Theses of doctoral (PhD) dissertation

Hydrogenation of α,β-unsaturated aldehydes and lipids by water-soluble transition metal complex catalysts

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Introduction and objectives

Green chemistry and environment-friendly solutions get growing interest in synthetic and catalytic processes. One of the principles of green chemistry includes that if the use of auxiliary substances (e.g. solvent) is necessary then we have to use alternative, "green" solvents. Water is a very special and useful "green" solvent because it is suitable for the replacement of toxic, flammable and polluting solvents; furthermore the recovery and recirculation of the catalyst can be possible.

The selective hydrogenation of either C=C or C=O bond of α,β-unsaturated ketones and aldehydes is an important objective in organic chemistry, fragrance and fine chemical industry.

An important application of water-soluble hydrogenation catalysts is the modification of biological membranes through the change of the cell membrane fluidity which can be achieved by catalytic hydrogenation of its unsaturated lipid constituents.

The replacement of hydrophobic ligands with their water-soluble analogues is necessary to get water-soluble transition metal complex catalysts. For water-soluble ligands examples are sulphonated triphenylphosphine (*m*tppms) and sulphonated salen. However, in the latter an in its analogues the imine bonds often hydrolyse in aqueous reaction mixtures, that's why the hydrolytically more stable sulphonated tetrahydrosalen (sulphosalan, HSS), its derivatives and their metal complexes are more applicable in aqueous media.

During my work my objective was the investigation of the catalytic activity of Na_2[PdHSS] in aqueous media in the hydrogenation of unsaturated lipids and α,β-unsaturated oxo compounds.

In addition, my further objective was the synthesis of new, water-soluble Ru-carboxylato complexes with *m*tppms ligands that contain relatively long

aliphatic carbon chain which promotes incorporation to the lipid layers. I had also the objective to investigate the catalytic behaviour of these new complexes, as well as the known [RuH(OAc)(*m*tppms)$_3$] in hydrogenation of liposomes.

The selectivity of [RuH(OAc)(*m*tppms)$_3$] and Na_2[PdHSS] in saturation of C=C and C=O groups was not studied earlier. In order to get information about the selectivity, my objective was to investigate the aqueous-organic biphasic hydrogenation of cinnamaldehyde with both catalysts.

Applied experimental techniques

^{1}H-, ^{31}P-NMR and IR-spectroscopy were applied to investigate the structure of the synthesized complexes. NMR spectra were recorded on Bruker AV 360 MHz at room temperature. IR measurements were carried out in KBr pellet or by ATR technique on the Perkin Elmer Spectrum One FT-IR spectrometer.

The hydrogenation and transfer hydrogenation reactions were carried out in Schlenk-vessels or pressure resistant glass tube reactors (till 12 bar total pressure). The constant temperature was held by Thermo Scientific Haake DC10-K10 thermostat. The sonication was carried out in Branson Sonifier 250 (Branson Ultrasonics, Danbury, CT 06810, USA) instrument; the ampules were thermostated in a MBT 250 block thermostat.

The α,β-unsaturated aldehydes and their hydrogenated derivatives were identified and quantified by gas chromatography using an Agilent 7890A gas chromatograph with HP-5 column. The carrier gas was nitrogen.

The hydrogenated products of fatty acids, lipids and cell membrane were identified by Hewlett-Packard 5890 Series II gas chromatograph with FID, the carrier gas was argon. The type of the column depended on the type of substrate: SP2330, HP-ULTRA2 and HP-88 columns were applied.

The ^{1}H-NMR spectra of cholesterol and its derivatives were recorded on BRUKER DRX 400 at room temperature.

Each fraction of the *Pseudomonas putida F1* bacteria culture was centrifuged on a MLW T24 instrument at 900 rpm, then the cells were suspended in water and the lipid composition of bacterium was determined. The growth curves of the bacteria were measured in BSM growth media and in BSM containing Na_2[PdHSS] complex in catalytic concentration by measuring the

optical density values at 600 nm and the curves were compared to determine the toxicity of the compound.

