



BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GYÖRGY OLÁH DOCTORAL SCHOOL

Resolution of P-heterocycles with tartaric acid derivatives

Thesis

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1. Introduction

My doctoral work is focused on the resolution of P-chiral phosphine oxides. P-Chiral compounds mostly used in enantioselective homogenous catalytic reactions as ligand of transition metal catalysts, but a few of them are applied as drug.¹ From practical point of view, preparation and resolution of racemic phosphine oxides followed by deoxygenation is more appropriate than enantioselective synthesis. Despite the fact that P-chiral organophosphorus compounds could not be found in enantiomeric forms in the natural pool of chirality and their synthesis are difficult, the field has grown enormously in the last few decades, thanks to several fields of chemistry, such as chemotherapy, plant protection, bioorganic chemistry, asymmetric synthesis and catalysis.²

During the last three years I worked at the Budapest University of Technology and Economics, at the Department of Organic Chemistry and Technology with *Dr. Elemér Fogassy* and *Dr. György Keglevich* and *Dr. Tibor Novák* (till Dec. 31. 2007.) and *József Schindler*. The Department has a long tradition in the synthesis of P-heterocycles. Several methods for the preparation of a variety of five-, six- and seven-membered P-heterocycles including bridged derivatives have been developed to make P-ligands available. These molecules have in many cases phosphorus asymmetric centre that raises the possibility of the preparation of them in optically pure form.

Our aim was to develop an efficient method for the resolution of P-chiral P-heterocycles. The easily accessible 3-methyl-3-phospholene 1-oxides were chosen as test compounds. The purpose of this research was not just to obtain the enantiomerically pure compounds, but to develop an industrial scale applicable procedure. Furthermore, as an extension, we wished to study the separation of the antipodes of other P-heterocycles as well, in order to prove the generality of our method.

2. Literature

Methods are described in the literature for the resolution of P-chiral compounds are based on the formation of separable diastereomeric salts, diastereomeric molecular complexes, transition metal complexes or covalent diastereomers, as well as chromatographic separation or chemical and enzymatic kinetic resolution.³ These approaches, however, proved to be useful only in special cases and were expensive procedure because of the price of

¹ Quin, L. D. *A guide to organophosphorus chemistry*; John Wiley & Sons: New York, 2000.

² Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.

³ Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev.* **1994**, *94*, 1375-1411.

resolving agent applied. The 3-methyl-3-phospholene 1-oxides do not have acidic or basic groups, but have groups that are suitable for the formation of secondary interactions, therefore could be resolved via molecular complex formation.

The natural (+)-(2*R*,3*R*)-tartaric acid (TA) and its derivatives are among the most commonly used chiral reagents in organic synthesis. Hundreds of racemic bases have been resolved using TA and its derivatives, such as (-)-(2*R*,3*R*)-*O,O'*-dibenzoyl-tartaric acid (DBTA) or (-)-(2*R*,3*R*)-*O,O'*-di-*p*-toluyl-tartaric acid (DPTTA).^{4,5} TADDOL derivatives could be synthesized also by modification of the hydroxy groups of TA. One of the most famous representative of these compounds is the (-)-(4*R*,5*R*)-4,5-bis(diphenylhydroxymethyl)-2,2-dimethyldioxolane (TADDOL) and the (-)-(2*R*,3*R*)- $\alpha,\alpha,\alpha',\alpha'$ -tetraphenyl-1,4-dioxaspiro[4.5]decan-2,3-dimethanol (spiro-TADDOL).^{6,7}

TADDOL derivatives, beside the formation of intramolecular hydrogen bond, are able to form strong intermolecular hydrogen bond with H-acceptors. This recognition may lead to the formation of adducts in an enantioselective manner during crystallization process, and may eventually make possible the separation of racemic compounds, that cannot be separated via traditional diastereomeric salt formation.⁶ Toda and co-workers examined several chiral compounds as host of molecular complexes and recognized the value of TADDOL derivatives in this field of chemistry.⁸

Based on the previous results of our research group, salts of TA derivatives can be excellent resolving agent by the combination of the coordination ability of a metal ion and the exceptional behaviour of DBTA in chiral recognition processes.⁷

