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FACULTY OF CHEMICAL AND BIOENGINEERING
GYÖRGY OLÁH PHD-SCHOOL

Synthesis and characterization of P-heterocyclic ligands and their Pt(II)-complexes

PhD Thesis

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I. Introduction

Transition metal complexes, containing organic phosphorus ligands are widely applied in homogenous catalytic reaction which play significant role in the economic synthesis of several intermediates, curative/medicinal and other organic compounds. With my PhD work I have latched on to this field of investigation at the Department of Organic Chemistry and Technology of the Budapest University of Technology and Economics under the supervision of Prof. György Keglevich.

II. Objectives

During my PhD work we've designed to do the preparation of new phosphorus heterocycles potentially used as ligands of transition metal in homogenous catalysis in the following types: (**A**) 5- and 6-membered phosphorus heterocycles, (**B**) dibenzo[*c.e*][1,2]oxaphosphorines and (**C**) benzo[1,3,2]dioxaphospholanes.

The sensitivity of P(III) ligands toward air are well-known therefore the purification and the long-term storageof the ligands could be achieved by transforming them into oxides and borane complexes. Since the complex formation is only feasible when phosphorus atom is trivalent, we examined the following possibilities:

a) direct transformation of P(III) compounds to Pt(II) complexes

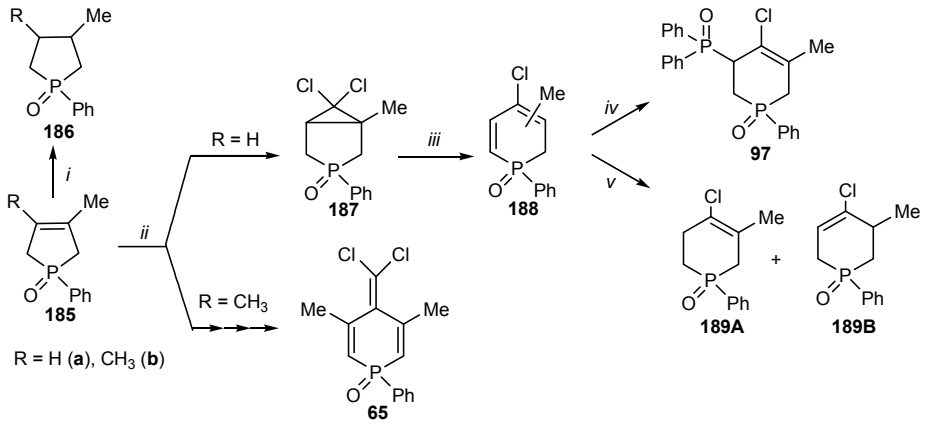
b) deoxigenation of P-oxides followed by the complex formation

c) removal of boronato-group followed by the complex formation

d) direct transformation of borane complexes to Pt(II) complexes

III. Results and discussion

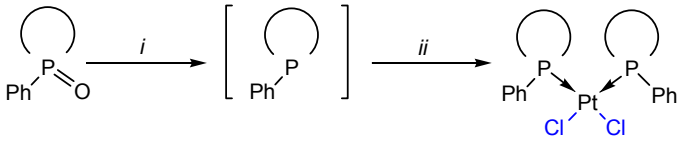
1. **A.** From phenyl-phospholane (**185**) prepared by *McCormack* cycloaddition, we could successfully generate phospholanes (**186**) and after the addition of dichlorocarbene dihydro- (**188**) and tetrahydrophosphinine-derivatives (**189**), and dichloromethylene-1,4-dihydro-3,5-dimethyl-1-phenylphosphinine-1-oxide (**65**). In a diastereoselective *Michael*-addition reaction dihydrophosphinines (**188**) could be converted to a derivative contains an exocyclic phosphorus function (**97**).