Abbreviations

BSM: Basalt Salt Medium broth

DBN: 1,5-diazabicyclo[4.3.0]non-5-ene

cinnamaldehyde: 3-phenyl-2-propenal

cinnamalcohol: 3-phenyl-2-propen-1-ol

*m*tppms: sodium salt of 3-diphenylphosphinobenzenesulphonic acid

HSS: sulphonated tetrahydrosalen, sulphosalan

OAc: acetate

OD_{600}: optical density at 600 nm

OLau: laurate (dodecanoate)

OOc: octanoate

Tris: tris(hydroxymethyl)aminomethane

New scientific results

1. Two new, water-soluble Ru(II)-carboxylato complexes: [RuH(OOc)(mtppms)$_3$] and [RuH(OLau)(mtppms)$_3$] were synthesized in solid form and they were characterized by ^{1}H-, ^{31}P-NMR and/or IR spectroscopy. The ^{1}H- and ^{31}P-NMR parameters of the known[1] [RuH(OAc)(mtppms)$_3$] complex catalyst were also determined.

New complexes were synthesized according to the known[1] method of synthesis of the analogous [RuH(OAc)(*m*tppms)$_3$] complex. The structures of the three complexes were characterized by IR and/or ^{1}H- and ^{31}P-NMR spectroscopy. According to the IR data the bidentate coordination of the carboxylate ligand was established in case of all three complexes. Due to the spectroscopic data following general structure was suggested for the complexes (Figure 1).

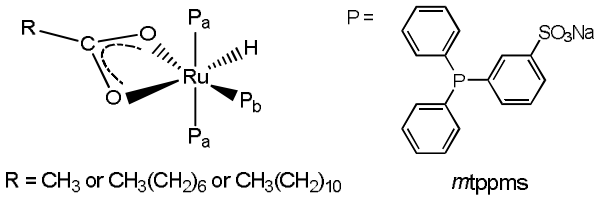

Figure 1: Suggested structure of [RuH(OAc)(*m*tppms)$_3$], [RuH(OOc)(*m*tppms)$_3$] and [RuH(OLau)(*m*tppms)$_3$] complexes

[1] Z. Tóth, F. Joó, M. T. Beck (1980) *Inorg. Chim. Acta*, 42, 153–161

2. It was demonstrated that the [RuH(OAc)(mtppms)$_3$] complex catalyst is active and selective in catalytic hydrogenation of cinnamaldehyde.

The [RuH(OAc)(*m*tppms)$_3$] complex was active in aqueous-organic biphasic hydrogenation of cinnamaldehyde at 80 °C in aqueous media, at 4-10 bar pressure of hydrogen gas. In the reaction mixture the organic phase composed by cinnamaldehyde (A) and its hydrogenated products: cinnamalcohol (B), 3-phenyl-1-propanal (C) and 3-phenyl-1-propanol (D).

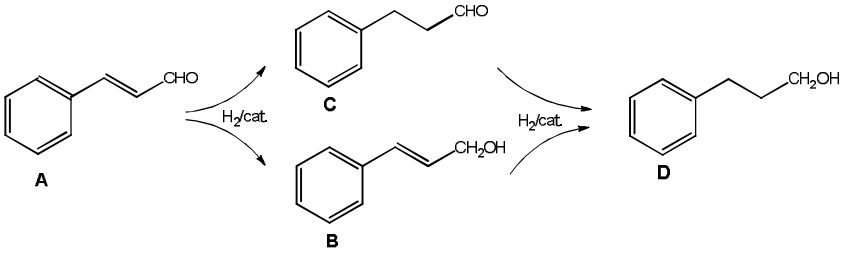

Figure 2: Hydrogenation of cinnamaldehyde

The selectivity of hydrogenation reaction for C=O bond depended on the pH and pressure of hydrogen gas, but it was above 59% in all cases. The hydrogenation activity of the complex was slightly decreased by application of phosphate buffer, but acetate buffer had no such effect. Increase of pH increased the value of conversion and selectivity in case of both buffers.

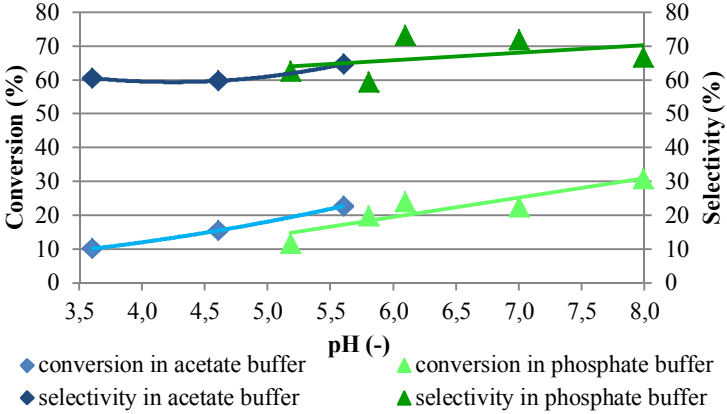

Figure 3: pH-dependence of hydrogenation of cinnamaldehyde by [RuH(OAc)(*m*tppms)$_3$] catalyst

Reaction conditions: n(complex) = 10^{-5} mol, n(cinnamaldehyde) = 8×10^{-4} mol, V(buffer) = 3 ml, T = 80 °C, t = 2 h, p(H_2) = 7 bar

3. It was established that the synthesized [RuH(OAc)(mtppms)$_3$] and [RuH(OOc)(mtppms)$_3$] complexes catalyse the hydrogenation of soybean lecithin liposomes under mild conditions, too.