3. Methods

The structures of the molecules were determined by ³¹P, ¹³C and ¹H NMR (Bruker DRX-500) The stoichiometry of the diastereomeric complexes were determined by ¹H NMR. Yield of the enantiomer is based on the half of the racemate. The enantiomeric excess (ee) values were determined by chiral HPLC (Chiralpack[®] AD-H, AD, Chiralcel[®] OD or Kromasil[®] 5-Cellucoat column, Daicel Chem. Ind.) or by chiral GC (Agilent 4890D instrument equipped with a BETA DEX[™] 120 column). The diastereomeric excess (de)

⁴ Jacques, J.; Collet, A.; Wilen, S. H. In *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981; pp. 259-260.

⁵ Ács, M.; Fogassy, E.; Kassai, C.; Kozma, D.; Nógrádi, M. *CRC Handbook of Optical Resolutions via Diastereoisomeric Salt Formation*, Kozma ed.; CRC Press: Boca Raton, 2002.

⁶ Seebach, D.; Beck, A.; Heckel, A. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 92-138.

⁷ Faigl, F.; Kozma, D. In *Enantiomer Separation: Fundamentals and Practical Methods*; Toda, F. Ed.; Kluwer Academic Press: Dordrecht, 2004; pp. 73-101.

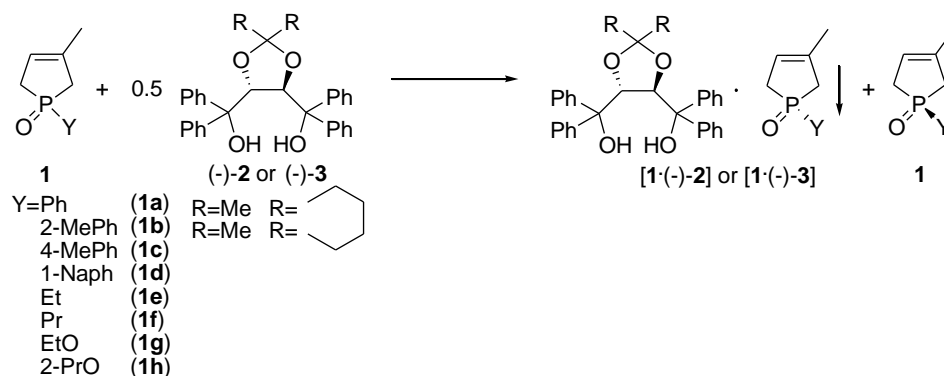
⁸ Toda, F.; Tanaka, K. *Tetrahedron Lett.* **1988**, *29*, 551-554.

values were determined by ^{31}P NMR. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Differential scanning calorimetry (DSC) measurements were carried out on a Setaram DSC92 apparatus, simultaneous thermogravimetric (TG) and differential thermal analytical (DTA) measurements were carried out on a STD 2960 Simultaneous DTA-TGA apparatus (TA Instruments Inc., New Castle DE, USA). FTIR spectra of samples were measured by an Excalibur Series FTS 3000 (Bio-Rad) FTIR spectrophotometer. XRD patterns were registered on a X'pert PRO MPD (PANalytical, The Netherlands) X-ray powder diffractometer using $\text{Cu K}\alpha$ radiation with Ni filter and X'Celerator detector. The UV-VIS spectra were recorded on an Agilent 8453 diode array spectrometer, the CD spectra were recorded with a Jasco J-810 spectropolarimeter. The analyses were performed by *Dr. Miklós Kubinyi*, *Dr. Mihály Kállay* and *Zsuzsa A. Mayer*. The single crystal X-ray diffraction analyses were carried out on a Rigaku R-AXIS Rapid IP diffractometer by *Dr. Mátyás Czugler*.

