



---

**BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS FACULTY OF  
CHEMICAL AND BIOENGINEERING  
GEORGE OLÁH DOKTORAL SCHOOL**

# **Adduct formation by carbenes: structure and preparation – molecular tuning**

Theses of the Doctoral Dissertation

Author: **Zsolt Kelemen**

Supervisor: **László Nyulászi**

Budapest University of Technology and Economics Faculty of Chemical and Bioengineering  
Department of Inorganic and Analytical Chemistry

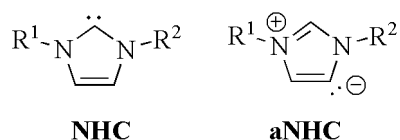
2015

## 1. Introduction

Carbenes are subvalent compounds with only 6 electron on the valence shell. Due to their specific structural properties and their wide applicability they were extensively investigated during the past decades. The most applied structural motifs of carbenes are the N-heterocycle carbenes (NHC **Scheme 1**, in particular imidazole-2-ylidene, which has a less stable isomer the imidazole-4-ylidene called abnormal NHC (aNHC), with attractive properties being explored only very recently.

Imidazol-ylidenes form adducts with several molecules, changing often their original polarity, and thus reactivity. Among these the adducts with hydroxycarbenes, the so called Breslow-intermediate, are of particular importance (**Scheme 2**). These compounds are formed from the reaction of the NHC with aldehydes, and after isomerisation they facilitate C-C bond formation reactions, such as the benzoin condensation. Although Breslow-analogues containing heteroelements (**Scheme 2: 2 and 3** X: CH<sub>2</sub>, SiH<sub>2</sub>, NH, PH, O S) are also known, they were not investigated in detail, furthermore no structural studies on the analogous aNHC adducts were carried out.

The Breslow intermediate should form in the reaction of an aldehyde and a carbene precursor, which is an azolium salt in the presence of added base, which facilitates the formation of the NHC by deprotonation. In this respect it was of high interest, whether imidazolium acetate, featuring the basic acetate ion has a sufficient NHC concentration to provide the Breslow intermediate, allowing then the benzoin condensation. The possibility to use imidazolium-acetate as an NHC precursor came from a recent result from the research group: the NHC having been detected from the vapour of imidazolium-acetate, albeit no direct evidence was found for the presence of the carbene in the liquid phase. A further topic of my studies – connect tightly to the above discussed field – the investigation of the reaction in which imidazolium acetate ionic liquids act as alternative NHC-source. Although our research group could detect the presence of NHC in the vapor of imidazolium acetate unambiguously, there is no spectroscopical evidence for the formation of NHC in liquid phase. Thus the question arises whether the concentration of NHC could be enough high to observe organocatalytic activity, furthermore formation of other NHC adducts are possible, especially the carbon dioxid adducts due its role in the environment.



**Scheme 1:** The structure of imidazole-2-ylidene and imidazole-4-ylidene, which belong to the family of NHC and aNHC, respectively.