Both [RuH(OAc)(*m*tppms)$_3$] and [RuH(OOc)(*m*tppms)$_3$] proved to be suitable for hydrogenation of lipids under mild conditions. Similar to the hydrogenation of cinnamaldehyde, it was established that in case of [RuH(OAc)(*m*tppms)$_3$] catalyst the application of phosphate buffer as solvent resulted in lower conversions in contrast to the reaction in deionized or neat water (at 40 °C, under 5 bar hydrogen gas, 2 h reaction time the conversion is 11% instead of 21%). According to the data of Table 1, [RuH(OAc)(*m*tppms)$_3$] is more active than [RuH(OOc)(*m*tppms)$_3$] (at 40 °C, under 1 bar hydrogen gas, 2 h reaction time the conversion was 8% instead of 1%), but this difference decreases by the increase of pressure of hydrogen gas (11,3% instead of 10,6%).

Table 1: Hydrogenation of soybean lecithin liposome in phosphate buffer

Catalyst	T (°C)	p_{H2} (bar)	t (h)	Conversion (%)
[RuH(OAc)(*m*tppms)$_3$]	25	1	2	0.2
	25	4	2	1.2
	25	5	2	3.7
	40	1	2	8.4
	40	5	2	11.3
[RuH(OOc)(*m*tppms)$_3$]	40	1	1	0.8
	40	1	2	1.2
	40	1	3	2.0
	40	5	2	10.6

Reaction conditions: n(catalyst) = 4.6×10^{-6} mol, m(soybean lecithin) = 4 mg, V(buffer) = 3 ml, pH = 6.93

4. It was demonstrated that the known[2], hydrolytically stable Na_2[PdHSS] complex is outstandingly active in hydrogenation reaction of model compounds that contain different C=C and C=O bonds.

Na_2[PdHSS] proved to be an outstandingly active catalyst in hydrogenation of saturated and unsaturated aldehydes (Table 2). In case of cinnamaldehyde and croton aldehyde — as representative α,β-unsaturated aldehydes — the catalyst was selective for hydrogenation of C=C bond in contrast to saturation of C=O bond. During the investigation of pH-dependence of hydrogenation reaction of cinnamaldehyde it was established, that the increase in pH decreases both the conversion and the selectivity in case of all applied buffers (acetate, Tris.HBF_4 and phosphate).

Table 2: Hydrogenation of saturated and unsaturated aldehydes by Na_2[PdHSS] complex

Entry	Substrate	Conversion (Selectivity[a]), % (%)
1	cinnamaldehyde	99.9 (93)
2[b]	cinnamaldehyde	87 (96)
3[c]	cinnamaldehyde	86 (98)
4[b, d]	4-methoxycinnamaldehyde	98 (57)
5[c, d]	4-nitrocinnamaldehyde	3 (100)
6[d]	croton aldehyde	66 (100)
7[d]	3-methyl-2-butenal	22 (72)
8	hexanal	11
9	decanal	3
10	benzaldehyde	90
11	4-fluoro-benzaldehyde	89
12	4-(trifluormethyl)-benzaldehyde	84
13	3-fluoro-benzaldehyde	2
14	3-methyl-benzaldehyde	14
15	vanillin	5

Reaction conditions: $n(Na_2[PdHSS]) = 2.5\times10^{-7}$ mol, $n(aldehyde) = 2.5\times10^{-4}$ mol, $V(H_2O) = 3.15$ ml, T = 80 °C, t = 2 h, $p(H_2) = 5$ bar, [a] ratio of saturated aldehyde among the products, [b]solvent: 3.1 ml H_2O and 63 µl toluene, [c]solvent: 0.65 ml H_2O and 2.5 ml toluene, [d]t = 4 h

[2] K. Voronova, M. Purgel, A. Udvardy, A. C. Bényei, Á. Kathó, F. Joó (2013) *Organometallics*, 32(15), 4391–4401

5. It was demonstrated, that the Na_2[PdHSS] complex is catalytically active in transfer hydrogenation of cinnamaldehyde from 2-propanol in the presence of various bases, furthermore it catalyses the reduction by sodium-borohydride, too.