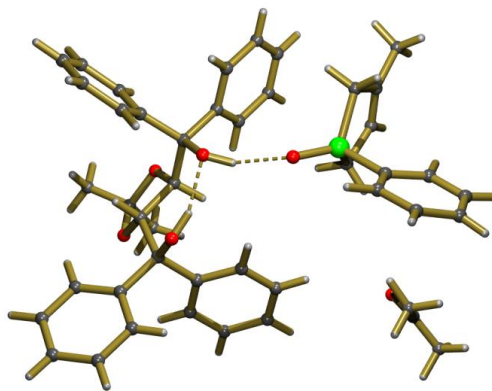
4. Results

4.1 Resolution of *P*-heterocycles with TADDOL-derivatives

An efficient method was developed for the separation of the antipodes of 1-phenyl-3-methyl-3-phospholene 1-oxide (**1a**) using chiral agent, TADDOL [(-)-**2**] or spiro-TADDOL [(-)-**3**].^[1] The method was extended for the resolution of other seven derivatives, such as 1-aryl-, 1-alkyl- and 1-alkoxy-3-methyl-3-phospholene 1-oxides (**1b-h**). The racemic phospholene 1-oxides (**1a-h**) were resolved with 0.5 equivalent of (-)-TADDOL **2** or spiro-TADDOL (-)-**3** and in most cases 1:1 crystalline diastereomeric complexes were formed. The diastereomeric complexes were purified by recrystallization and enantiomers of 3-phospholene 1-oxide (**1**) were recovered by flash column chromatography. From among the 3-phospholene 1-oxides (**1**) obtained, seven species could be resolved with ee of >95%.^[2-4]



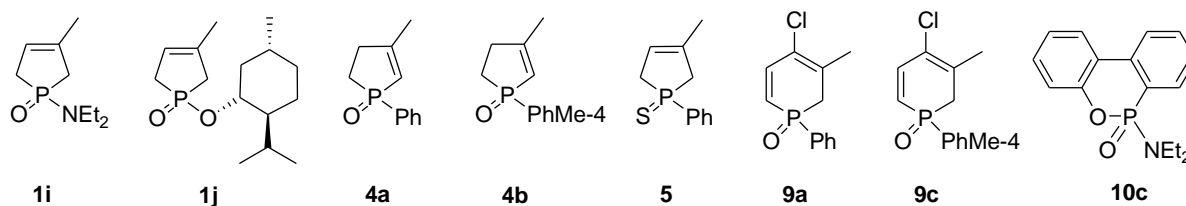
The diastereomeric complexes of [(*S*)-**1a**•(-)-**2**•aceton] (scheme), [(*R*)-**1e**•(-)-**3**] [(*R*)-**1f**•(-)-**2**] and [(*S*)-**1a**•(-)-**3**•aceton] were subjected to single crystal X-ray analysis and the supramolecular formations were evaluated and the absolute configurations determined. The primary interactions in the crystals are the intermolecular hydrogen bond between one of the hydroxy groups of TADDOL derivatives [(-)-**2** or (-)-**3**] and the oxygen atom of P=O function of guest molecules and the intramolecular hydrogen bond between the hydroxy groups of TADDOL derivatives [(-)-**2** or (-)-**3**].[1,2] Absolute configuration in the other cases (**1b-d,g-h**) was determined by UV absorption and CD spectroscopy and analyzed on the basis of theoretical calculations.[2,5]



It was found that the maximum resolving capability could be obtained by the use of 0.5 equivalent of resolving agent. The time of crystallization did not affect significantly the resolving capability. The resolution can be accomplished in a mixture of ethyl acetate-hexane or acetone-pentane. In many cases the acetone was incorporated in the crystal structure or sometimes, displaced the phospholene oxides entirely. According to our results, possible H-acceptor can be applied as solvent during the resolution, but the amount of solvent must be optimized. The presence of acetone affected significantly the chiral recognition process.[6]

