



BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS

Faculty of Chemical Technology and Biotechnology

Oláh György Doctoral School

**Synthesis of biomass-based ionic liquids and their
application in transition-metal-catalyzed
coupling reactions**

Theses of PhD dissertation

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1 INTRODUCTION

Biomass played a decisive role in the life of mankind until the industrial revolution, since that time we have obtained highly functionalized chemical end products primarily through the transformation of fossil raw materials (first coal, later oil and natural gas). The rapid decline in fossil fuel reserves has led to the recognition that this source of raw materials should be gradually replaced by renewables wherever possible. In addition to technological feasibility, a key issue for the biomass-based chemical industry is whether the available cultivable land, given the size of the market for chemical raw materials, is sufficient to produce the required raw materials. Calculations have shown that the demand for raw materials for transport cannot be covered on biomass basis,¹ however the replacement of some fossil based chemicals used in smaller quantities (e.g. some solvents) with renewable-based ones can make a significant contribution to reducing the area's need for fossil-based raw materials and making a given process more environmentally friendly.

Solvents, a significant portion of which are petroleum-based, are almost indispensable processing aids in the chemical industry, but their toxicity, high vapor pressure, and flammability mean a serious risk during use. Replacing conventional solvents with green ones with more favorable properties (lower vapor pressure, lower toxicity, lower flammability) can be an important step towards achieving a cleaner chemical industry. By choosing these carefully, we can fulfil the fifth principle of green chemistry: “the use of auxiliary substances (solvents, separation aids, etc.) should be minimized and, if still necessary, they should be green”.²

Ionic liquids are popular environmentally friendly solvents nowadays due to their extremely low vapor pressure, low flammability and easily tunable properties, and when produced on the basis of biomass, they have a distinct environmental benefit. The aim of my doctoral dissertation was to combine the benefits of using environmentally friendly solvents with the possibility of replacing fossil raw materials, for which I produced new biomass-based ionic liquids and explored their applicability as solvents.

(1) Cséfalvay, E.; Akien, G. R.; Qi, L.; Horváth, I. T.. *Catal. Today* **2015**, 239, 50–55.

(2) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University: Oxford, 1998.

2 LITERATURE REVIEW

The most commonly used solvents are typically harmful to the environment and health. Known examples are the ozone depleting effects of CFCs (chlorofluorocarbons, i.e. hydrocarbons containing chlorine and fluorine substituents),³ the toxicity of chlorinated hydrocarbons, the high vapor pressure of conventional solvents in general, the tendency of ethers to form peroxides,⁴ and so on. The advantage of solvent-free chemistry is that we can get rid of the problems emerging from the use of solvents. In practice, however, our ability to leave solvents is limited, as mixing, heat transfer, material transfer, and workup in most cases in a liquid medium are the most efficient. Therefore, if the process cannot be carried out without solvents, the use of an environmentally friendly, so-called green solvent should be a priority. Research to make chemical transformations more environmentally friendly has led to water, fluorine solvents, supercritical carbon dioxide, and ionic liquids being considered green solvents.

Ionic liquids are molten salts with a melting point below 100 °C, but in practice they are usually considered liquid ionic compounds at room temperature. Their growing popularity (Figure 1) also indicates that they are at the focus of green solvent research; a number of industrially important transformations have been carried out in ionic liquids, some of which are also used in an industrial scale.

In general, the cations of ionic liquids used nowadays are large, typically asymmetric, organic cations (e.g., ammonium, phosphonium, imidazolium, pyrimidinium, pyrrolidinium), and the anions are halide ions (chloride, bromide), complex metal ions (aluminium-heptachloride, iron-heptachloride, etc.) or simple organic anions (trifluoromethanesulfonate, acetate, trifluoroacetate, bis-trifluoromethanesulfonyl-imide, etc.).⁵ Ionic liquids are preferred green reaction

