Final report

NKFIH - PD116096

The preparation and utilization of optically active phosphine oxides

According to the workplan, research was conducted on the field of optically active organophosphorus compounds. Our aim was to prepare the enantiomers of phosphine oxides bearing a *P*-stereogenic center, use cyclic halophosphonium salts for the transformation of organophosphorus compounds, and to utilize the cyclic or acyclic P(III)-derivatives as ligands or as organocatalysts.

Resolution of several acyclic and a cyclic P-stereogenic phosphine oxide with TADDOL-derivatives and Ca^{2+}-salts of tartaric acid derivatives[2,4,6-8,10,15,16]

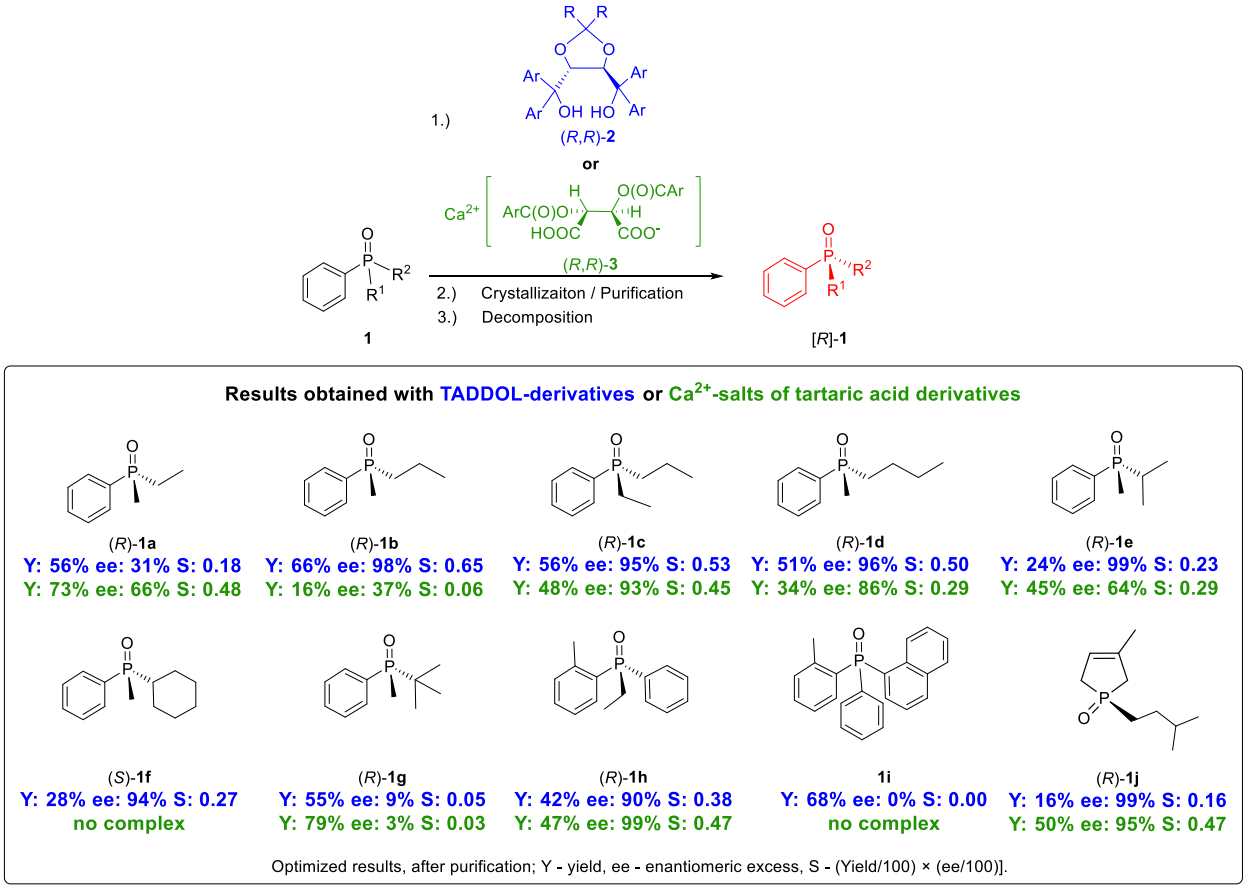
Several acyclic phosphine oxides (**1**) were prepared in racemic form, and the optical resolution of those compounds was studied. The enantiomeric separation of the dialkyl-arylphosphine oxides was thoroughly investigated (**1a-g**). These compounds can be regarded as challenging substrates, as the two alkyl groups may hinder the interactions between the *P*-oxide and the resolving agent. This might be the reason why the literature lacks efficient resolution methods for dialkyl-arylphosphine oxides (**1a-g**). The ethyl-(2-methylphenyl)phenyl-phosphine-oxide (**1h**) and the (2-methylphenyl)-(1-naphthyl)phenylphosphine oxide (**1i**) were also prepared as examples of the diaryl-alkyl- and triaryl phosphine oxides (Scheme 1.).

The optical resolution was elaborated applying either TADDOL-derivatives [(*R*,*R*)-**2**] or Ca^{2+}-salts of tartaric acid [(*R*,*R*)-**3**] derivatives. The crystallization conditions and the purification of the enantiomeric / diastereomeric mixtures were optimized. Six phosphine oxides were prepared with an ee > 94 %. In a few instances, the diastereomeric intermediates were investigated by single crystal X-ray diffraction, which allowed us to determine the main intermolecular interactions responsible for the enantiomeric recognition. An efficient method was also found for the racemization of the unwanted phosphine oxide enantiomers via the formation of chlorophosphonium salts. Moreover, the organic solvent nanofiltration (OSN) technique was used for the decomposition of the spiro-TADDOL – phosphine oxide diastereomers, and for the recovery of the corresponding enantiomers and resolving agents, within the framework of a

collaboration with Dr. György Székely (University of Manchester; KAUST). Previously, the decomposition of the diastereomers was accomplished by column chromatography, as the polarity of the phosphine oxides and the TADDOL-derivatives is similar. The chromatography could be replaced by OSN, which is a scalable technique, that uses less solvent, and the solvent recycling is more effective.