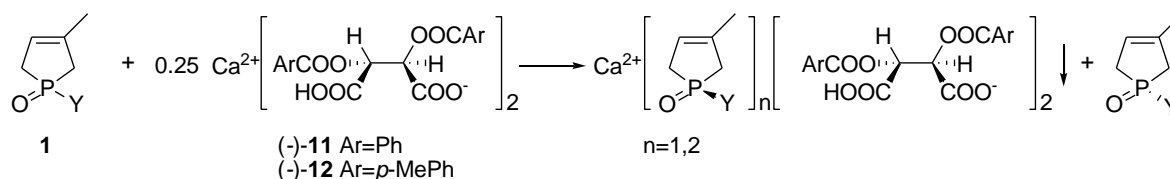
The efficiency of a resolution could be improved in the presence of structurally similar derivatives of the substrate or molecules applied or obtained during the synthesis. The enantiomeric excess of a resolution could be also improved by the application of the mixture of resolving agents [(-)-**2** and (-)-**3**] and additional information could be obtained about the relative stability of the diastereomeric complexes.[2]

Our resolution method was extended to the resolution of the 1-diethylamino- (**1i**) and 1-menthyl-3-phospholene 1-oxides (**1j**), 2-phospholene 1-oxides (**4a-b**), 1-phenyl-3-phospholene 1-sulfide (**5**),[2] 1,2-dihydrophosphinine 1-oxides (**9a,c**) and dibenzooxaphosphorine 6-oxide (**10c**). Hence the method elaborated is of general value.

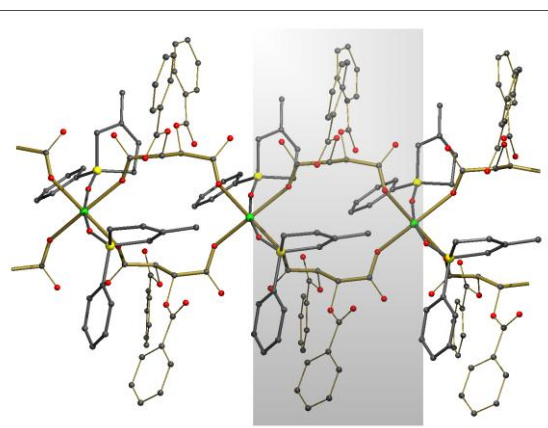


4.2 Resolution of P-heterocycles with salts of tartaric acid-derivatives

A novel and convenient method was developed for the resolution of 1-phenyl- and 1-naphthyl-3-methyl-3-phospholene 1-oxides (**1a** and **1d**) with calcium hydrogen (–)-(2*R*,3*R*)-*O*,*O*'-dibenzoyl-tartrate or (–)-(2*R*,3*R*)-*O*,*O*'-di-*p*-toluyl-tartrate [(–)-Ca(H-DBTA)₂, (–)-**11** or (–)-Ca(H-DPTTA)₂, (–)-**12**] via diastereomeric coordination complex formation. Phospholene oxides (**1a** or **1d**) were crystallized with 0.25 equivalent of resolving agent [(–)-**11** or (–)-**12**]. The diastereomeric complexes were further purified by digestion, then the enantiomers of phospholene oxides (**1a** or **1d**) were recovered by simple extraction, the treatment of the complexes with aqueous ammonia. The resolution process was easily scalable, and with our method we could obtain ~4 g of (*R*)-**1a** with an ee of 96%. [4,7]



The single crystal X-ray analysis of the coordination complex [Ca((*R*)-**1a**)₂(H-DBTA)₂] shows that the Ca²⁺ ions are coordinated by six ligands through oxygen atoms and form an acceptably regular octahedron. Ca²⁺ ions are instrumental in the creation of the macroscopic crystal such a way that these metal ions connect the H-DBTA units and establish an infinite chain. [7]



The resolution method via coordination complex formation was extended for the resolution of other 3-methyl-3-phospholene 1-oxides (**1b,c,e-h**) using (–)-**11** or (–)-**12**, but the refinement of the condition of the resolutions was needed to increase the efficiency of the separation process. The composition of the precipitated complexes was the same

[Ca(**1**)₂(TA[#])₂] (where TA[#] is H-DBTA or H-DPTTA). The only exceptions were the [Ca((*S*)-**1a**)(H-DPTTA)₂(H₂O)] and the [Ca((*S*)-**1f**)(H-DBTA)₂(H₂O)]. After decomposition of the diastereomeric complexes, from among the 3-phospholene 1-oxides (**1**) studied, six species could be resolved with ee of >90%.[8] Complete resolution processes were elaborated to separate both enantiomers of phospholene oxides (**1a,d,f**) using only natural TA derived resolving agents [(-)-**11** or (-)-**12**].[7,8]