## 2. Background

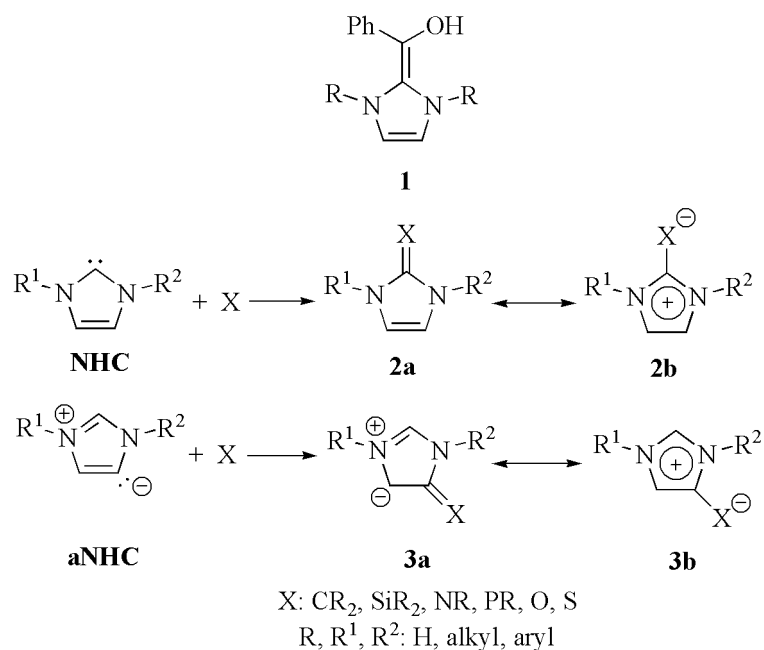
Stable singlet carbenes are excellent nucleophiles due to the lone pair at the carbon atom, therefore they easily react with electrophiles (proton, aldehydes, polarized double bond containing systems, transition metals). At the same time they also possess a vacant orbital which is perpendicular to the molecular plane (and the lone pair) having consequently  $\pi$ -acceptor ability. Due to the above discussed two orbitals carbenes can mimic transition metals, with their various catalytic activity.<sup>1</sup> Furthermore, upon adduct formation these compounds can change the usual polarity of an atom, stabilizing or activating them accordingly, acting finally as umpolung catalyst. The most discussed species of this catalytic cycle is the Breslow-intermediate,<sup>2</sup> which was only once detected, although its H-shift isomer and protonated form (none of them exhibiting the expected reactivity) were observed.<sup>3</sup> Interestingly, neither the relative stability nor the interconversion of these isomers have been investigated before in detail.

The deoxy-Breslow-intermediate – which has enhanced stability – has a similar structure to the Breslow-intermediate, furthermore its analogues containing other heteroatoms also exist (**Scheme 2: 1 and 2**). Interestingly the so-called abnormal analogues (**3**) of these compounds are also known. Although, several of these compounds known in the literature their stability, bonding situation and possible reactivity have not been comprehensively investigated.

<sup>1</sup> D. Martin, M. Soleilhavoup, G. Bertrand, *Chem. Sci.* **2011**, 2, 389-399.

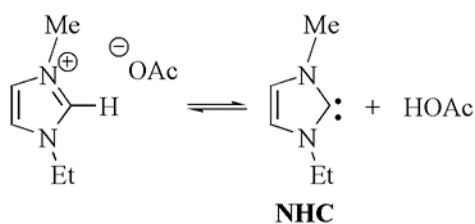
<sup>2</sup> R. Breslow, *J. Am. Chem. Soc.* **1958**, 80, 3719-3726.

<sup>3</sup> A. Berkessel, S. Elfert, K. Etzenbach-Effers, J. H. Teles, *Angew. Chem. Int. Ed.* **2010**, 49, 7120-7124.



**Scheme 2:** The Breslow-intermediate (**1**) and its analogues (**2**, **3**).

Most commonly, NHCs are generated from azolium salts via deprotonation, thus the chemistry of these compounds connects to the NHCs as well. Since several azolium salts have low melting points (below 100 °C), they are ionic liquids (ILs).<sup>4</sup> In the presence of a proper external base, the imidazolium-based ionic liquids exhibit organocatalytic activity due to the formation of NHCs. Thus, the question arises, whether NHCs can be formed using a more basic anion. Earlier calculations of our research group predicted, photoelectron- and mass spectroscopic measurement indeed revealed the presence of the NHC-acetic acid structure (instead of the ion pairs) in the vapour of 1-ethyl-3-methylimidazolium acetate ionic liquid (**Scheme 3**).<sup>5</sup>



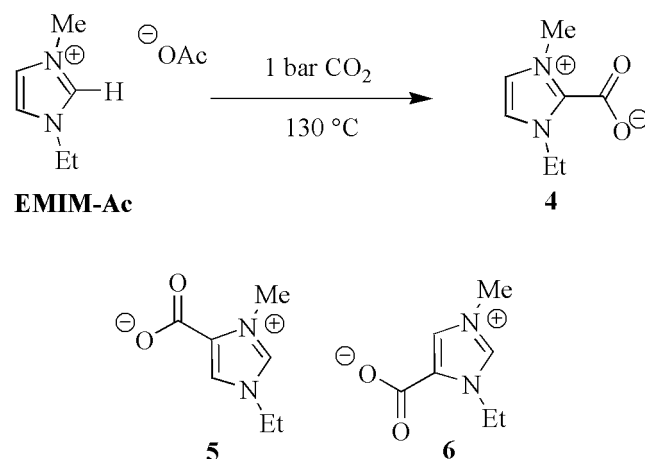
**Scheme 3:** Equilibrium of EMIM-Ac in the gas phase.