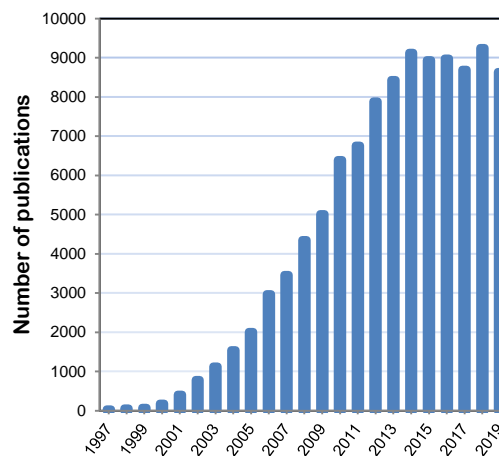


Figure 1 Number of results on „ionic liquid” in SciFinder data base

- (3) Andino, J. M. *Scientific American online*
<https://www.scientificamerican.com/article/chlorofluorocarbons-cfcs/> (Access: 26. Apr. 2020.)
- (4) Aycock, D. F. *Org Proc. Res. Dev.* **2007**, *11*, 156–159.
- (5) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chem.* **2002**, *182–183*, 419–437.

media for synthetic transformations. Their popularity is mainly due to their extremely low vapor pressure (eg 1-butyl-3-methylimidazolium hexafluorophosphate: 10^{-10} Pa at 25 °C),⁶ which excludes the loss of evaporation, thus not polluting neither the closer, nor the wider environment. By changing the constituent ions or their substituents, the properties of the ionic liquids can be varied and tuned widely, such as polarity, hydrophilicity, miscibility with other solvents. They have in common a high thermal stability (up to 250–300 °C), so we can perform reactions in ionic liquids that we would not be able to perform in conventional media. Their wide applicability is shown by the fact that we can find examples of almost all industrially important reactions in ionic liquids (Table 1).

Table 1 First publication of industrially important reactions carried out in room temperature ionic liquids

Reaction	Ionic liquid		Author	Year
	type	m.p. (°C)		
Friedel–Crafts reaction	[EMIM][Al ₂ Cl ₇]	< -25	Wilkes	1986
Hydrogenation	[BMIM][PF ₆]	-8	Chauvin	1995
Hydroformylation	[BMIM][PF ₆]	-8	Chauvin	1995
Alkoxy-carbonylation	[BMIM][BF ₄]	-75	Monteiro	1998
Heck reaction	[BMIM][PF ₆]	-8	Seddon	1999
Suzuki coupling	[BMIM][BF ₄]	-75	Welton	2000
Negishi coupling	[BMIM][BF ₄]	-75	Knochel	2000
Stille coupling	[BMIM][BF ₄]	-75	Handy	2001
Olefin metathesis	[BMIM][PF ₆]	-8	Bujsman	2001
Ullmann-type coupling	[BMIM][I]	< -50	Ren	2003
Sonogashira coupling	[BMIM][PF ₆]	-8	Ryu	2002
Hiyama coupling	[C ₅ MPyrr][Tf ₂ N]	10	Slattery	2009

The green chemical advantages of ionic liquids are overshadowed by the fact that the production of conventional ionic liquids require much more reaction steps than conventional fossil or biomass-based solvents, thus producing more waste (Figure 2). Philip Jessop's summary of green solvents highlights the need to prioritize ionic liquids that can be obtained

(6) Paulechka, Y.U.; Kabo, G.J.; Blokhin, A.V.; Vydrov, O.A.; Magee, J.W.; Frenkel, M. *J. Chem. Eng. Data* **2003**, *48*, 457–462.

by converting biomass, especially those that can be produced in few steps under relatively mild conditions.⁷ γ -Valerolactone (GVL) can be synthesized from biomass in just two steps, from which alkyl-4-alkoxyvalerates can be prepared in 1 step. These compounds are converted to 4-hydroxyvalerate and 4-alkoxyvalerate anions in basic media, which opens the way for the production of partially or entirely biomass-based ionic liquids.

