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Application of a novel heterogeneous silver catalyst for diverse synthesis methods under batch and continuous flow conditions

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1. Introduction and aims

Silver-catalyzed reactions are of significant importance in organic synthesis. Soluble salts are employed typically as catalytic sources in such transformations. However, efficient and reusable silver-containing catalytic systems are scarce.

In our work we synthesized a novel silver–bismuth hybrid material (AgBi-HM) as solid catalyst for different silver-catalyzed synthesis methods. After the promising catalyst synthesis, our aim was to apply the material in silver-mediated synthesis processes under batch and continuous-flow conditions. Before the detailed flow experiments, we planned to test the stability of the hybrid material in different solvents under a variety of continuous-flow conditions.

Alkynes are significant molecules in several catalytic transformations, such as diverse coupling and cyclization reactions. Nitriles are effective building blocks in the synthesis of pharmaceuticals and natural products. On the other hand, most of their classical synthesis methods involve the use of hazardous reaction partners. Our aim was to apply the prepared AgBi-HM material as a solid catalyst for nitrogenation of alkynes with $TMSN_3$ as nitrogen source. During a through optimization procedure, we intended to explore the role of temperature and reaction time as well as the effects of various solvents and additives. The scope of the reaction with different aliphatic and aromatic alkynes was in the focus of our experiments as well. Furthermore, we intended to examine the reusability and robustness of the catalyst and planned to extend our examination of the used/reused catalyst.

The oxidation of diverse alcohols to their appropriate carbonyl compounds is one of the most fundamental functional group transformations in organic chemistry and it is also common in academic and industrial area. We proposed to explore a novel flow-chemistry method for the dehydrogenation of benzyl alcohols to the corresponding carbonyl compounds in the presence of the AgBi-HM catalyst. Our goal was to investigate the main reaction parameters: flow rate (residence time), temperature, and concentration of the substrate, as well as the examination of the scope of the reaction.

Carboxylic acids are inexpensive and useful starting materials for several transformations, such as protodecarboxylations and related decarboxylative couplings (formation of C–C, C–X, and C–H bonds). However, the most common catalysts for protodecarboxylations are typically homogeneous (copper or silver salts, etc.) in combination with various ligands or bases. We intended to explore decarboxylation and decarboxylative deuteration methods catalyzed by our heterogeneous AgBi-HM preparation under batch and flow conditions. Before the chemically intensified continuous-flow process was developed, an initial batch method was established. We intended to explore the applicability and the scope of the batch and flow methods through decarboxylations of a diverse set of aromatic and fused heteroaromatic carboxylic acids. Furthermore, we aimed to explore the silver-catalyzed decarboxylative deuteration using D_2O as a readily available deuterium source.

2. Methods

Reagents and materials were commercially available and used as received. When necessary, the synthesized products were separated and purified by column chromatography on silica gel. The reaction products were characterized by NMR and MS techniques.

Batch reactions were carried out as follows: the appropriate solvent, the corresponding starting material (reagent if necessary), and the silver-containing hybrid material as catalyst were combined in an oven-dried Schlenk tube equipped with a magnetic stir bar. Flow reactions were performed in “home-made” flow reactors consisting of HPLC pumps, stainless steel HPLC columns as the active reactor zone, a stainless steel preheating coil, and commercially available backpressure regulators. The parts of the system were connected with stainless steel and PEEK capillary tubing. The stainless steel HPLC pump and the preheating coil were immersed in a heated oil bath.

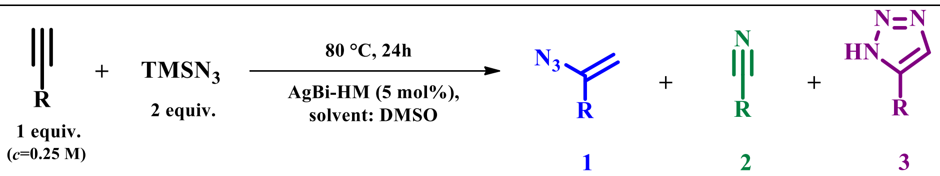
3. Results and discussion

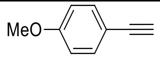
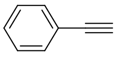
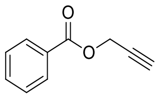
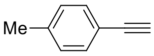
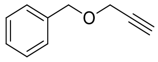
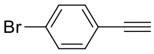
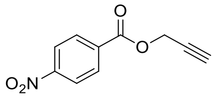
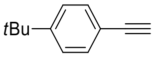
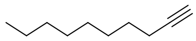
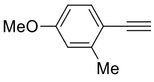
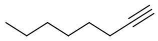
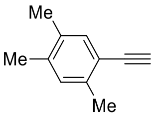
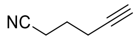
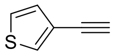
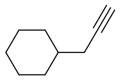
3.1 Silver-catalyzed direct synthesis of nitriles from terminal alkynes