We examined the application of the calcium dibenzoyl-tartrate Ca(DBTA), other metal salts of dibenzoyl-tartaric acid and the calcium salt of other resolving agent for the resolution of phospholene oxides (**1**), but only the Mg(H-DBTA)₂ was effective and only with this compound was enantiomeric discrimination observed.[8] The resolution method via coordination complex formation using (-)-**11** or (-)-**12** was extended for the resolution of 6-diethylamino-dibenzo[*c.e*][5,6]oxaphosphorine 6-oxide (**10c**).

5. Thesis

1. I found that, the TADDOL derivatives [(–)-**2** or (–)-**3**] and the calcium salt of tartaric acid derivatives [(–)-**11** or (–)-**12**] are suitable resolving agents for the separation of enantiomers of 3-methyl-3-phospholene oxides (**1a-h**). I developed methods for the separation of mixture of diastereomers by crystallization, purification by recrystallization and digestion, as well as recovering the enantiomers from the diastereomers by flash column chromatography and by extraction. The resolution process via coordination complex formation is easily scalable and even can be applied in industrial scale.[1-4,7,8]
2. The enantiomers prepared by the resolution of eight racemic phospholene oxides (**1a-h**) are new compounds. I determined the specific rotations of them. I developed chiral HPLC or GC methods for the determination of the enantiomeric excesses.[2,8]
3. Five diastereomeric complex structures and the absolute configurations of enantiomers (**1a,e,f**) were determined by single crystal X-ray analysis. The primary interaction in the molecular complexes is the intermolecular hydrogen bond between one of the hydroxy groups of TADDOL derivatives [(–)-**2** or (–)-**3**] and the oxygen atom of P=O function of guest molecules (**1**). In the coordination complex, Ca²⁺ ions are instrumental in the creation of the macroscopic crystal, such a way that these metal ions connect the H-DBTA units to establish an infinite chain. Phospholene oxide molecules are coordinated to the central ion perpendicularly to the plane of the chain.[1,2,7]
4. I uncovered that during the resolution using TADDOL derivatives a possible H-acceptor compound can be applied as solvent just the amount of it must be optimized. During both of the two resolution processes, enantiomeric excesses of the products could be improved by changing the composition of the solvents and the amounts of resolving agents.[6,8]
5. I developed methods for the separation of both enantiomers of 3-methyl-3-phospholene oxides (**1a,d,f**) using just the natural tartaric acid derivatives. It was proved in the tested cases:
 - with resolving agents with identical configuration and skeleton, but with different substitution pattern, the formed diastereomeric complexes contains the other enantiomer of the substrate.[7]

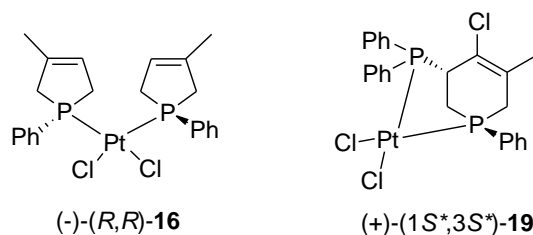
- after the separation of the crystallized diastereomers, the enantiomeric mixture in the mother liquor can be reresolved using the same resolving agent and the antipode could be further enriched in the mother liquor.[7]
 - by the change of the mixture of solvents used for the separation, resolving agent can form crystalline diastereomers with one or the other enantiomers of the substrate.[8]
6. I found that, during the resolution of 1-phenyl-3-methyl-3-phospholene oxide (**1a**) and -sulfide (**5**), the efficiency of a resolution could be improved in the presence of structurally similar derivatives of the substrate or molecules applied or obtained during the synthesis (crude product). The enantiomeric excess of the resolution of 3-methyl-3-phospholene oxide (**1**) could be also improved by the application of the mixture of resolving agents [(–)-**2** and (–)-**3**] and additional information could be obtained about the relative stability of the formed diastereomeric complexes.[2,6]
7. I applied my molecular complex formation method for the resolution of the 1-diethylamino-, 1-[(1'*R*,2'*S*,5'*R*)-menthyl]-3-methyl-3-phospholene 1-oxides, 3-methyl-2-phospholene 1-oxides, 1-phenyl-3-methyl-3-phospholene 1-sulfide,[2] 1,2-dihydrophosphinine 1-oxides and 6-diethylamino-dibenzo-oxaphosphorine 6-oxide.