The Na_2[PdHSS] complex proved to be active in transfer hydrogenation of cinnamaldehyde from 2-propanol in the presence of various bases (Table 3). Among the applied organic and inorganic bases NaOH, KOH and DBN proved to be optimal. In these cases the catalyst showed high selectivity for saturation of the C=C bond in contrast to the C=O bond.

Table 3: Effect of bases on hydrogenation of cinnamaldehyde in transfer hydrogenation reaction

Basis	**Conversion (%)**
NaOH	100
KOH	89
Na_2CO_3	45
Cs_2CO_3	44
K_2CO_3	42
$KHCO_3$	13
1,5-diazabicyclo[4.3.0]nonene	70
diethyl-amine	47
triethyl-amine	22
CH_3COONa	5
HCOONa	4

Reaction conditions: $n(Na_2[PdHSS]) = 2.5\times10^{-7}$ mol, $n(base) = 1.25\times10^{-4}$ mol, $n(cinnamaldehyde) = 2.5\times10^{-4}$ mol, $V(H_2O) = 2.45$ ml, V(2-propanol) = 0.7 ml, T = 80 °C, t = 2 h, p(Ar) = 1 bar

In case of application of sodium-borohydride the selectivity changed: till 11% conversion cinnamalcohol (B) was the main product, above 11% the saturated alcohol (D) became the main product. The ratio of the saturated aldehyde (C) was just 1% in the reaction mixture even in case of 90% conversion, too.

6. It was established that the Na_2[PdHSS] complex shows outstanding activity in hydrogenation of cinnamalcohol under mild conditions.

Na_2[PdHSS] complex catalyst was active at 20 °C, under 5 bar hydrogen gas in hydrogenation of cinnamalcohol. In 1 hour, ~8% conversion can be achieved at 20 °C and this value increases at 80 °C to ~98% (Table 4). It was established from the composition of reaction mixtures that during the reaction not just hydrogenation but redox isomerization also occurs (Figure 4).

Table 4: Temperature-dependence of the yields of the various products in hydrogenation of cinnamalcohol

	T (°C)							
	20		40		60		80	
t (h)	1	2	1	2	1	2	1	2
Cinnamalcohol **(B)**	91.7	89.8	73.7	69.2	8.0	1.1	2.1	0.3
3-Phenyl-1-propanol **(D)**	3.0	5.2	20.8	21.5	77.5	96.5	87.2	96.4
3-Phenyl-1-propanal **(C)**	1.4	0.3	1.1	1.2	10.2	1.7	5.6	3.3
Cinnamaldehyde **(A)**	4.0	4.7	4.3	8.1	4.3	0.7	5.1	0

Reaction conditions: n(Na_2[PdHSS]) = 2.5×10^{-7} mol, n(cinnamalcohol) = 2.5×10^{-4} mol, V(H_2O) = 3.15 ml, p(H_2) = 5 bar

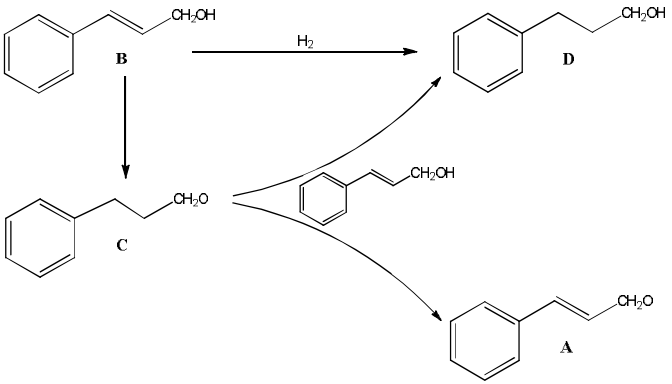

Figure 4: Hydrogenation and redox isomerization of cinnamalcohol

7. On the basis of my measurements, a possible mechanism of Na_2[PdHSS]-catalysed hydrogenations was suggested.

The steps of the suggested mechanism are the following:

1. Coordination of H_2 to palladium.
2. Heterolytic cleavage of the coordinated H_2 to a hydride and a proton.
3. Coordination of the hydride to palladium.
4. Binding of the proton to one of the phenolate oxygens.
5. Coordination of the substrate to palladium.
6. Hydride transfer from the palladium to one of the carbon atoms of the C=C bond.
7. Protonation of the Pd-alkyl intermediate from the neighbouring phenolic OH group.
8. Decoordination of the product and coordination of the phenolate oxygen to the palladium (the complex is ready for a new catalytic cycle).