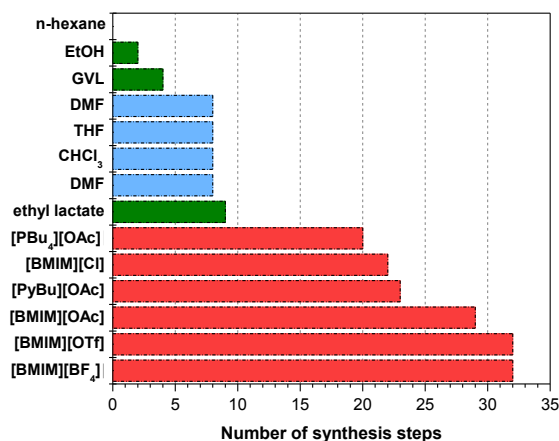


Figure 2. Number of steps of synthesis of different solvents.⁷ ■: biomass-based solvents, ■: conventional solvents, ■: conventional RTIL

3 EXPERIMENTAL METHODS

NMR spectra were recorded on a Bruker Avance 250 MHz spectrometer. Water content of the synthesised ionic liquids were determined by Karl Fischer titration with a HANNA Instruments 904. The exact molar masses were determined by high-resolution Q-Exactive Focus hybrid quadrupole-orbitrap mass spectrometer equipped with electrospray ion source (ESI) (Thermo Fisher Scientific, Bremen, Germany). The samples were dissolved in a water-acetonitrile 1:1 solution containing 0.1% (V/V) formic acid, the compounds were measured as their protonated form ($[M+H]^+$).

The density of ionic liquids containing tetraalkylammonium cation was measured with a pycnometer, their viscosity with a Höppler viscometer, and their conductivity with a Radelkis OK-114 conductometer, the latter was calibrated with 0.01 mol KBr solution.

The density of ionic liquids containing tetrabutylphosphonium cation was measured with Anton Paar DMA 4500 M, viscosity with Anton Paar Physica MCR 301, and conductivity was measured with WTW inoLab® Cond 7110. The vapor pressures of GVL-based biooxygenates and ionic liquids were determined with a 25 ml Hasteloy-C Parr reactor and a connected Rosemount® Hasteloy-HC-276 digital vapor pressure gauge.

(7) Jessop, P. G. *Green Chem.* **2011**, *13*, 1391–1398.

4 RESULTS

4.1 SYNTHESIS AND CHARACTERIZATION OF BIO-OXYGENATES

The preparation of GVL-based alkyl 4-alkoxyvalerates (Figure 3) is a known reaction, but the temperature dependence of their vapor pressure has not been previously studied. As expected, these compounds have much lower vapor pressures than conventional solvents and are more preferred in green chemistry aspects over conventional esters (e.g., ethyl acetate) due to their low vapor pressure, but ionic liquids formed in further reactions from these molecules also have a number of other advantageous properties, so I focused on the preparation and applicability of these ionic liquids.

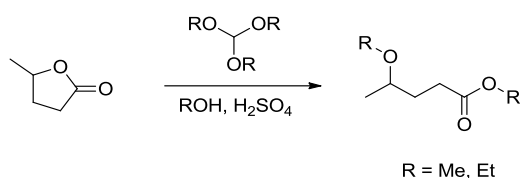


Figure 3 GVL-based biooxygenates

4.2 PREPARATION AND CHARACTERISATION OF IONIC LIQUIDS CONTAINING TETRAALKYLAMMONIUM CATIONS

It is well known that esters decompose to alcohol and the salt of the corresponding carboxylic acid in alkalic media, and in the case of cyclic esters the same happens with the opening of the ring. In the reaction of tetraalkylammonium hydroxide and GVL, I prepared three room temperature ionic liquids: tetramethylammonium 4-hydroxyvalerate ([TMA][4HV]), tetrabutylammonium 4-hydroxyvalerate ([TBA][4HV]), and choline-4-hydroxyvalerate ([Chol][4HV]). Both the anion and the cation of choline-4-hydroxyvalerate are of natural origin, so it can be called fully “bio-ionic liquid” (Figure 4).

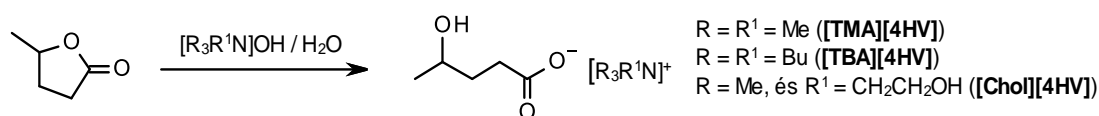


Figure 4 Preparation of GVL-based ionic liquids containing tetraalkylammonium cations

I determined the most important physicochemical parameters of the produced ionic liquids: temperature dependence of density, conductivity and viscosity, which were close to the data of other similar ionic liquids, but when examining the temperature dependence of vapor pressure, rapid decomposition was observed over 100–120 °C. This property limits the applicability of these compounds at higher temperatures, so I aimed to prepare and study ionic liquids containing phosphonium cation with higher thermal stability.

