4		100	93 (85)	7

^a5 mmol substituted salicylaldoxime, 5 mmol triethylamine, 0.5 g Cu²⁺-4A catalyst, 10 ml acetonitrile, 82 °C, 16 h. ^bGC-MS conversion. ^cIsolated yields are in parenthesis, the product purity was checked using GC-MS and ¹H NMR.

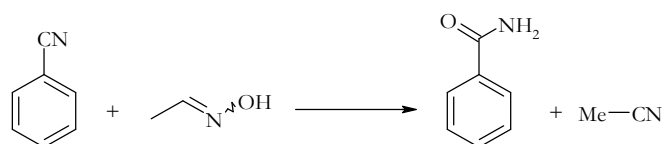
The reuseability of the catalyst proved to be excellent in the benzaldehyde - benzonitrile model reaction. The catalyst could be used at least 10 times without significant loss of activity.



Taking also into account the published propositions for the mechanism of the reaction, the concerted, metal-mediated mechanism was verified. The reaction needs nitrile type solvent, the water from the aldoxime, reacting with the solvent forms acetamide by-product.



2.4. I have developed a method for the hydration of different nitriles to amides in the presence of Cu^{2+} -4A catalyst using acetaldoxime reagent^{7,8}.



I obtained the desired amides with excellent yield. The yield was evenly good in different solvents under mild reaction conditions. The following amides were synthesized (Table 6).

Table 6 Hydration of nitriles to amides using Cu^{2+} -4A catalyst^a

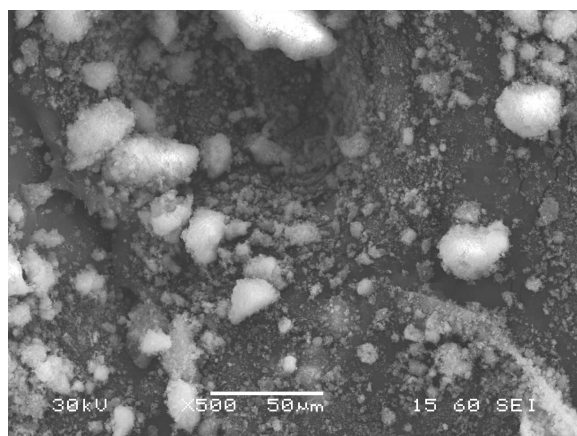
Entry	Nitrile	Conversion ^b (%)	Amide ^{b, c} (%)
1		100	100(98)
2		100	100(98)
3		96	71 ^d (62)
4		81	58 ^e (50)
5		100	100(97)
6		100	100(97)
7		100	100(96)
8		100	0 ^f
9		100	100(94)
10		100	100(95)
11		98	98(93)
12		97	97(95)
13		100	54[46] ^g
14 ^h		100	73[27] ^g

^a2 mmol nitrile, 6 mmol acetaldoxime, 0.2 g Cu^{2+} -4A catalyst, 4 ml MeOH, 65 °C, 4h. ^bGC-MS conversion. ^cIsolated yields are in parenthesis, the product purity was checked using GC-MS and ¹H NMR. ^d25% of an unidentified byproduct was formed. ^e23% of an unidentified byproduct was formed. ^f80% of 1-(3,4-dimethoxyphenyl)-propan-2-one oxime was formed. ^gMonoamide in parenthesis; based on ¹H NMR spectra. ^h2 mmol substituted nitrile, 12 mmol acetaldoxime, 0.4 g Cu^{2+} -4A, 8 mL MeOH, 4 h, 65 °C

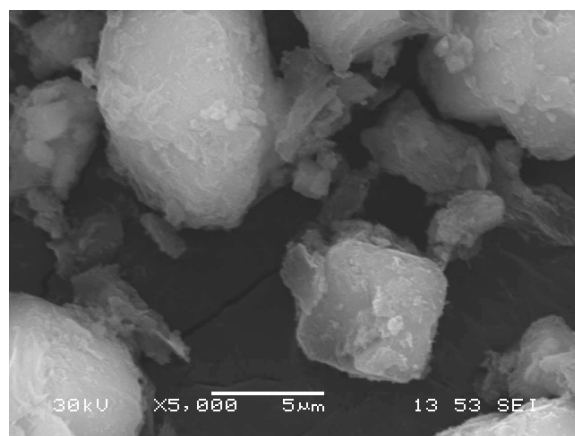
- Kiss, Á.; Hell, Z.: A heterogeneous catalytic method for the conversion of nitriles to amides using molecular sieve modified with copper(II) *Tetrahedron Lett.* **2011**, 52, 6021-6023.
- Kiss, Á.; Hell, Z.: Cu^{II} -MS4Å for Hydration of Nitriles into Amides *Synfacts* **2012**, 8(1), 0105.