For the model reaction of direct nitrogenation, *p*-methoxyphenylacetylene with $TMSN_3$ as nitrogen source was chosen. The catalytic activity of AgBi-HM was directly compared with commercially available Ag(I) salts. $AgBF_4$ and Ag_2CO_3 showed comparable results to those of the hybrid material; however, other Ag(I) salts resulted in lower product selectivities or/and incomplete conversions. The role of the reaction medium was examined and strong dependence was observed on the quality of the solvent applied. Only dipolar aprotic solvents with an amide moiety and dimethyl sulfoxide (DMSO) proved to be acceptable. A substantial increase in the reaction rate was observed with the elevation of the temperature. On the other hand, higher temperatures promoted the formation of the triazole side product via thermal azide–alkyne cycloaddition. In the investigation of the role of the reaction time, the total conversion was observed to increase gradually with the reaction time.

Based on the findings of parameter optimization, the reaction was operated most efficiently with 24-h reaction time, at 80 °C reaction temperature with a substrate concentration of 0.25 M, 2 equiv. $TMSN_3$, 5 mol% AgBi-HM catalyst, and DMSO as solvent (Table 1). Both aromatic and aliphatic terminal alkynes reacted with excellent conversions and selectivities under these conditions.

Table 1. *Substrate scope of the AgBi HM-catalyzed direct alkyne nitrogenation*



Entry	Alkyne	Conv. (%)^a	Product select. (%)^a			Entry	Alkyne	Total conv. (%)a	Product select. (%)a		
			1	2	3				1	2	3
1		100	0	90	10						
2		100	0	91	9	**9**		100	0	74	26
3		100	0	92	8	**10**		100	0	81	19
4		100	0	90	10	**11**		95	0	73	27
5		100	0	93	7	**12**		100	0	89	11
6		100	0	94	6	**13**		100	0	90	10
7		100	0	94	6	**14**		96	0	93	7
8		100	0	90	10	**15**		98	0	87	13

^{a} *Determined by ^{1}H-NMR analysis of the crude product*

Upon investigating catalyst reusability, the same amount of AgBi-HM catalyst was applied in the reaction of *p*-methoxyphenylacetylene with $TMSN_3$ was carried out repeatedly under the optimal conditions. The catalyst was removed by centrifugation and reused after washing and drying between each cycle. Decrease in selectivity or activity was not observed even after 10 consecutive catalytic cycles. The conversion of *p*-methoxyphenylacetylene was almost complete in every case (97–100%), and the selectivity of the nitrile product was found to be around 90% in all reactions. The hot filtration test was also carried out in order to verify the heterogeneous nature of the reaction. Furthermore, many of the methods applied for the freshly-made material were utilized for the structural characterization of the used catalyst as well.

3.2 Investigating the stability and solvent compatibility of AgBi-HM under continuous-flow conditions

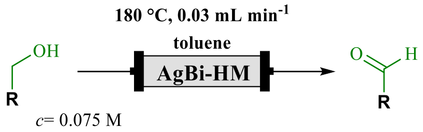
The effects of diverse solvents and reaction conditions on the structure of the catalyst material were explored to obtain valuable data on the applicability of AgBi-HM for organic synthesis in continuous-flow mode. For these experiments, a simple flow reactor set-up was applied. An extensive list of solvents was compiled for the stability tests including CH_2Cl_2, $CHCl_3$, EtOAc, acetone, diethyl ether, MeOH, EtOH, propan-2-ol, H_2O, MeCN, THF, NMP, *n*-hexane, toluene, DMF, DMSO, and DMA. The tests were performed at temperatures of 25, 50, 100, 150, and 200 °C typically used in catalytic flow reactions. In each test, the appropriate solvent was pumped for 90 min at 0.05 mL min^{-1} flow rate through a catalyst bed containing a sample of AgBi-HM. The treated hybrid material sample was examined by XRD and IR spectroscopy in every case.