Although the NHC could be detected in the gas phase, there is no spectroscopic evidence of the presence of carbenes in the liquid phase, thus the question is apparent: Is the NHC concentration in imidazolium-acetate ionic liquids high enough to observe organocatalytic activity?

<sup>4</sup> (a) J. P. Hallett, T. Welton, *Chem. Rev.* **2011**, *111*, 3508-3576. (b) T. Welton, *Chem. Rev.* **1999**, *99*, 2071-2083.

<sup>5</sup> O. Hollóczki, D. Gerhard, K. Massone, L. Szarvas, B. Németh, T. Veszprémi, L. Nyulászi, *New J. Chem.* **2010**, *34*, 3004.

Further potential applicability of the ionic liquids is the absorption of the carbon dioxide.<sup>6</sup> In general imidazolium based ionic liquids dissolved carbon dioxide well physically, but using the basic acetate anion this solubility can be increased via formation of an NHC-carbon dioxide adduct, suggesting the application of this IL in CO<sub>2</sub> sequestration. So far only the formation of **4** (Scheme 4) was known even higher temperature,<sup>7</sup> while by using other synthetic routes for **4** the formation of **5** and **6** was reported at elevated temperatures.<sup>8</sup>



**Scheme 4:** Formation of **4** at atmospheric pressure in EMIM-Ac. The two other isomers (**5** and **6**) remained unobserved in the same reaction.

### 3. Applied methods

During my PhD work I have used computational chemistry in a parallel fashion with the synthetic work to understand the observations and also to predict the behaviour and reactivity of the investigated systems.

<sup>6</sup> (a) F. Jutz, J.-M. Andanson, A. Baiker, *Chem. Rev.* **2011**, *111*, 322-353. (b) J. L. Anderson, J. K. Dixon, J. F. Brennecke, *Acc. Chem. Res.* **2007**, *40*, 1208-1216. (c) J. F. Brennecke, B. E. Gurkan, *J. Phys. Chem. Lett.* **2010**, *1*, 3459–3464.

<sup>7</sup> M. B. Shiflett, B. A. Elliott, S. R. Lustig, S. Sabesan, M. S. Kelkar, A. Yokozeki, *Chem. Phys. Chem.* **2012**, *13*, 1806–1817.

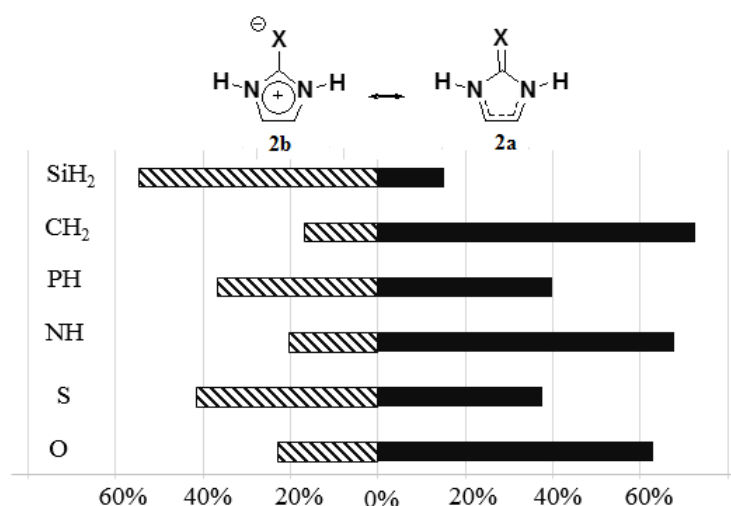
<sup>8</sup> (a) I. Tommasi, F. Sorrentino, *Tetrahedron Lett.* **2006**, *47*, 6453-6456. (b) T. Jahn, G. M. Kçnig, A. D. Wright, G. Wçrheide, J. Reitner, *Tetrahedron Lett.* **1997**, *38*, 3883-3884.