Reaction conditions: (*i*) H_2/Pd/C; (*ii*) $CHCl_3$, NaOH/H_2O, TEBAC; (*iii*) Δ, 3.5 min; (*iv*) $Ph_2P(O)H$, Me_3Al, $CHCl_3$; (v) $BH_3{\cdot}SMe_2$, H_2O

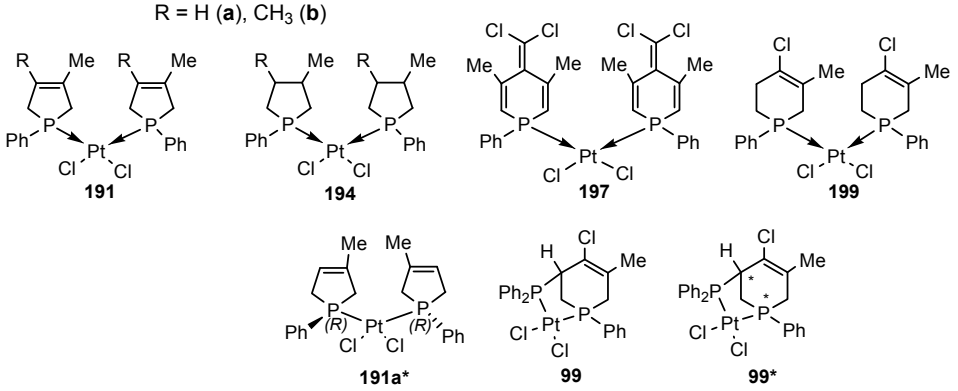
Scheme 1.

2. After complete the deoxygenation step we could perform the complex formation with dichlorodibenzonitrile-platinum. The outcome of the reaction was *cis* type complexes all cases, which were proved by stereospecific $J_{Pt\text{-}P}$ couplings (3512-3602 Hz). [10]



Reaction conditions: (*i*) Cl_3SiH, pyridine, toluene, 110 °C/$PhSiH_3$, *in subst*., 80 °C;
(*ii*) $(PhCN)_2PtCl_2$, toluene, 26 °C

R = H (**a**), CH_3 (**b**)

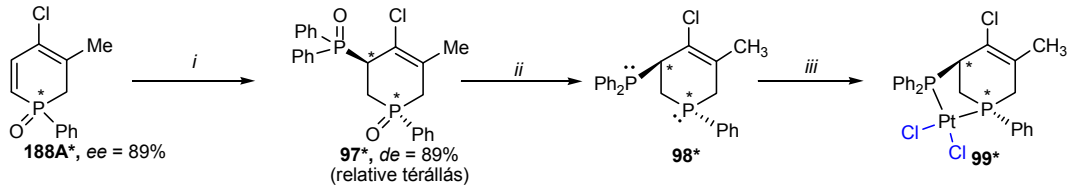


Scheme 2.

3. The stereostructures of the monodentate Pt(II) complexes (**191**, **191a***, **194**, **197**, **199**) were evaluated by quantum chemical calculations using B3LYP/6-31G(d) and in respect of the platinum atom, by the LANL2DZ ECP methods. In the Pt-complex (**191**) π-HC stacking can be found as a slight stabilization effect. These complexes are racemates therefore in case of asymmetric compounds (**191a**, **194a**, **199**) both the homo- and the heterochiral diastereomers appear in the ^{31}P NMR spectra of the complexes. When the complex contains symmetric ligand (**191b**, **194b**, **197**) the spectra becomes less complex: it contains one signal accompanied by a satellite. ^{31}P NMR spectra of the complex (**191a***)

prepared from the optically active 3-methyl-1-phenyl-phospholene (**185a***) (*ee*=96%) is also simpler.

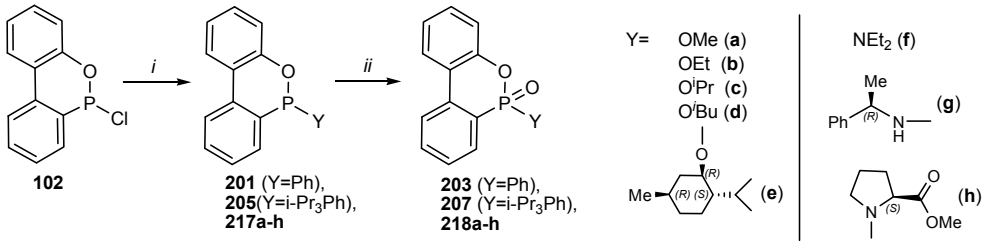
4. Starting from the dihydrophophinine (**188A***), with the enantiomeric purity of 89% we synthesized a bidentate complex (**99***) through **97*** *Michael*-adduct and **98*** diphosphine.