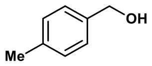
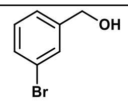
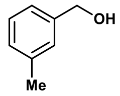
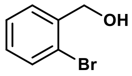
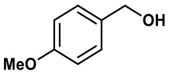
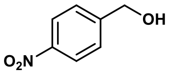
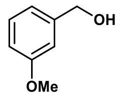
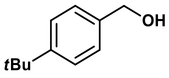
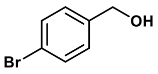
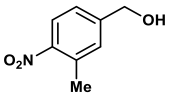
3.3 Silver-catalyzed benzyl alcohol dehydrogenations under continuous-flow conditions

The catalytic dehydrogenation of 4-methylbenzyl alcohol was selected as a model reaction to explore the effects of the most important reaction conditions. The AgBi-HM catalyst proved to be compatible with various solvents even at high temperatures. Consequently, a comprehensive solvent screening was performed at 180 °C. The best result was registered in toluene (92%); therefore, it was selected as solvent for additional parameter optimization. The reaction temperature was found to have a significant effect on the conversion and selectivity. Specifically, the conversion was improved remarkably upon a gradual increase of the temperature. 92% conversion and 100% selectivity were detected at 180 °C, whereas at 200 °C, the benzylation reaction of toluene with the substrate appeared a competing side reaction. On the reaction outcome, the residence time also had significant impacts. At 0.02 mL min^{-1} flow rate (residence time of approximately 75 min), the conversion reached 100%. However, increasing gradually the flow rate to 0.15 mL min^{-1}, the conversion gradually decreased (from 100% to 64%). At the same time, at a flow rate of 0.02 mL/min^{-1}, the competing benzylation reaction was observed, which reduced the selectivity to 52%. The effects of substrate concentration were also explored.

Based on the findings of the extended optimization, reactions were carried out most effectively at 0.03 mL min^{-1} flow rate and 180 °C reaction temperature with a substrate concentration of 0.075 M. We set out to explore the substrate scope of the method with these optimized conditions in hand (Table 2). In the case of *para*-substituted benzyl alcohol derivatives containing methyl, methoxy, bromo, and nitro groups, outstanding conversions were found. The transformation also worked well with benzyl alcohols substituted at the *meta* position. In all reactions, selective aldehyde formation took place without any side products.

Table 2. *AgBi-HM-catalyzed dehydrogenation of benzyl alcohols with a diverse substitution pattern under continuous-flow conditions*



Entry	Substrate	Conversion[a] (%)	Selectivity[a] (%)	Entry	Substrate	Conversion[a] (%)	Selectivity[a] (%)
1		92	100	6		59	100
2		82	100	7		18	100
3		95	100	8		73	100
4		36	100	9		43	100
5		70	100	10		40	100

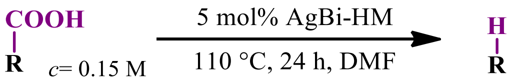
[a] *Determined by ^1H NMR analysis of the crude product*

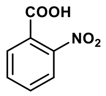
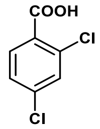
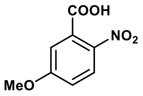
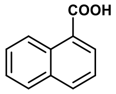
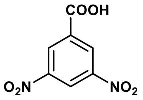
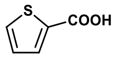
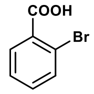
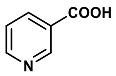
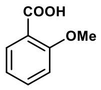
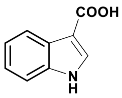
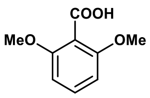
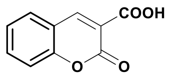
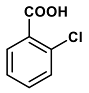
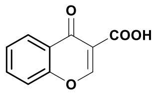
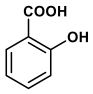
3.4 Silver-catalyzed decarboxylation of carboxylic acids and silver-catalyzed decarboxylative deuteration under batch and flow conditions

For the catalytic model reaction, the decarboxylation of 2-nitrobenzoic acid was chosen to demonstrate the catalytic performance of the AgBi-HM. In this reaction type, the most frequently applied noble metal catalysts are silver- and copper-containing salts or complexes; hence, the hybrid material was compared with these commercially available catalysts. In the case of copper salts, the conversion was acceptable, but AgOAc, Ag_2O, Ag_2CO_3, and $AgNO_3$ revealed similar results compared to those of the hybrid material. Besides DMF, dipolar aprotic solvents MeCN and DMA proved to be suitable reaction medium. The conversion increases gradually with the reaction time reaching completion after 24 h. At higher temperatures, however, the formation of nitrobenzene was promoted with a full conversion at 110 °C. As well as, we examined the effect of concentration, catalyst loading, and the quantity of KOH base was also investigated.