4.3 PREPARATION AND CHARACTERISATION OF IONIC LIQUIDS CONTAINING TETRAALKYLPHOSPHONIUM CATIONS

With a structure similar to tetraalkylammonium cation, tetraalkylphosphonium cation is also known as a building block of ionic liquids. The reaction of tetraalkylphosphonium hydroxide ([TAP][OH]) with GVL and alkyl 4-alkoxyvalerates results in compounds with a structure very similar to ammonium cation-containing ionic liquids (tetrabutylphosphonium 4-hydroxyvalerate ([TBP][4HV]), tetrabutylphosphonium 4-methoxyvalerate ([TBP][4MeOV]), tetrabutylphosphonium 4-ethoxyvalerate ([TBP][4EtOV])) (Figure 5).

I also determined the physicochemical parameters of the new type of ionic liquids: the temperature dependence of vapor pressure, density, conductivity and viscosity were investigated. Compared with ionic liquids containing tetraalkylammonium cation, tetrabutylphosphonium-based ionic liquids have lower viscosity and vapor pressure and have higher thermal stability.

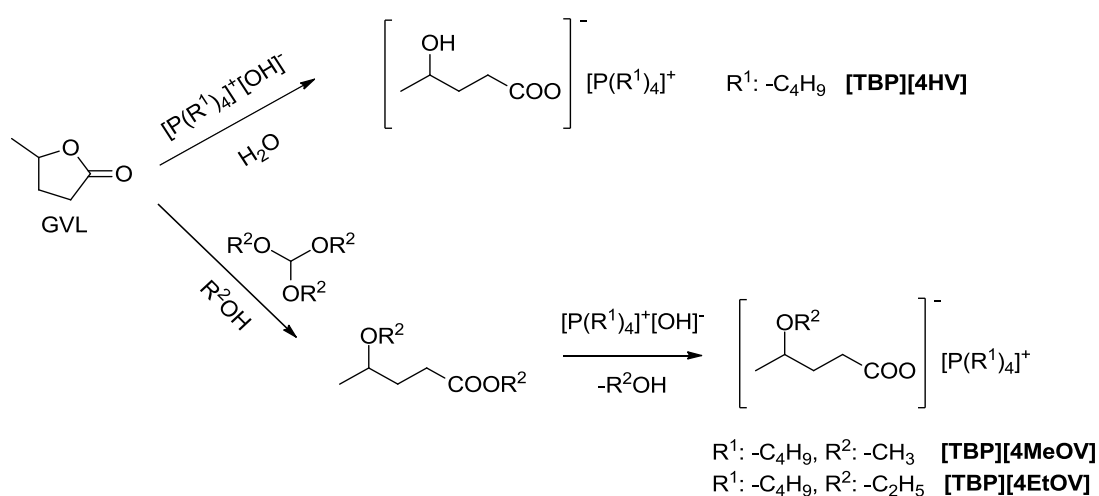


Figure 5 Modular synthesis of GVL-based ionic liquids containing tetraalkylphosphonium cations

4.4 CATALYTIC ULLMANN-TYPE C–N COUPLING REACTIONS

The applicability of ionic liquids as solvents in cross-coupling reactions was first investigated in Ullmann-type coupling. Compared to conventional and other GVL-based ionic liquids, I achieved the highest isolated production in [TBP][4EtOV] in the model reaction. I proved that by carrying out the reaction in an ionic liquid of tetrabutylphosphonium 4-ethoxyvalerate ([TBP][4EtOV]), no additional auxiliary aids are needed but CuI catalyst, and I proved that the process is also hardly sensitive to water content. By coupling iodobenzene with 10 different amines, and benzylamine with 10 different iodobenzene derivatives containing electron withdrawing and electron donating groups, 20 different aromatic amines were prepared with 50–87% isolated yield (Figure 6).