Reaction conditions: (*i*)$Ph_2P(O)H$, 0 °C, 20 h; H_2O; (*ii*)$PhSiH_3$, 80 °C, 3 days; (*iii*) $PtCl_2(PhCN)_2$, toluene, 26 °C, 6 h

Scheme 3.

5. **B.** During the investigations of dibenzo[*c.e*][1,2]oxaphosphorines we tried to produce phosphorus ligands from chloro-dibenzooxaphosphorine (**102**) which was placed at our disposal by the company called *Nitrokémia* 2000. By the application of *Grignard*-reaction we made monodentate phosphorus ligands (**201**, **205**). [1] During the preparation of **201**, a ring-opening product (**202**) was formed by a second equivalent *Grignard*-reagent. After the optimization of the reaction conditions **202** could be prepared in good yield. (Scheme 6.) [4]

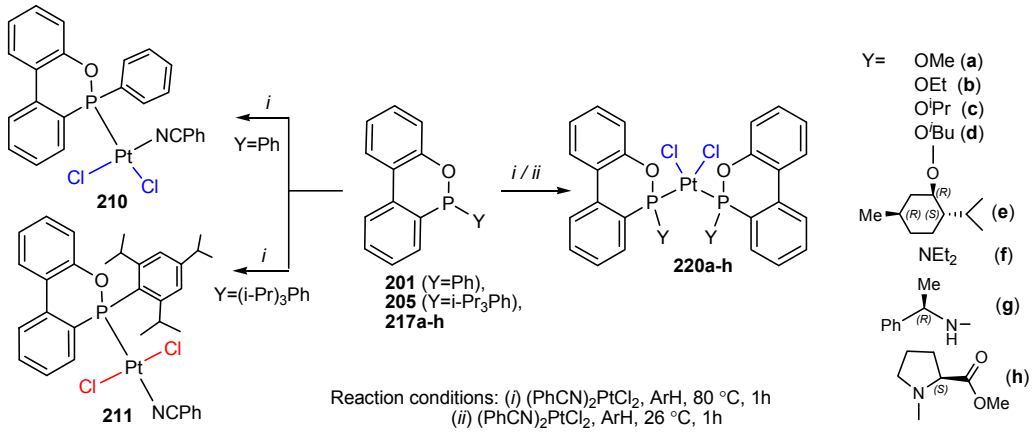


Reaction conditions: (*i*) 0 °C→26 °C, YMgBr, THF (**201** és **205**); HY, TEA, 26 °C (**217**)
(*ii*) H_2O_2 / H_2O, 0 °C, 1 h

Scheme 4.

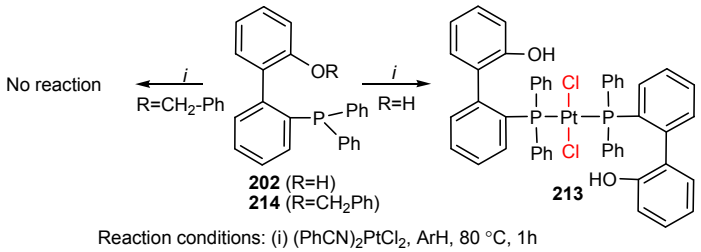
6. Substitution reactions of **102** resulted alkoxy- (**217a-e**) and amino derivatives (**217f-h**) which were converted to the corresponding oxides (**203**, **207**, **218**) and borane-complexes. [9] Stereostructure of **218f** was proved by single crystal X-ray analysis. The optically active phosphonic derivatives (**218e**,**g**,**h**) were formed as a mixture of diastereomers. One of the diastereomers of the menthyl-derivatives (**218e**) were separated by fractional crystallization in a *de* 71%, and the single crystal X-ray analysis of it revealed that the absolute configuration of the P-atom was found to be *R*, and the least-squares planes of the two phenyl rings have a setting angle of 13.7(4)°.[2]

7. With two exceptions (**211**, **213**) (Scheme 5-6.), complex formation resulted *cis* complexes identified by stereospecific couplings (J_{Pt-P}=4239-5233 Hz).[3],[7] The tri*iso*propylphenyl substituted complex (**211**, J_{Pt-P}=2900 Hz) was formed in *trans* disposition, which may be the consequence of the precense of sterically more demanding isopropyl groups.