After establishing an optimal set of conditions, we set out to examine the applicability and scope of the synthesis method for the decarboxylation of 2-nitrobenzoic acid (DMF as solvent, 0.15 M concentration, 110 ºC temperature, and 24 h reaction time). The scope of the reaction was explored using various substituted aromatic carboxylic acids (Table 3).

Table 3. *Exploring the decarboxylation of various carboxylic acids under batch conditions*



Entry	Substrate	Conversion[a] (%)	Selectivity[a] (%)	Entry	Substrate	Conversion[a] (%)	Selectivity[a] (%)
1		100	100	9		92	100
2		100	100	10		49	100
3		100	100	11		100	100
4		80	100	12		86	100
5		74	100	13		100	100
6		65	100	14		100	100
7		traces	-	15		97	100
8		traces	-				

[a] *Determined by* ^{1}*H NMR analysis of the crude product*

We investigated the reusability and robustness of our catalyst in the AgBi-HM-catalyzed decarboxylation reaction. The reaction of 2-nitrobenzoic acid was explored repeatedly (conditions: 110 °C, DMF as solvent, 15 mol% KOH, 24 h, 5 mol% catalyst loading) applying the same amount of AgBi-HM. The catalyst was removed after each cycle by centrifugation and it was reused after washing and drying steps. Decrease in the activity or selectivity was not registered after 10 consecutive catalytic cycles. The selectivity was 100% in all reactions, and the conversion was steady in the range of 82–100%.

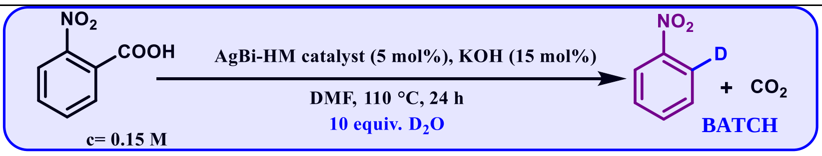
After establishing the appropriate conditions of the batch experiments, we started to study the effects of the major reaction parameters in order to determine the optimum conditions for a sustainable flow process of the decarboxylation of carboxylic acids. We tested dipolar aprotic solvents under flow conditions, because these showed the best performances under batch conditions. Satisfactory results were observed in DMF, MeCN, and DMA; however full conversion and selectivity were only achieved in MeCN. These results showed that concentrations had only a mild influence on the reaction. However, full conversion and selectivity were realized only at a concentration of 0.1 M at a temperature of 170 ºC. At the optimal flow rate (0.05 mL min^{-1}) the residence time was 10.5 min.

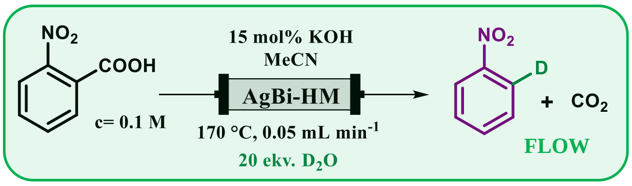
Outstanding results were achieved for various *ortho*-substituted or disubstituted benzoic acids and in the case of 1-naphtoic acid. Furthermore, for carboxylic acids containing hydroxyl group (activating substituents), acceptable results were also achieved. The fused heteroaromatic substrates gave complete conversion and selectivity under flow conditions. No side-product formation was observed and the selectivity was 100% for all substrates used.

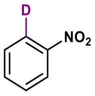
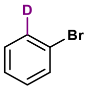
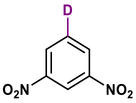
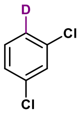
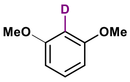
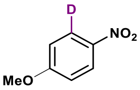
The transformation of 2-nitrobenzoic acid was repeated in a gram-scale test to explore the preparative capabilities of the silver-mediated decarboxylation of carboxylic acids. In this investigation, a 20-h reaction window was monitored with a reduced residence time (5 min corresponding to a flow rate of 0.1 mL min^{-1}) using 15 mol% KOH at a temperature of 170 ºC and a pressure of 100 psi. To our delight, no side-product formation was found and the conversion remained steady around 80%. Then, only a slight loss in catalytic activity was observed, and a satisfying conversion of 71% could still be detected at the end of the experiment. Finally, 1.207 g of nitrobenzene was isolated after purification corresponding to an overall yield of 82%. To make sure of the hybrid material was not suffered structural damage or change under the reusability and the scale up experiments, the used catalysts were explored extensively by TG, SEM-EDX, and XRD methods.