6. Possible applications

Our resolution methods via molecular and coordination complex formation proved to be efficient for the resolution of 1-aryl-, 1-alkyl- and 1-alkoxy-3-phospholene 1-oxides (**1a-h**). Both of our new methods may be of more general value and may be suitable for the resolution of other tertiary phosphine oxides or phosphine sulfides as well, that was partially verified by our other successful experiments.

It seems, that using resolving agents $(-)\text{-Ca(H-DBTA)}_2$ and $(-)\text{-Ca(H-DPTTA)}_2$ the separations can be almost as efficient as with TADDOL derivatives. Resolution processes via diastereomeric transition-metal centered coordination complexes are widely known even in phosphorus chemistry, but methods using Ca^{2+} or Mg^{2+} salts are much less known and are a significant step toward the development of an accessible method for the enantiomeric separation of P-chiral phosphorus heterocycles. Further advantages of the use of calcium salts are the low-cost, simple preparation of the resolving agents, easier resolution process and simple decomposition of the diastereomeric complexes. So the process can be carried out easily and economically on larger scale.

P-Chiral compounds are mainly used in enantioselective homogenous catalytic reactions as ligands in transition metal catalysts. To show the practical usefulness of the prepared enantiomers, platinum complexes $[(-)\text{-16}]$ and $[(+)\text{-19}]$ were prepared from the (*R*)-1-phenyl-3-methyl-3-phospholene 1-oxide [*(R)*-**1a**] and (+)-1-phenyl-3-diphenylphosphinoxido-1,2,3,6-tetrahydrophosphinine-1-oxide [*(+)*-**17**], respectively, that are under investigation in the hydroformylation reaction of styrene.



7. Publications

7.1 Publications of Thesis

1. Novák, T.; Schindler, J.; Ujj, V.; Czugler, M.; Fogassy, E.; Keglevich, G. *Tetrahedron: Asymmetry* **2006**, *17*, 2599-2602. [IF: 2,468, C: 5, IC: 2]
2. Novák, T.; Ujj, V.; Schindler, J.; Czugler, M.; Kubinyi, M.; Mayer, Z. A.; Fogassy, E.; Keglevich, G. *Tetrahedron: Asymmetry* **2007**, *18*, 2965-2972. [IF: 2,634, C: 4, IC: 2]
3. Novák, T.; Schindler, J.; Ujj, V.; Czugler, M.; Fogassy, E.; Keglevich, G. *Phosphorus, Sulfur, Silicon* **2008**, 543-546. [IF: 0,669 (2007) C: 1]
4. Fogassy, E.; Keglevich, G.; Novák, T.; Schindler, J.; Ujj, V. *Hun. Pat.* **2007**, P0700278.
5. Mayer, Z. A.; Kállay, M.; Kubinyi, M.; Keglevich, G.; Ujj, V.; Fogassy, E. *J. Mol. Struct.-Theochem* **2009**, *906*, 94-99. [IF: 1,112 (2007)]
6. Ujj, V.; Szuhánszki, T.; Schindler, J.; Czugler, M.; Fogassy, E.; Keglevich, G. *Hun. J. Ind. Chem.* **2008**, *36*, 131-136.
7. Ujj, V.; Schindler, J.; Novák, T.; Czugler, M.; Fogassy, E.; Keglevich, G. *Tetrahedron: Asymmetry* **2008**, *19*, 1973-1977. [IF: 2,634 (2007)]
8. Ujj, V.; Schindler, J.; Bagi, P.; Madarász, J.; Fogassy, E.; Keglevich, G. *Chirality* **2009**, under publication. [IF: 2,436 (2007)]