Scheme 5.

Also a complex (**213**) exhibiting the P-ligands in *trans* disposition was formed from the ring-opened product (**202**). Quantum chemical calculations substantiated stabilizing H-bond in the ligand (**202**) and in the platinum complex (**213**) too, but interaction between the phenolic hydroxy function and the phosphorus atom of the PPh_2 group in the ligand (**202**) did not prevent the complex formation. It's interesting that if no H-bond exists, formation of platinum complex from the benzyl derivative (**214**) of ligand **202** is prevented.[4]



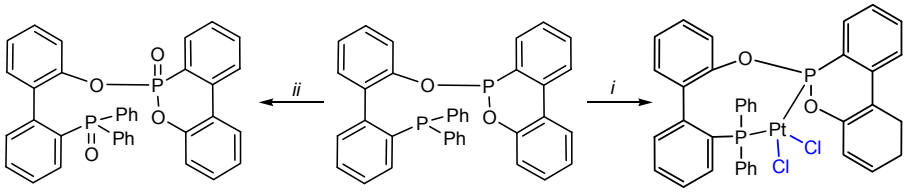
Scheme 6.

8. We observed that at preparation of monodentate complexes (**213**, **220**) the ligand:precursor ratio did not influenced the complex formation, in all cases bis type complexes formed, however using a 2:1=ligand:precursor ratio much pure product formed in better yield. [7] In the ^{31}P NMR spectrum of complexes (**220a-d,f**) signals of the homo- and heterochiral isomers are noticable. If the complex contain chiral ligand (**220e**,**g**,**h**), the ^{31}P NMR spectra is much complex. Beside the signals of the heterochiral form, those of the

two diastereomeric derivatives containing the homochiral phosphorous unit can be also observed.

9. The structure of the heterochiral form of *cis* platinum complex (**220b**) was calculated by B3LYP/6-31G* and LANL2DZ ECP methods which support the formation of the *cis* disposition and indicate higher stability of heterochiral form. [7] Single crystal X-ray analysis of complex containing methoxy substituent (**220a**) indicates that a solvent molecule ($CHCl_3$) is linked to the complex and inside the crystal structure it making rotating movement.[11]

10. During the preparation of bidentate ligands the reaction with ortho-arylphenol (**202**) and chloro-dibenzooxaphosphorine (**102**) we obtained **221** which were characterized as oxide. [8],[9] To our surprise the purification of **221** – in spite of two tervalent P-function - could be carried out by column chromatography. The slight sensitivity towards air can be attributed to the presence of sterically more demanding substituents. Attempts on the separation of the two diastereomers of **222** -prepared from **221** - by column chromatography failed due to a partial isomerisation by rotation around the biphenyl axis. The barrier heights for the interconversion of the atropisomers (diastereomers) of **221** were found to be 6.9 and 5.1 kcal/mol by PM3 calculations. [4]