We have carried out a deuteration experiment in the batch system testing the AgBi-HM catalyst in a model reaction. We used the same conditions applied in simple decarboxylation of 2-nitrobenzoic acid, but added 10 equiv. D_2O to the system. The result of this study, performed in 24 h at 110 ºC, was convincing: the conversion was 100% and the deuterium incorporation was 98%. After the successful batch results, we tested the hybrid material catalyst in decarboxylative of 2-nitrobenzoic acid in a flow reactor using 20 equiv. D_2O. Complete deuterium incorporation with 100% conversion in 10.5 min residence time was realized.

Table 4. *Exploring the decarboxylative deuteration of various carboxylic acids under batch and flow conditions*





	Product	Conversion[a] (%) (batch)	D%[a] (%) (batch)	Conversion[a] (%) (flow)	D%[a] (%) (flow)
1		100	98	100	100
2		88	100	100	100
3		100	100	100	100
4		100	100	-	-
5		79	76	100	100
6		100	86	100	71

[a] *Determined by ^{1}H NMR analysis of the crude product. Selectivity was 100% in every cases under both batch and continuous flow conditions.*

With these optimized protocols in hand, we investigated the applicability of the reaction with other substituted benzoic acids in both systems (Table 4).

List of publications and lectures

Papers related to the thesis

I. Sándor B. Ötvös, Rebeka Mészáros, Gábor Varga, Marianna Kocsis, Zoltán Kónya, Ákos Kukovecz, Péter Pusztai, Pál Sipos, István Pálinkó, Ferenc Fülöp
A mineralogically-inspired silver–bismuth hybrid material: an efficient heterogeneous catalyst for the direct synthesis of nitriles from terminal alkynes
Green Chemistry, **2018**, *20*, 1007-1019. IF.: 9.405

II. Rebeka Mészáros, Sándor B. Ötvös, Gábor Varga, Éva Böszörményi, Marianna Kocsis, Krisztina Karádi, Zoltán Kónya, Ákos Kukovecz, István Pálinkó, Ferenc Fülöp
A mineralogically-inspired silver–bismuth hybrid material: Structure, stability and application for catalytic benzyl alcohol dehydrogenations under continuous flow conditions
Molecular Catalysis, **2020**, *498*, 111263. IF.: 5.062

III. Rebeka Mészáros, András Márton, Márton Szabados, Gábor Varga, Zoltán Kónya, Ákos Kukovecz, Ferenc Fülöp, István Pálinkó, Sándor B. Ötvös
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Green Chemistry, **2021**, 23, 4685-4696. IF.: 10.182 (2020)

Other papers

IV. Sándor B. Ötvös, Ádám Georgiádes, Mónika Ádok-Sipiczki, Rebeka Mészáros, István Pálinkó, Pál Sipos, Ferenc Fülöp
A layered double hydroxide, a synthetically useful heterogeneous catalyst for azide−alkyne cycloadditions in a continuous-flow reactor
Applied Catalysis A: General, **2015**, *501*, 63-73. IF.: 4.012

V. Márton Szabados, Rebeka Mészáros, Szabolcs Erdei, Zoltán Kónya, Ákos Kukovecz, Pál Sipos, István Pálinkó
Ultrasonically-enhanced mechanochemical synthesis of CaAl-layered double

hydroxides intercalated by a variety of inorganic anions
Ultrasonics Sonochemistry, **2016**, *31*, 409-416. IF.: 4.218

VI. Rebeka Mészáros, Sándor B. Ötvös, Zoltán Kónya, Ákos Kukovecz, Pál Sipos, Ferenc Fülöp, István Pálinkó
Potential solvents in coupling reactions catalyzed by Cu(II)Fe(III)-layered double hydroxide in a continuous-flow reactor
Reaction Kinetics, Mechanisms and Catalysis, **2017**, *121*, 345-351. IF.: 1.515

VII. Sándor B. Ötvös, Ádám Georgiádes, Rebeka Mészáros, Koppány Kis, István Pálinkó, Ferenc Fülöp
Continuous-flow oxidative homocouplings without auxiliary substances: Exploiting a solid base catalyst
Journal of Catalysis, **2017**, *348*, 90-99. IF.: 6.759