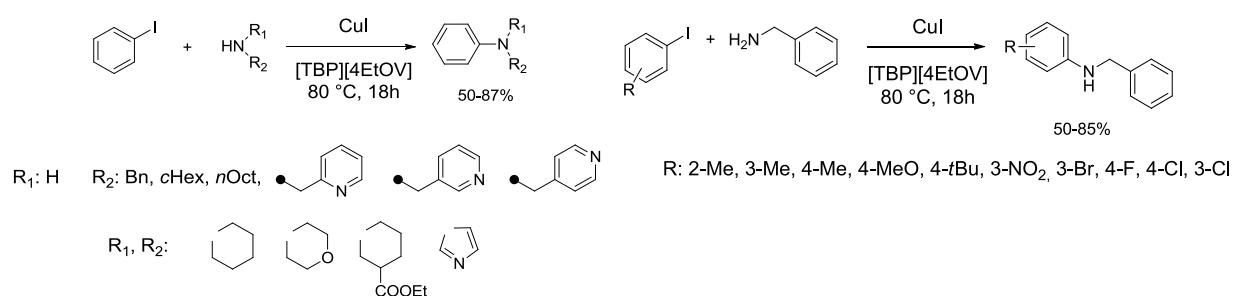


Figure 6 Ullmann-type coupling reactions in [TBP][4EtOV] ionic liquid

4.5 PALLADIUM-CATALYSED SONOGASHIRA REACTION

After the success of Ullmann-type coupling, the [TBP][4EtOV] ionic liquid was utilized in the Sonogashira reaction. According to the results, the coupling also takes place in conventional ionic liquids in the presence of the commonly used base and copper co-catalyst, but these and the added ligand can also be omitted in the case of [TBP][4EtOV] reaction medium. It was shown that the catalytic system I have developed is not sensitive to water content in Sonogashira coupling, neither. In the coupling reaction of iodobenzene derivatives and other iodoaromatic compounds (pyridine and thiophene) containing electron-withdrawing and electron-donating groups and 4 different monosubstituted acetylene compounds, 21

disubstituted acetylene derivatives were synthesized in 52–99% isolated yield (Figure 7). I proved that the catalytic system, although with significant loss of activity, can be reused at least in 4 cycles.

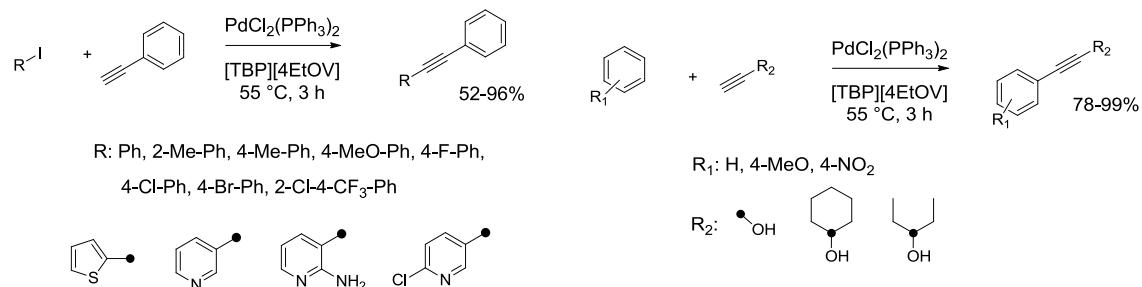


Figure 7 Sonogashira-reaction in [TBP][4EtOV] ionic liquid

4.6 CATALYTIC HIYAMA COUPLING

Via Ullmann-type and Sonogashira coupling, I have shown that GVL-based [TBP][4EtOV] ionic liquid can be a suitable medium for transition metal-catalyzed cross-coupling reactions, so I extended its applicability to Hiyama coupling, as well. Compared to conventional and other GVL-based ionic liquids, I achieved the highest isolated yields in [TBP][4EtOV] in the model reaction. Coupling of 15 iodoaromatics with phenyltriethoxysilane was performed in 45–72% isolated yield (Figure 8).