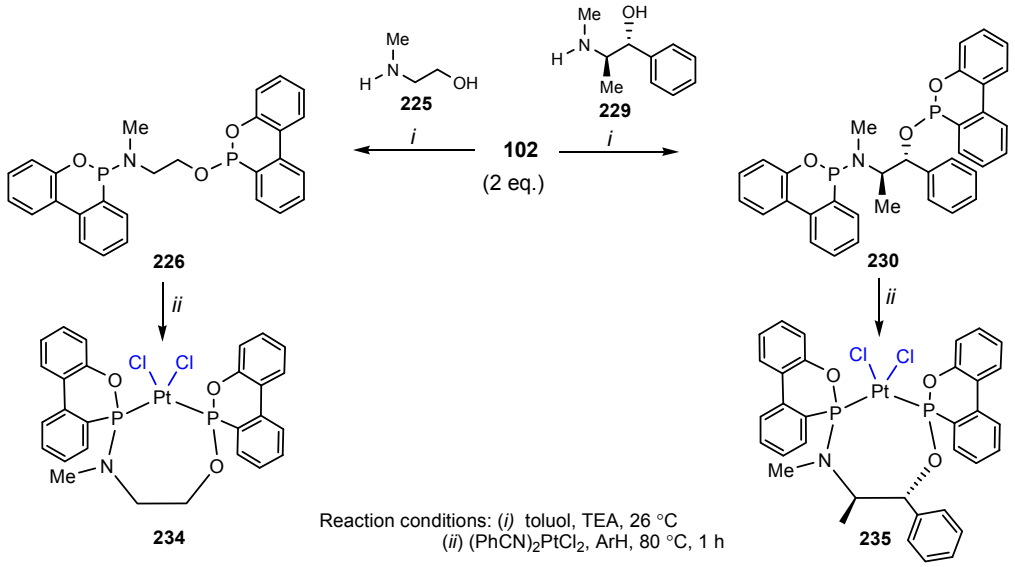
Reaction conditions: (*i*) $(PhCN)_2PtCl_2$, ArH, 80 °C, 1 h; (*ii*) H_2O_2/H_2O

Scheme 7.

The stereostructure of the platinum complex (**233**) made from the bidentate phosphine-phosphite ligand (**221**) was evaluated by B3LYP/3-21G* and B3LYP/LAN2DZ calculation.[4]

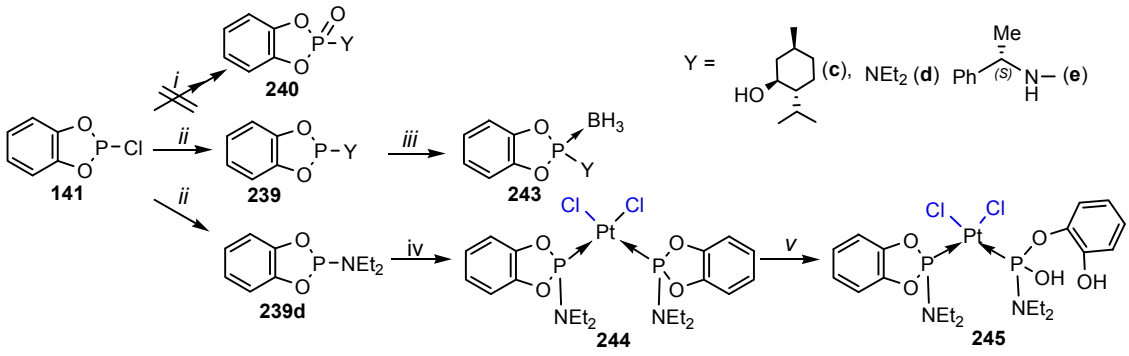
11. After the experiments with 2-methylamino-ethanol (**225**) we prepared chiral bidentate ligand (**230**), when we reacted **102** derivatives and (+)-ephedrine (**229**). [8] Ligands (**226**, **230**) were characterized as their oxides. Due to the starting composition of isomers, platinum complexes formed as two or four diastereomers, generating quite complex spectrum. The structures for the most stable isomers of complexes (**234**) and (**235**) were obtained by B3LYP/6-31G* and LANL2DZ ECP calculations, and it can be

concluded that the 7-membered ring in **235** is more strained and more deformed as compared to **234**. [6]



Scheme 8.

12. **C.** Among benzo[1,3,2]dioxaphospholanes, by substitution reactions of chloro atom of P-chloro-benzodioxaphospholane (**141**), we could synthetize new P-ligands. In this case the oxidizing method to protect the tervalent function of phosphorus was not able to use because of the high sensitivity of benzodioxaphospholanes toward water, therefore we synthetized their borane complexes (**243**). The most stable compound was the diethylamino derivative (**239c**), therefore we attempted to perform the complex formation with this ligand. It was observed that if the moisture was not excluded carefully, one of the strained hetero ring in **244** suffered ring-opening with water to provide platinum complex **245.** [10]



Scheme 9.