7.2 Other publications

9. Keglevich, Gy.; Sipos, M., Ujj, V., Körvélyesi, T. *Lett. In Org. Chem.* **2005**, *2*, 608-612. [IF: 1,122, C: 5]
10. Sipos, M., Körvélyesi, T., Ujj, V., Ludányi, K., Vékey, K., Keglevich, Gy. *Heteroatom Chem.* **2007**, *18*, 747-753. [IF: 0,984, C:1]
11. Keglevich, Gy.; Kerényi, A.; Sipos, M.; Ujj, V.; Makó, A.; Csontos, I.; Novák, T.; Bakó, P.; Greiner, I. *Periodica Politechnika* **2007**, *51*, 53-56.

7.3 Presentations

12. Ujj, V.: 3-Metil-3-foszfólen-1-oxidok reszolválása, *Oláh György Doktori Iskola - IV. Doktoráns Konferencia*, Budapest, February 07, 2007.
13. Novák, T.; Schindler, J.; Ujj, V.; Deme, J.; Bódis, Á.; Fogassy, E.; Keglevich, Gy.: Chiral P-heterocycles: Efficient method for the optical resolution of 3-methyl-3-phospholen 1-oxides, *17th International Conference on Phosphorus Chemistry*, Xiamen, China, April 15-19, 2007.

14. Novák, T.; Schindler, J.; Ujj, V.; Czugler, M.; Fogassy, E.; Keglevich, Gy.: Optikailag aktív dihidro-1H-foszfol-oxidok hozzáférhetővé tétele, *Centenáriumi Vegyészkonferencia*, Sopron, May 29 - June 1, 2007.
15. Novák, T.; Schindler, J.; Ujj, V.; Czugler, M.; Fogassy, E.; Keglevich, Gy.; Faigl, F.: Chiral P-heterocycles: Efficient method for the optical resolution of 3-methyl-3-phospholen 1-oxides, *COST D40, Workshop on Innovative Catalysis*, Dublin, Ireland, May 21-22, 2007. (poster).
16. Ujj, V.; Schindler, J.; Novák, T.; Czugler, M.; Fogassy, E.; Keglevich, Gy.: P-Aszimmetria centrumot tartalmazó gyűrűs foszforvegyületek optikai izomerjeinek elválasztása, *Műszaki Kémiai Napok '08*, Veszprém, April 22-24, 2008.
17. Ujj, V.; Schindler, J.; Czugler, M.; Fogassy, E.; Keglevich, Gy.: P-Heterociklusok optikai izomerjeinek elválasztása, *Heterociklusos Kémiai Munkabizottság*, Balatonszemes, May 21-23, 2008.
18. Ujj, V.; Schindler, J.; Czugler, M.; Fogassy, E.; Keglevich, Gy.: P-Heterociklusok optikai izomerjeinek elválasztása, *Vegyészkonferencia*, Hajdúszoboszló, June 19-21, 2008.
19. Ujj, V.; Szuhánszki, T.; Bagi, P.; Schindler, J.; Czugler, M.; Fogassy, E.; Keglevich, Gy.: P-Heterociklusok optikai izomerjeinek elválasztása, *Terpenoidkémiai és Elemorganikus Munkabizottság*, Budapest, September 19, 2008.
20. Ujj, V.; Schindler, J.; Bagi, P.; Szuhánszki, T.; Czugler, M.; Fogassy, E.; Keglevich, Gy.: P-Heterociklusos vegyületek rezolválása borkósav származékokkal diasztereomer komplex képzésen keresztül, *Oláh György Doktori Iskola - VI. Doktoráns Konferencia*, Budapest, February 4, 2009.
21. Ujj, V.; Schindler, J.; Bagi, P.; Czugler, M.; Fogassy, E.; Keglevich, Gy.: Resolution of P-Heterocycles with Tartaric Acid Derivatives via Diastereomeric Complex Formation, *Tenth Tetrahedron Symposium*, Paris, June 23-26, 2009. (poster).