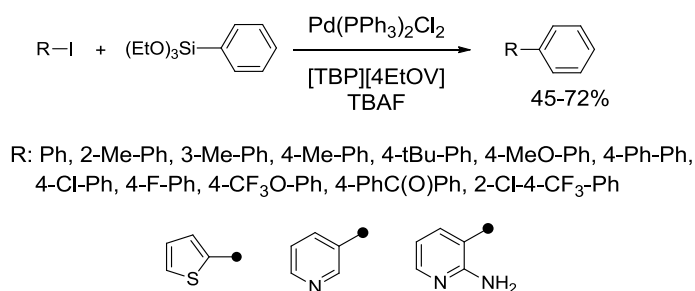


Figure 8 Hiyama-reaction in [TBP][4EtOV] ionic liquid

4.7 ASSESSMENT OF APPLICABILITY OF NOVEL IONIC LIQUIDS

In summary, the GVL-based ionic liquids can be promising media for transition metal-catalyzed coupling reactions, however, based on experimental observations during the preparation and isolation of more than 50 compounds, the solubility properties of the ionic liquids may limit the workup possibilities and their effective reuse, which unfortunately limits their scope. Fine-tuning the consisting ions of the novel ionic liquids might be a solution to modify the solubility properties. Examining the reactions from a green chemistry perspective it can be concluded that due to the remarkable solvent demand of extraction and chromatographic purification the use of new ionic liquids results in a relatively high environmental factor, which, however, can be reduced by reprocessing the easily distillable solvents.

5 THESES

1. I was the first to demonstrate that the aqueous phase reaction of γ -valerolactone and the corresponding tetraalkylammonium hydroxide produces new, room-temperature, completely (choline-4-hydroxyvalerate) or partially bio-ionic liquids (tetramethylammonium 4-hydroxy-valerate and tetrabutylammonium 4-hydroxyvalerate), containing tetraalkylammonium cation. [1]
2. I was the first to prepare a new, room temperature, partially bio-ionic liquid (tetrabutylphosphonium-4-hydroxyvalerate) by the aqueous phase reaction of γ -valerolactone and the corresponding tetraalkylphosphonium hydroxide. I was the first to prepare new, room-temperature, partially bio-ionic liquids containing tetraalkylphosphonium cation (tetrabutylphosphonium 4-methoxyvalerate and tetrabutylphosphonium 4-ethoxyvalerate) in the reaction of the γ -valerolactone-derived alkyl-4-alkoxyvalerates and the corresponding tetraalkylphosphonium hydroxide in aqueous phase. [2]

3. I proved that the viscosity of ionic liquids containing tetraalkylphosphonium cation, even at lower water content, at the same temperature is lower than that of ionic liquids containing the corresponding tetraalkylammonium cation. I further demonstrated that in the case of γ -valerolactone-based ionic liquids, the replacement of the ammonium cation with a phosphonium cation results in lower vapor pressure and greater thermal stability. [1][2]
4. I was the first to demonstrate the applicability of tetrabutylammonium 4-ethoxyvalerate as a solvent in Ullmann-type, Sonogashira and Hiyama coupling reactions through the preparation and isolation of 20, 21, and 15 compounds, respectively. [2][3][4]
5. I was the first to demonstrate that in tetrabutylammonium 4-ethoxyvalerate solvent, the added base and ligand can be omitted from the reaction mixture in the case of Ullmann-type coupling, and the copper co-catalyst, the auxiliary base and ligand in the case of Sonogashira coupling. [2][3]

6 APPLICATION POSSIBILITIES

By modular synthesis of GVL-based ionic liquids, fine-tuning either the cation or the anion, new reaction media with various properties can be prepared. Based on the success of the three catalytic transformations shown, it can be assumed that partially or fully bio-ionic liquids can be used in other reactions.