IV. Thesis

1. We've elaborated a process for the preparation of 16 new ligands in the following type: five- and six-membered monocyclic phosphorus heterocycles, tricyclic dibenzo[c.e][1,2]oxaphosphorines and benzo[1,3,2]dioxaphospholanes. By the use of these ligands we've prepared 23 new mono- [1],[3],[4],[7] and bidentate [4],[6] Pt(II) complexes which were characterised by ^{31}P NMR spectroscopy and in some cases by quantum chemical calculations.

2. We successfully stabilized the air sensitive P(III) ligands as oxides and borane complexes, which are appropriate for purification and we can store them as precursors and we've also elaborated a process to liberate P(III) ligands from their oxide and borane-complexes. [2],[9]

3. We've successfully separate the diastereomers of dibenzooxaphosphorine-oxide containing chiral substituent by crystallization. Single crystal X-ray analysis revealed the absolute configuration of the compound and the stereostructures were also supported by quantum chemical calculations. [2]

4. We've certified on the basis of stereospecific $J_{Pt\text{-}P}$ coupling that with two exceptions the geometry of the obtained complexes were *cis*. [3],[7] In one case this was proved by quantum chemical calculations [7] and single crystal X-ray analysis too. [11]

5. In case of racemate or diastereomer complexes, the mixture of homo- and heterochiral isomers form. The presence and the ratio of the isomers can be determined by ^{31}P NMR spectrum. The higher stability of the heterochiral form was proved by quantum chemical calculations of the complex with dibenzooxaphosphorine framework containing ethoxy substituent. [7]

6. Starting from an optically active phospholene and tetrahidrophosphinine derivatives, new Pt(II) complexes were prepared bearing enantiomerically pure phosphorus ligands. [10]

7. During the preparation of Pt(II) complexes containing five- and six membered phosphorus heterocycles or dibenzooxaphosphorine framework, is not necessary to perform the reaction at high temperature because the expected complexes were formed at room temperature. The molar ratio of the components did not affect the outcome of the reaction, in all cases *bis* complexes formed with 2:1 ligand:precursor ratio. [3], [7]

8. We've elaborated a process to produce the ring-opened product – observed during the preparation of aryl substituted dibenzooxaphosphorine - with good yield [1], and utilized it to form new Pt(II) complex. [4] The intramolecular interactions in the ring-opened product did not prevent the complexation of the phosphorus atom, however in case of termination no complex can be formed.

9. Due to the water sensitivity of benzodioxaphospholane derivatives, oxide formation can not be use as stabilizing method. We've successfully achieved the stabilization by borane complex formation. In case of even the most stable diethylamino derivative, a hydrolytic ring-opening occurs during the preparation of Pt(II) complex. [10]

V. Utilization possibilities of the achieved results

We hope that Pt(II) complexes containing new phosphorus ligands will be used as catalyst in homogenous reactions of organic compounds, among others in stereoselective hydroformylations and in enantioselective hydrogenations.

VI. List of publications served as fundamentals of dissertation

PUBLICATIONS:

1. Keglevich, Gy.; Szelke, H.; Kerényi, A.; Imre, T.; Ludányi, K.; Dukai, J.; Nagy, F.; Arányi, P.: 2-Aryl-dibenzo-1,2-oxaphosphorine as a ligand in borane and in Pt(II) complexes. *Heteroatom Chemistry* **2004**, *15*, 459. (IF: 0.830)

2. Keglevich, Gy.; Szelke, H.; Kerényi, A.; Kudar, V.; Hanusz, M.; Simon, K.; Imre, T.; Ludányi, K.: New chiral P-ligands: P-amino- and P-cycloalkoxy dibenzo[c.e][1,2]oxaphosphorines. *Tetrahedron Asymmetry* **2005**, *16*, 4015. (IF: 2.429)

3. Keglevich, Gy.; Szelke, H.; Kerényi, A.; Imre, T.: Bis(dibenzo[c.e][1,2]oxaphosphorino-)dichloroplatinum complexes. *Transition Metal Chemistry* **2006**, *31*, 306. (IF: 0.918)