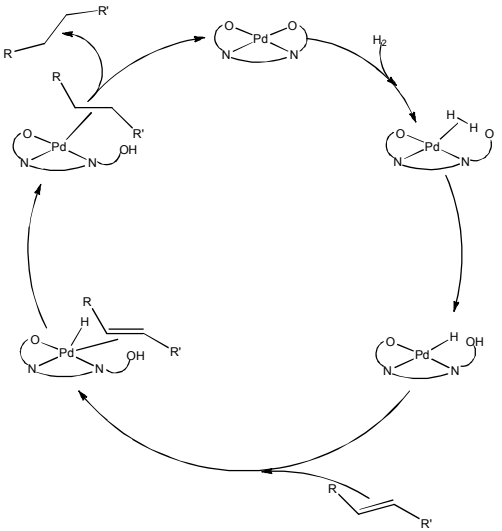

Figure 5: Suggested mechanism of Na_2[PdHSS]-catalysed alkene hydrogenation

8. It was established that the Na_2[PdHSS] complex is catalytically active and selective in hydrogenation of different lipid compounds in aqueous dispersions, under mild conditions.

The Na_2[PdHSS] complex catalyst proved to be active in hydrogenation of free fatty acids (oleic acid, linoleic acid), soybean lecithin, the mixture of soybean lecithin and cholesterol, the mixture of ethyl-esters of long-chain polyunsaturated fatty acids (eicosapentanoic acid, docosahexanoic acid) under mild conditions (25–37 °C, 1–7 bar H_2).

It was established that during the hydrogenation of oleic acid not just saturation but isomerization reactions also take place; large amounts of elaidic acid appear in the reaction mixture.

It was shown in case of hydrogenation of soybean lecithin that increase of the pressure of hydrogen gas only slightly increases the conversion and the increase of reaction time from 3 h to 20 h results in just a 20% increase in the conversion. This refers to the fact that because of the structure of the model membrane not all of the unsaturated bonds are accessible for the catalyst.

Similarly, in the mixture of soybean lecithin and cholesterol by increase of amount of cholesterol the conversion decreased (during the process the hydrogenation of cholesterol did not occur).

Hydrogenation of ethyl-esters of longer-chain polyunsaturated fatty acids (eicosapentanoic acid, docosahexanoic acid) did not occur, but in case of a mixture with soybean-lecithin the catalyst was able to access the unsaturated bonds and showed limited activity in hydrogenation (the conversion was ~10%).

9. It was established that the Na_2[PdHSS] complex is suitable for the modification of the membrane of Pseudomonas putida F1 by catalytic hydrogenation.

It was established that the decrease of the degree of unsaturation is ~10% in case of Na_2[PdHSS]-catalysed hydrogenation of cell membranes of *P. putida F1* (37 °C, 4 h, 3 bar H_2) (Table 5). It was demonstrated that not just hydrogenation but positional and geometric (*cis-trans*) isomerization of C=C bonds also occurred. The hydrogenation and its conditions had no influence on the viability of cells.

Table 5: Ratio of the major lipid constituents of *Pseudomonas putida F1* bacterium before and after hydrogenation (determined by gas chromatography; area% data)

Fatty acid	Control	Hydrogenated
16:0	30.9	35.9
16:1	9.2	13.5
16:1	24.6	14.1
17:0	4.7	3.1
18:0	5.2	10.1
18:1	1.5	2.0
18:1	2.2	4.6
18:1	21.7	16.7

Reaction conditions: $n(Na_2[PdHSS]) = 7.5\times10^{-7}$ mol, $V(H_2O) = 3.04$ ml, T = 37 °C, t = 4 h, $p(H_2) = 3$ bar

10. It was demonstrated that the Na_2[PdHSS] compound is not toxic in catalytic concentration to Pseudomonas putida F1 bacteria.

According to the growth curves (Figure 6) in BSM growth medium with or without Na_2[PdHSS] complex in catalytic concentration it was established that the compound is not toxic to the bacterium cell and it had no influence on viability, reproduction and growth of the culture.