7 PUBLICATIONS

Publications serving as the basis of the doctoral dissertation:

- [1] Fegyverneki, D.; **Orha, L.**; Láng, Gy.; Horváth I. T. Gamma-valerolactone-based solvents. *Tetrahedron* **2010**, *66*, 1078–1081. DOI: 10.1016/j.tet.2009.11.013. IF: 3,011; C: 144; IC: 139

- [2] **Orha, L.**; Tukacs, J. M.; Gyarmati, B.; Szilágyi A.; Kollár, L.; Mika, L. T. Modular Synthesis of γ -Valerolactone-Based Ionic Liquids and Their Application as Alternative Media for Copper-Catalyzed Ullmann-type Coupling Reactions. *ACS Sustainable Chem. Eng.* **2018**, *6*, 5097–5104. DOI: 10.1021/acssuschemeng.7b04775. IF: 6.970; C: 7; IC: 4
- [3] **Orha, L.**; Tukacs, J. M.; Kollár, L.; Mika, L. T. Palladium-catalyzed Sonogashira coupling reactions in γ -valerolactone-based ionic liquids. *Beilstein J. Org. Chem.* **2019**, *15*, 2907–2913. DOI: 10.3762/bjoc.15.284. IF: 2.595; C: 0 IC: 0
- [4] **Orha, L.**; Papp, Á.; Tukacs, J. M.; Kollár, L.; Mika, L. T. Tetrabutylphosphonium 4-ethoxyvalerate as a biomass-originated media for homogeneous palladium-catalyzed Hiyama coupling reactions *Chem. Papers* **2020**. *74*, 4593-4598. DOI: 10.1007/s11696-020-01287-y. IF: 1.680, C: 0, IC: 0

Other publications:

- [5] Mika, L.T.; **Orha, L.**; Farkas, N.; Horvath, I.T. Efficient Synthesis of Water-Soluble Alkyl-bis(m-sulfonated-phenyl)- and Dialkyl-(m-sulfonated-phenyl)-phosphines and Their Evaluation in Rhodium-Catalyzed Hydrogenation of Maleic Acid in Water. *Organometallics* **2009**, *28*, 1593–1596 DOI: 10.1021/om800570r IF: 4.204
- [6] Mika, L. T.; **Orha, L.**; Driessche, E.; Garton, R.; Zih-Perenyi, K.; Horvath, I. T. Water-Soluble-Phosphines-Assisted Cobalt Separation in Cobalt-Catalyzed Hydroformylation. *Organometallics* **2013**, *32*, 5326–5332. DOI: 10.1021/om400579f IF: 4.253
- [7] **Orha, L.**; Rábai, J. Preparation of Novel Fluorous Alkylating Agents and Pyrrolidines from Fluorous γ -Lactone Precursors. *Fluorine Notes* **2017**, *110*, 1–2. DOI: 10.17677/fn20714807.2017.01.01

Book chapter:

- [8] **Orha, L.**; Akien, G. R.; Horváth I. T. Handbook of Green Chemistry. Part 7. Green Synthesis. 4. Synthesis in Green Solvents. Wiley-VCH Verlag GmbH & Co. 2012. DOI: 10.1002/9783527628698.hgc075

Lecture in the topic of the doctoral dissertation:

- [9] **Orha, L.**; Mika, L. T. *Cross coupling reactions in gamma-valerolactone-based ionic liquids*. 45th International Conference of Slovak Society of Chemical Engineering. Tatranské Matliare, Slovakia, 21–25 May, 2018.

Other lectures:

- [10] **Orha, L.**; Koltai, E.; Farkas, N.; Alexin, A.; Faiglné Birkás E. *Synthesis of ^{14}C -labelled AFMB (^{14}C -izotóppal jelzett AFBM szintézise)*. Őszi Radiokémiai Napok, Siófok, 8–10 October, 2012.
- [11] **Orha, L.**; Koltai, E.; Farkas, N.; Alexin, A.; Faiglné Birkás E. *Challenges in the reductions of the [ring- ^{14}C]-labelled fluoro-nitrobenzene derivatives*. 12th International Symposium on the Synthesis and Applications of Isotopes and Isotopically Labelled Compounds, Princeton, NJ, USA, 7–11 June, 2015.
- [12] **Orha, L.**, Fuchs, A.; Kiss, F.; Kladni, L.; Koltai, E.; Sebők, P.; Vargadi, T.; Alexin, A. *Synthesis of ^{14}C -labelled sulfonylurea type pesticides*. 13th International Symposium on the Synthesis and Applications of Isotopes and Isotopically Labelled Compounds, Prague, Czech Republik, 3-7 June, 2018.