An additional advantage of this method that in the presence of hydrolysis-sensitive functional groups (for example ester group) the amides can be synthesized selectively. The catalyst can be recycled easily in this case, too.

2.5. Both Ni^{2+} -MgLaO and the Cu^{2+} -4A were characterised using X-ray diffraction, X-ray photoelectrone spectroscopy, infrared spectroscopy and scanning electron microscopy (Scheme 1 and 2).



Scheme 1 Ni^{2+} -MgLaO



Scheme 2 Cu^{2+} -4A

I established that Ni^{2+} -MgLaO is a $\text{Mg}(\text{OH})_2$ - $\text{La}(\text{OH})_3$ mixture, in which magnesium atoms on the surface were partially exchanged to nickel. The catalyst Cu^{2+} -4A is an A-type zeolite, which is partially copper-exchanged on the surface.

3. THESIS STATEMENTS

1. Catalysts, containing different metals on different supports were tested in the Kumada-Corriu coupling. I have established that the best catalyst was nickel(II) on magnesium-lanthanum mixed oxide support (Ni^{2+} -MgLaO). Using this catalyst I have developed a new and efficient method for the formation of carbon-carbon bond using Grignard compounds and aryl halogenides as starting materials. I have examined the reaction conditions, the effect of metal amount used, the reaction time, the effect of the halogene, the cross-coupling of different aryl-halogenides and the effect of the substituents. In contrast of the frequently used homogeneous catalytic methods metal or ligand did not contaminate the product¹.

2. 4 Å molecular sieve impregnated with copper(II) (Cu^{2+} -4A) proved to be the best catalysts in the so called A^3 (alkyne-aldehyde-amine) coupling. Different supported metal catalysts were tested in the reactions. Examination of other metals on the same support indicated that beside the best Cu(II) Fe(III) showed also significant activity. In the presence of Cu^{2+} -4A catalyst the coupling of alkynes, aliphatic aldehydes and secondary amines at room temperature under solvent-free conditions gave the corresponding propargylamines with excellent yields. In the case of aromatic aldehydes the use of toluene solvent and reflux temperature was necessary to achieve good yield. The catalyst could be easily separated from the reaction mixture and could be reused without significant loss of activity².

3. I have successfully converted aldoximes into nitriles using Cu^{2+} -4A catalyst in acetonitrile solvent. Examining different metals on the same support I was led to the conclusion that 4 Å molecular sieve modified with palladium(II) was similarly active catalyst in the reaction. The reaction conditions, the amount of the metal and solvent was optimized. In the case of salicylaldehyde I did not obtain the desired salicylonitrile with good yield, but using triethylamine as additive to the reaction mixture I achieved good results in this case also. The reusability of the catalyst proved to be excellent. The catalyst could be used at least 10 times without significant loss of activity. Taking also into account the published propositions reaction mechanism was examined and verified³.

4. I have developed a method for the hydration of different nitriles to amides in the presence of Cu^{2+} -4A catalyst using acetaldoxime reagent. I obtained the desired amides with excellent yield. The yield was evenly good in different solvents under mild reaction conditions. An additional advantage of this method that in the presence of hydrolysis-sensitive functional groups (for example ester group) the amides can be synthesized selectively^{4,5}.

5. Both Ni^{2+} -MgLaO and the Cu^{2+} -4A were characterised using X-ray diffraction, X-ray photoelectron spectroscopy, infrared spectroscopy and scanning electron microscopy. I established that Ni^{2+} -MgLaO is a $\text{Mg}(\text{OH})_2$ - $\text{La}(\text{OH})_3$ mixture, in which magnesium atoms on the surface were partially exchanged to nickel. The catalyst Cu^{2+} -4A is an A-type zeolite, which is partially copper-exchanged on the surface.