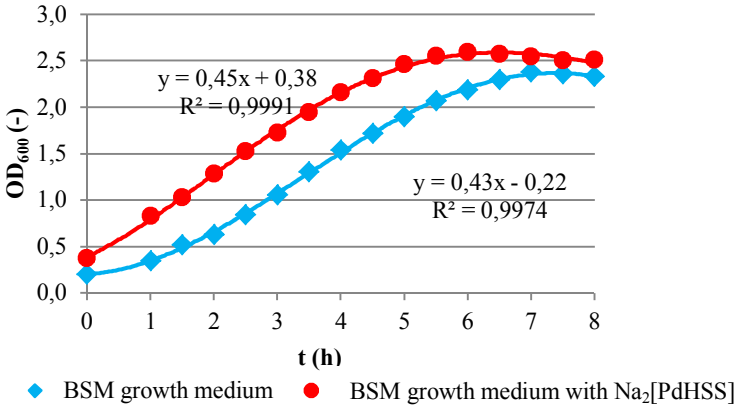

Figure 6: Growth curves of *Pseudomonas putida F1* bacteria in BSM growth medium with Na_2[PdHSS] complex (●) and without Na_2[PdHSS] complex (◆)

List of publications

Publications related to the dissertation:

Foreign language scientific articles in international journals:

1. Réka Gombos, Brigitta Nagyházi, Ferenc Joó: Hydrogenation of α,β-unsaturated aldehydes in aqueous media with a water-soluble Pd(II)-sulfosalan complex catalyst *Reaction Kinetics, Mechanisms and Catalysis* **2019,** *126*, 439–451 (IF: 1.428)
2. Réka Gombos, Ferenc Joó: Selective hydrogenation of cinnamaldehyde and phospholipids in aqueous-organic biphasic systems with ruthenium(II) complex catalysts *Green Processing and Synthesis* **2014**, *3,* 127-132, (IF. (5-year): 1.170)

Poster presentations related to the dissertation:

1. Réka Gombos, Ferenc Joó: Selective hydrogenations in aqueous-organic biphasic systems with ruthenium(II) complex catalysts, 1st EuCheMS Congress on Green and Sustainable Chemistry, 2013, Budapest, Hungary (Book of abstracts P-12, 84.o.)
2. Réka Gombos, Brigitta Nagyházi, Ferenc Joó: Application of a Pd(II)-sulfosalan complex in hydrogenation reactions, XXII. International Conference on Chemistry, 2016, Timisoara, Romania (Book of abstracts 95.o.)
3. Réka Gombos, Brigitta Nagyházi, Ferenc Joó: Application of a Pd(II)-sulfosalan catalyst in aqueous hydrogenation reactions, EuCheMS International Organometallic Conference XXII, 2017, Amsterdam, The Netherlands (Book of abstracts, Poster 81.)

Other poster presentations:

4. Eleonora Marian, Tünde Jurca, Mihály Braun, Réka Gombos, Imre Tóth: Comparative study of five herbal products from Salvia officinalis using ICP-AES and ATR techniques, XX. International Conference on Chemistry, 2014, Cluj-Napoca, Romania (Book of abstracts 112.o.)
5. Réka Gombos, Edina Baranyai, Sándor Harangi, Tamás Kézi, Károly Tőkési Major and trace elements in animal bones - search for environmental effects, 27th International Conference on Atomic Collisions in Solids (ICACS-27), 2016, Lanzhou, China (Programme and Book of abstract 210. o.)
6. Tamás Varga, Róbert Janovics, Árpád Bihari, Réka Gombos, Levente Karaffa, Ferenc Joó, Mihály Molnár: Investigation of TCE digestion by bacteria using radiocarbon labelling, 2nd International Radiocarbon in the Environment Conference, 2017, Debrecen, Hungary (Book of abstracts 114.o.)

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List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

1. **Gombos, R.**, Nagyházi, B., Joó, F.: Hydrogenation of α,β-unsaturated aldehydes in aqueous media with a water-soluble Pd(II)-sulfosalan complex catalyst.
   React. Kinet. Mech. Catal. 126 (1), 439-451, 2019. ISSN: 1878-5190.
   DOI: http://dx.doi.org/10.1007/s11144-018-1488-8
   IF: 1.428 (2018)

2. **Gombos, R.**, Joó, F.: Selective hydrogenation of cinnamaldehyde and phospholipids in aqueous-organic biphasic systems with ruthenium(II) complex catalysts.
   Green Process. Synth. 3 (2), 127-132, 2014. ISSN: 2191-9542.
   DOI: http://dx.doi.org/10.1515/gps-2014-0003
   IF: 1.125

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