4. Keglevich, Gy.; Kerényi, A.; Szelke, H.; Ludányi, K.; Körtvélyesi, T.: 2-Diphenylphosphino-2'-hydroxybiphenyl-based P-ligands and their platinum(II) complexes. *J. Organometallic Chemistry* **2006**, *691*, 5038. (IF: 2.332)

5. Keglevich, Gy.; Kerényi, A.; Sipos, M.; Ujj, V.; Makó, A.; Csontos, I.; Novák, T.; Bakó, P.; Greiner, I.: Green chemical approaches and tools in the development of environmentally friendly synthetic methods. *Periodica. Politechnica Chemical Engineering* **2007**, *51*, 53.

6. Kerényi, A.; Balassa, A.; Körtvélyesi, T.; Ludányi, K.; Keglevich, Gy.: Synthesis and complexation of novel dibenzo[*c.e*][1,2]oxaphosphorine-based P-ligands. *Transition Metal Chemistry* **2008**, *33*, 459. (IF: 0.997)

7. Keglevich, Gy.; Kerényi, A.; Mayer, B.; Körtvélyesi, T.; Ludányi, K.: Platinum(II) complexes of 2-alkoxy-dibenzo[*c.e*][1,2]oxaphosphorines. *Transition Metal Chemistry* **2008**, *33*, 505. (IF: 0.997)

8. Keglevich, Gy.; Kerényi, A.; Sipos, M.; Balassa, A.; Körtvélyesi, T.: Novel heterocyclic P-ligands: Synthesis and application in Pt(II) complexes. *Phosphorus, Sulfur, Silicon* **2008**, *183*, 440. (IF: 0.692)

9. Keglevich, Gy.; Kerényi, A.: Synthesis of dibenzo[c.e][1,2]oxaphosphorines and their application in transition metal complexes. *Trends in Organic Chemistry* **2008**, *12*, 73.

10. Kerényi, A.; Keglevich, Gy.: Platinum complexes of P-heterocycles. *Asian Chemistry Letters* **2008**, *12*, 92.

11. Holczbauer, T.; Keglevich, Gy.; Kerényi, A.; Czugler, M.: Dichloridobis(2-methoxydibenzo[c.e][1.2]oxaphosphorine-κP)platinum(II) trichloromethane solvate. *Acta Crystallographica*. **2009**, *E65*, 347. (IF: 0.367)

PRESENTATIONS:

12. Kerényi, A.; Keglevich, Gy.: Komplexekben hasznosítható akirális és királis P-ligandok szintézise. XXIX. Kémiai Előadói Napok, Szeged, 2006. okt. 30-31.

13. Kerényi, A.; Keglevich, Gy.: Komplexekben hasznosítható P-ligandok szintézise. Budapesti Műszaki és Gazdaságtudományi Egyetem, Vegyészmérnöki és Biomérnöki Kar, Oláh György Doktori Iskola, Doktoránskonferencia 2007. február 7., Budapest

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14. Szelke, H.; Keglevich, Gy.; Kerényi, A.; Dukai, J.; Nagy, F.; Arányi, P.: Új P-ligandok: Dibenzo[c,e][1,2]oxafoszforin származékok. Vegyészkonferencia, MKE, Hajdúszoboszló, 2005. jún. 28-30.

15. Kerényi, A.; Sipos, M.; Körtvélyesi, T.; Novák, T.; Keglevich, Gy.: Synthesis of P-ligands utilized in various complexes. 1st European Chemistry Congress – EuCheMS, Budapest, 2006. aug. 27-31.

16. Kerényi, A.; Sipos, M.; Balassa, A.; Mayer, B.; Ludányi, K.; Körtvélyesi, T.; Keglevich, Gy.: Heterociklusos P-ligandok és átmeneti fém-komplexeik szintézise. Centenáriumi Vegyészkonferencia, Sopron, 2007. máj. 29-jún. 1.

17. Kerényi, A.; Keglevich, Gy.; Körtvélyes, T.; Kovács, V. Heterocyclic P-ligands and their platinum(II)-complexes, XI. Belgian Organic Synthesis Symposium, Gent, 2008.júl.13-18..