4. PUBLICATIONS

4.1. Published articles on the subject of the dissertation

1. **Kiss, Á.**; Hell, Z.; Bálint, M.: Nickel/magnesium-lanthanum mixed oxide catalyst in the Kumada-coupling *Org. Biomol. Chem.* **2010**, *8*, 331-335. (IF.: 3,451, I: 1)
2. Fodor, A.; **Kiss, Á.**; Debreczeni, N.; Hell, Z.; Gresits, I.: A simple method for the preparation of propargylamines using molecular sieve modified with copper(II) *Org. Biomol. Chem.* **2010**, *8*, 4575-4581. (IF.: 3,451, I: 3)
3. **Kiss, Á.**; Hell, Z.: A heterogeneous catalytic method for the conversion of aldoximes into nitriles using molecular sieve modified with copper(II) *Synth. Commun.* **2011**, közlésre elfogadva.
4. **Kiss, Á.**; Hell, Z.: A heterogeneous catalytic method for the conversion of nitriles to amides using molecular sieve modified with copper(II) *Tetrahedron Lett.* **2011**, *52*, 6021-6023.
5. **Kiss, Á.**; Hell, Z.: Cu^{II}-MS4Å for Hydration of Nitriles into Amides *Synfacts* **2012**, *8(1)*, 0105.

4.2. Further published articles

6. **Kiss, Á.**; Potor, A.; Hell, Z.: Heterogeneous Catalytic Solvent-free Synthesis of Quinoline Derivatives via the Friedländer Reaction *Catal. Lett.* **2008**, *125*, 250-253. (IF.: 1,907, I: 6)

4.3. Conference publications

7. **Kiss, Á.**: Examination of coupling reactions using solid base supported metal catalysts – *Sanofi-Aventis Thesis Day*, 2009 nov. 18., Budapest.
8. **Kiss, Á.**: Examination of organic reactions using solid base supported metal catalysts – *Sanofi-Aventis Thesis Day*, 2010 nov. 23., Budapest.
9. **Kiss, Á.**: Szerves kémiai reakciók vizsgálata szilárd bázis hordozós fémkatalizátorokkal – *Oláh György Doktori Iskola PhD Konferenciája*, 2011 feb. 3., Budapest.

4.4. Conference posters

10. Potor A., Hegedüs A., **Kiss Á.**, Vargadi T., Hell Z.: Heterociklusos vegyületek szintézise szilárd sav és szilárd bázis katalizátorok jelenlétében – *MKE Centenárium Vegyészkonferencia*, 2007 máj. 29.-jún. 1., Sopron.
11. Potor A., **Kiss Á.**, Vörös A., Fodor A. Németh J., Hell Z.: Szilárd sav-katalizált szerves kémiai reakciók vizsgálata - *MKE Vegyészkonferencia*, 2008 jún. 19-21., Hajdúszoboszló
12. **Kiss, Á.**; Hell, Z.: Examination of coupling reactions using solid base supported metal catalysts; The Kumada-Corriu Coupling - *Sanofi-Aventis Thesis Day*, 2008 dec. 4., Budapest.
13. **Kiss Á.**: Kapcsolási reakciók vizsgálata szilárd bázis hordozós fémkatalizátorokkal – *Oláh György Doktori Iskola PhD Konferenciája*, 2009 feb. 4., Budapest.
14. **Kiss, Á.**; Hell, Z.: Examination of coupling reactions using solid base supported metal catalysts; The Kumada-Corriu Coupling - *German-French-Hungarian Congress in Organic and Biomolecular Chemistry*, 2009 jún. 20-23., Budapest.
15. **Kiss Á.**: Kapcsolási reakciók vizsgálata szilárd bázis hordozós fémkatalizátorokkal – *Oláh György Doktori Iskola PhD Konferenciája*, 2010 feb. 4., Budapest.
16. **Kiss Á.**, Fodor A., Németh J., Hell Z.: Fémekkel módosított, ásványi alapú katalizátorok vizsgálata szerves kémiai reakciókban - *MKE Vegyészkonferencia*, 2010 jún. 30-júl. 2., Hajdúszoboszló.