## 4. Results

### 4. 1. The stability and reactivity of the deoxy-Breslow-intermediate and its analogues<sup>S1, S2</sup>

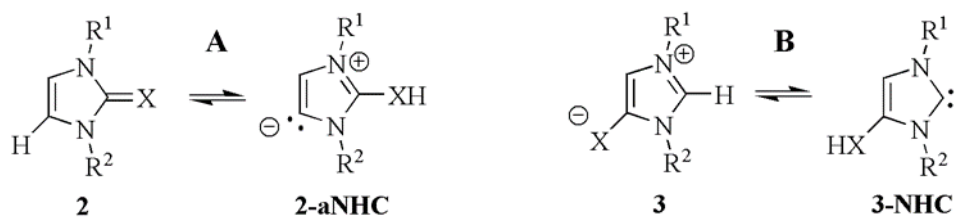
The bonding situation of the different deoxy-Breslow-intermediate analogues (**Scheme 2: 2**) and their abnormal form (**Scheme 2: 3**) was investigated to establish the bonding character between the imidazole unit and heteroatom.

While the first row elements exhibit larger double bond character (**2a**) according the NRT analysis, the ylidic character increases significantly in case of S and P and in case of Si the ylidic character (as expected) is overwhelmingly large due to the reduced isovalent hybridization. Analogues of **3** exhibit similar trends.



**Scheme 5:** The weight of **2a** and **2b** in % according the NRT analysis (The sum of the weight of two different structural motifs are not 100%, due the non-classical structures with low weight).

During the investigation of possible H-shift tautomeric equilibrium (**Scheme 6**) it was established that in case of equilibrium **A** the energy difference between the two H-shifted form too high to observe tautomeric equilibrium (the **2-aNHC** form is always less stable). Despite in case of equilibrium **B** **3-NHC** form is more stable than the zwitterionic **3** in the case of Si and C, for heteroatoms O and S reversed. For the N (in agreement with the earlier reports) and P analogues, the energy difference is small (<4-5 kcal/mol at B3LYP/6-311+G\*\* level of theory) between the two H-shifted forms giving rise to a possible tautomeric equilibrium, which could be fine tuned by substituents.



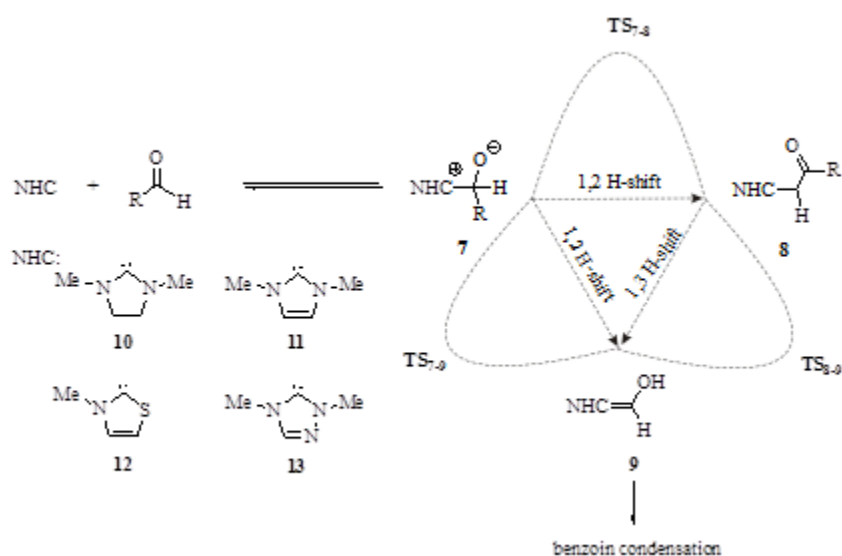
X: SiR<sub>2</sub>, CR<sub>2</sub>, NR, PR, O, S