VIII. Rebeka Mészáros, Bai-Jing Peng, Sándor B. Ötvös, Shyh-Chyun Yang, Ferenc Fülöp
Continuous-Flow Hydrogenation and Reductive Deuteration of Nitriles: a Simple Access to α,α-Dideutero Amines
ChemPlusChem, **2019**, *84*, 1508-1511. IF.: 2.753

Cumulative impact factor: 43.906

Scientific lectures related to the thesis

1. Mészáros Rebeka, Ötvös Sándor Balázs, Varga Gábor, Kocsis Marianna, Pálinkó István, Fülöp Ferenc:
Terminális alkinek közvetlen nitrillé alakítása újfajta heterogén ezüstkatalizátorral
Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2017. május 15-17.

2. Mészáros Rebeka:
Újfajta heterogén ezüst katalizátor alkalmazása terminális alkinek közvetlen nitrillé alakítására
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány tudományos előadóülése, Szeged, 2017. május 26.

3. Rebeka Mészáros, Sándor B. Ötvös, Gábor Varga, Marianna Kocsis, István Pálinkó, Ferenc Fülöp:
Characterization and a potential catalytic application of a novel silver-bismuth composite
International Conference on Coordination and Bioinorganic Chemistry, Smolenice, Slovakia, June 4-9, 2017

4. Rebeka Mészáros, Sándor B. Ötvös, Marianna Kocsis, Gábor Varga, István Pálinkó, Ferenc Fülöp:
   A novel silver-bismuth nanocomposite, an effective and reusable catalyst for nitrogenation and hydration of alkynes
   18th Tetrahedron Symposium, Budapest, Hungary, June 27–30, 2017

5. Mészáros Rebeka, Ötvös Sándor Balázs, Varga Gábor, Kocsis Marianna, Pálinkó István, Fülöp Ferenc:
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   Katalízis Munkabizottsági Ülés, Szeged, 2017. december 18.

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   Újfajta heterogén ezüst katalizátor alkalmazása terminális alkinek közvetlen nitrillé alakítására
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8. Mészáros Rebeka Ildikó:
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   ÚNKP előadónap - GYTK, Szeged, 2018. május 17.

9. Rebeka Mészáros, Sándor B. Ötvös, Marianna Kocsis, Gábor Varga, István Pálinkó, Ferenc Fülöp:
   A silver–bismuth hybrid material, an efficient catalyst for the direct synthesis of nitriles from terminal alkynes
   16th Belgian Organic Synthesis Symposium, Brussels, Belgium, July 8-13, 2018

10. Rebeka Mészáros, Sándor B. Ötvös, István Pálinkó, Ferenc Fülöp:
    Application of a heterogeneous silver catalyst in dehydrogenation and multicomponent coupling reactions in a continuous-flow system
    14th Pannonian International Symposium on Catalysis, 3-7. September 2018, Starý Smokovec, Slovakia

11. Mészáros Rebeka Ildikó:
    Terminális alkinek közvetlen nitrillé alakítása hatékony heterogén ezüstkatalizátorral
    Patonay Tamás-díj pályázat, 2019. március 13., Budapest

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13. Rebeka Mészáros, Sándor B. Ötvös, István Pálinkó, Ferenc Fülöp:
    Application of a heterogeneous silver catalyst in dehydrogenation reactions in a continuous-flow system

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14. Rebeka Mészáros, Sándor B. Ötvös, István Pálinkó, Ferenc Fülöp:
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15. Rebeka Mészáros, Márton Szabados, Pál Sipos, István Pálinkó:
Phenolate anions intercalated into CaAl-layered double hidroxide by mechano-hydrotreatment technique combinate with ultrasonic irradiation
18th International Symposium on Intercalation Compounds, Strasbourg, France, May 31-June 4, 2015

16. Rebeka Mészáros, Sándor B. Ötvös, Zoltán Kónya, Ákos Kukovecz, Pál Sipos, Ferenc Fülöp, István Pálinkó:
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17. Mészáros Rebeka, Ötvös Sándor Balázs, Pálinkó István, Fülöp Ferenc:
Nitrilek hidrogénezése és reduktív deuterálása egyszerű és fenntartható áramlásos módszerrel
MTA Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium, Kecskemét, 2019. szeptember 5-6.