R<sup>1</sup>, R<sup>2</sup> : H, Me

**Scheme 6:** Possible tautomeric equilibrium of **2** (**2-aNHC**) and **3** (**3-NHC**).

#### 4. 2. Possible carbene-aldehyde adducts and their possible interconversion

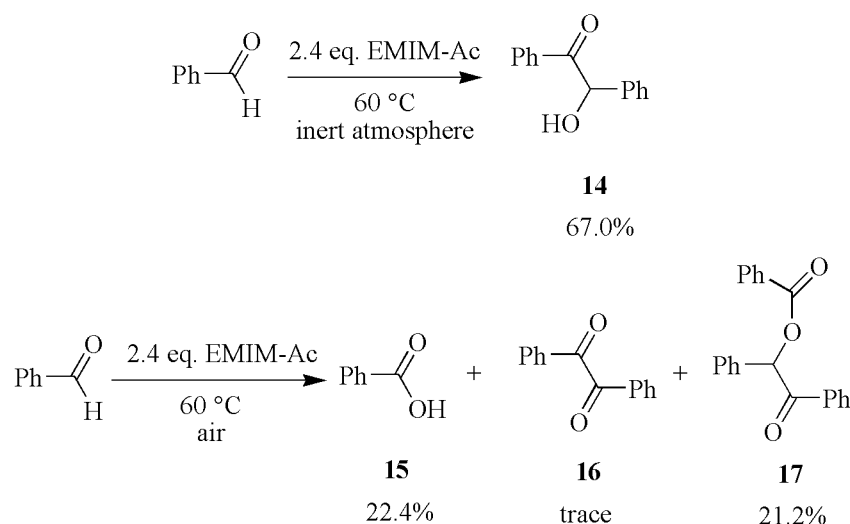
The most stable isomeric form of the NHC-aldehyde adduct was **8** (**Scheme 7**) for all of the investigated NHC (**10-13**) (except in the case of **10** and formaldehyde where **9** was the most stable one). While the interconversion via a protonation-deprotonation sequence via a solvent assisted mechanism is possible the monomolecular mechanism has a large barrier, (**Scheme 7: TS7-8, TS7-9 and TS7-6**). While in case of acetaldehyde **TS7-9** and **TS8-9** are quite high (67.3-70.8 and 34.7-42.3 kcal/mol at B3LYP/6-311+G\*\* level of theory) for all of the investigated NHCs, **TS7-8** exhibit somewhat lower barrier (18.0-23.4 kcal/mol). Since without the inversely polarized Breslow-intermediate the mechanism of the benzoin condensation is hard to describe, it could be established that no organocatalytic activity could be observed in proton arm condition (eg. in the gas phase), and only **7** and **8** but not the Breslow-intermediate is formed.



**Scheme 7:** NHC-aldehyde adducts and possible interconversion using different NHCs (**10-13**) and aldehydes (R: H, Me, Ph).

### 4. 3. An organocatalytic ionic liquid<sup>S3</sup>

During the investigation of the organocatalytic activity of the EMIM-Ac ionic liquids one of the most investigated catalytic reaction of carbenes, the benzoin condensation was chosen. While at room temperature no reaction was observed, after heating the reaction mixture at 60 °C benzoin (**14**) was formed with good yield (**Scheme 8**).

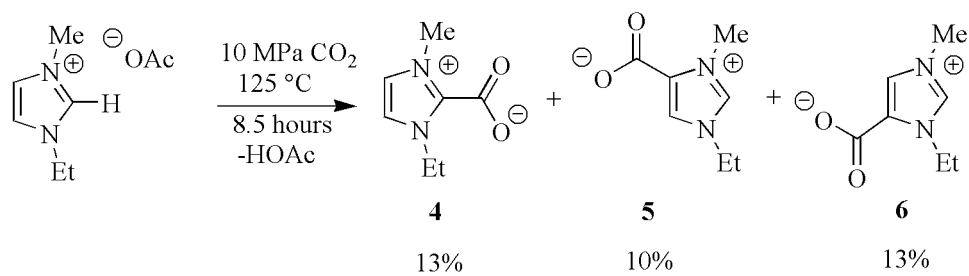


**Scheme 8:** Organocatalytic reactions of EMIM-Ac under inert conditions and air.

When the reaction was carried out under air other oxidized products were isolated such as benzoic acid (**Scheme 7: 15**), benzil (**16**) and an ester (**17**). While the formation of **15** and **16** could be described with an oxidation step from benzaldehyde and **16, 17** could be formed during a hydroacylation step in the reaction of benzaldehyde and **16**.

### 4. 4. Formation of aNHC-carbon dioxid adducts from imidazolium acetate ionic liquids<sup>S4</sup>

While in the reaction of EMIM-Ac and carbon dioxide under atmospheric pressure only the formation of **4** was reported earlier, when we carried out this experiment at 10 MPa and 125 °C not only **4**, but also **5** and **6** were formed (**Scheme 9**). Quantum chemical calculations revealed that **5** and **6** has no higher stability than **4**, the explanation of the formation and stabilization of these adducts could only be given considering the presence of the basic acetate anion. The high basicity of the system was ensured by the supercritical carbon dioxide, which extracts the acetic acid according to our gas chromatographic measurements. Several possible reaction mechanism was suggested according to our quantum chemical calculations.



**Scheme 9:** The reaction of EMIM-Ac with carbon dioxide and the formed **4-6** adducts at 10 MPa and 125 °C after 8.5 hours.

## 5. Theses

1. In case of hetero deoxi-Breslow intermediates it was revealed that while for the second row elements the bond between the imidazole unit and the heteroatom has dominant double bond character, in case of P and S the situation is well balanced, while for Si the ylidic structure has an overwhelming weight.<sup>S1</sup>
2. Among the abnormal hetero deoxi-Breslow intermediates not only the nitrogen analogue but the phosphorus analogue could exhibit a tautomeric equilibrium with its carbene isomer. This equilibrium can be fine-tuned by the substituent.<sup>S1, S2</sup>
3. Under proton-arm conditions the Breslow-intermediates can not form from the initial adduct, because the monomolecular interconversion is kinetically hindered, instead an isomeric oxo compound forms.
4. It was found experimentally that imidazolium acetate ionic liquids have NHC-organocatalytic activity (benzoin condensation, hydroacylation),<sup>S3</sup> suggesting that the NHC activity in these ionic liquids allows Breslow intermediate formation.
5. It was verified by NMR measurement, that in imidazolium acetate ionic liquids not only 2-carboxylate but also 4- and 5-carboxylate can be formed under high pressure (10MPa) and high temperature (125 °C). To understand the experimental results several possible reaction mechanism was suggested.<sup>S4</sup>

## 6. Publication data

### Publications Related to the Thesis

**S1** Z. Kelemen, R. Streubel, L. Nyulászi, Zwitterionic Carbene adducts and their Carbene Isomers, *RSC Adv.* **2015**, *5*, 41795-41802.

IF: 3.708 I: 0

**S2** P. K. Majhi, G. Schnakenburg, Z. Kelemen, L. Nyulászi, D. Gates, R. Streubel, Synthesis of an Imidazolium Phosphanide Zwitterion and Its Conversion into Anionic Imidazol-2-ylidene Derivatives, *Angew. Chem. Int. Ed.* **2013**, *52*, 10080-10083.

IF: 11.336 I: 10

**S3** Z. Kelemen, O. Hollóczki, J. Nagy, L. Nyulászi, An organocatalytic ionic liquid, *Org. Biomol. Chem.* **2011**, *9*, 5362-5364.

IF: 3.696 I: 34

**S4** Z. Kelemen, B. Péter-Szabó, E. Székely, O. Hollóczki, D. Firaha, B. Kirchner, J. Nagy, L. Nyulászi, An Abnormal N-Heterocyclic Carbene–Carbon Dioxide Adduct from Imidazolium Acetate Ionic Liquids: The Importance of Basicity, *Chem. Eur. J.* **2014**, *20*, 13002-13008.

IF: 5.696 I: 5

### Other Publications

**S5** O. Hollóczki, Z. Kelemen, L. Nyulászi, On the Organocatalytic Activity of N-Heterocyclic Carbenes: Role of Sulfur in Thiamine, *J. Org. Chem.* **2012**, *77*, 6014-6022.

IF: 4.638 I: 25

**S6** O. Hollóczki, Z. Kelemen, L. Könczöl, D. Szieberth, L. Nyulászi, A. Stark, B. Kirchner, Significant cation effects in carbon dioxide-ionic liquid systems, *ChemPhysChem* **2013**, *14*, 315-320.

IF: 3.36 I: 29

**S7** Z. Kelemen, O. Hollóczki, J. Oláh, L. Nyulászi, Oxazol-2-ylidenes. A new class of stable carbenes ?, *RSC Adv.* **2013**, *3*, 7970-7978.

IF: 3.708 I: 8

**S8** M. Thomas, M. Brehm, O. Hollóczki, **Z. Kelemen**, L. Nyulászi, T. Pasinszki, B. Kirchner, Simulating the vibrational spectra of ionic liquid systems: 1-Ethyl-3-methylimidazolium acetate and its mixtures, *J. Chem. Phys.* **2014**, *141*, 24510.

IF: 3.017 I: 4

### **Presentations in English**

**E1** **Z. Kelemen**, L. Nyulászi, „Hetero Breslow-analogues—the case of phosphorous” 10th European Workshop on Phosphorous Chemistry, Regensburg an der Donau, Germany, 2013.03.19.

**E2** **Z. Kelemen**, L. Nyulászi, „Comparing the  $\lambda^3$ -P=C and  $\lambda^5$ -P=C double bonds - Similarities and differences” 11th European Workshop on Phosphorous Chemistry, Sofia, Bulgaria, 2014.03.18.

**E3** **Z. Kelemen**, L. Nyulászi, „Ferrocene-based subvalent compounds” 12th European Workshop on Phosphorous Chemistry, Kassel, Germany, 2015.03.17.

### **Presentations in Hungarian**

**E4** **Z. Kelemen**, O. Hollóczki, L. Nyulászi „Oxazol-2-ilidén—stabil karbén?” KeMoMo-QSAR 2010 szimpózium, Szeged, 2010.04.29.

**E5** **Z. Kelemen**, L. Nyulászi „Karbén organokatalizált hidridtranszfer reakció vizsgálata” KeMoMo-QSAR 2011 szimpózium, Szeged, 2012.09.20.

**E6** **Z. Kelemen**, L. Nyulászi „Foszfinokarbénből abnormális karbénkomplex” Szervetlen és Fémorganikus Kémiai Munkabizottság és az Anyag- és Molekulaszerkezeti Munkabizottság Közös Munkabizottsági Ülése, Szeged, 2012.10.14.

**E7** **Z. Kelemen**, L. Nyulászi „Hetero-Breslow-analógok – A foszfor esete” KeMoMo-QSAR 2013 szimpózium, Szeged, 2013.04.29.

**E8** **Z. Kelemen**, L. Nyulászi „CO<sub>2</sub> oldódása imidazolium alapú ionos folyadékokban” Szervetlen és Fémorganikus Kémiai Munkabizottság Munkabizottsági ülése, 2013.11.16.

**E9** **Z. Kelemen**, L. Nyulászi „Karbének szerepe molekulák reaktivitásának megváltoztatásában” BME Oláh György Doktori Iskola XII. Doktoránskonferenciája, 2015.02.05.

**E10** **Z. Kelemen**, L. Nyulászi „Karbének szerepe molekulák reaktivitásának megváltoztatásában” Anyag- és Molekulaszerkezeti Munkabizottság munkabizottsági ülése, Mátrafüred, 2015.02.27-28.

## Poster Presentations

**P1 Z. Kelemen,** O. Hollóczki, B. Péter-Szabó, E. Székely, J. Nagy, B. Kirchner, T. Pasinszki, L. Nyulászi „Imidazolium acetate ionic liquids–new possibilities” BME Oláh György Doktori Iskola XI. Doktoránskonferenciája, 2014.02.06.

**P2 Z. Kelemen,** R. Pietschnig, D. Gudat, L. Nyulászi „Ferrocene-based subvalent compounds” 14<sup>th</sup> International Symposium on Inorganic Ring Systems, Regensburg an der Donau, Germany, 2015.07.29.