In the resolution studies, the enantiomers of (2-methylphenyl)-(1-naphthyl)- and the *t*-butyl-methyl-phenylphosphine oxides (**1g** and **1i**) could not be prepared with our resolution methods. It may be attributed to the increased steric bulk of these phosphine oxides hindering the interactions with the corresponding resolving agent, and leading to inefficient enantiomeric separation.

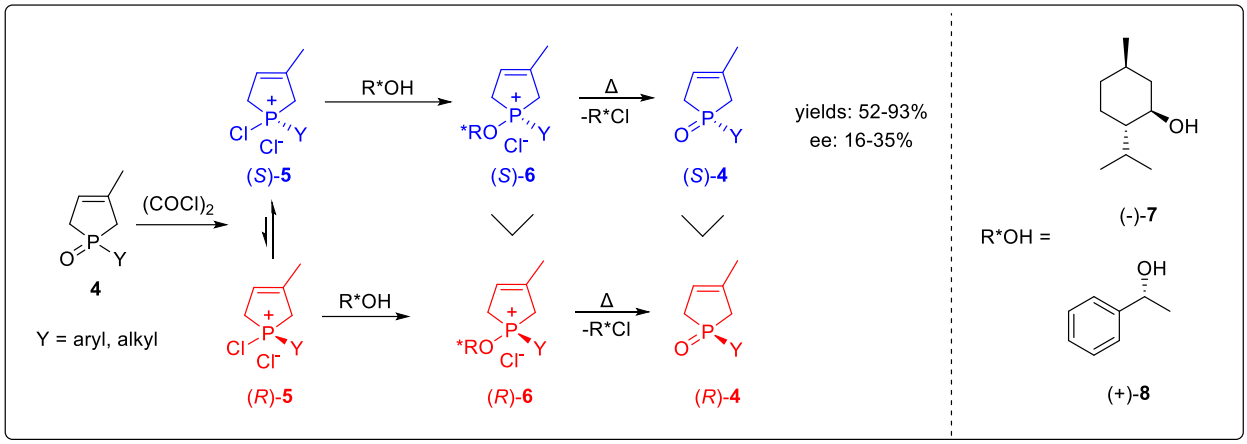
Besides the resolution of the acyclic phosphine oxides, the enantomeric separation of 1-isopentyl-3-methyl-3-phospholene oxide (**1j**) was also studied as an example of cyclic phosphine oxides. The enantiomers of the 1-isopentyl-phospholene oxide were prepared with an ee > 99%, and it were used in subsequent studies.



Scheme 1.

Dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene oxides via the formation of diastereomeric alkoxyphospholenium salts[3,9]

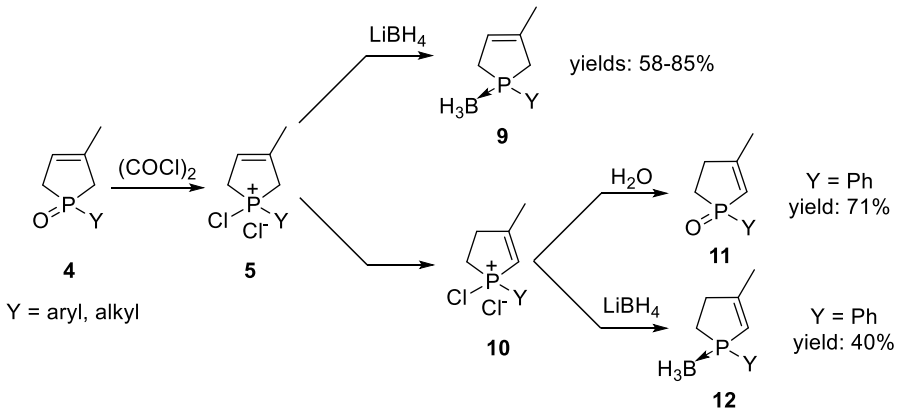
A dynamic kinetic resolution was elaborated to prepare optically active 1-substituted-3-methyl-3-phospholene oxides [(*S*)-**4**]. The first step of this process was the reaction of the racemic 3-phospholene oxides (**4**) with oxalyl chloride to give 1-chloro-3-methyl-3-phospholenium chlorides (**5**) containing a stereolabile *P*-chiral center. The enantiomers of the chlorophospholenium-salts (**5**) interconvert into each other in solution, which is prerequisite for a dynamic resolution. Then, the chlorophosphonium salts (**5**) were reacted with various chiral alcohols to form diastereomerically enriched alkoxyphosphonium salts [(*S*)-**6**]. 22 Different primary, secondary and tertiary chiral alcohols were tested, and the reaction conditions were optimized. From this pool of chiral auxiliaries, (−)-menthol [(−)-**7**] or (+)-1-phenylethanol [(+)-**8**] were the most suitable ones yielding the corresponding cyclic alkoxyphosphonium salts [(*S*)-**6**] with full conversion and with diastereomeric excess values of 16-35%. Upon heating, the optically active alkoxyphosphonium salts [(*S*)-**6**] were stereospecifically transformed to optically active 3-phospholene oxides [(*S*)-**4**] in an *Arbuzov*-type rearrangement. A series of optically active aryl- and alkyl-3-methyl-3-phospholene oxides [(*S*)-**4**] could be prepared in yield of 52-93% and with an ee of 16-35% (Scheme 2). The key step of this dynamic resolution was investigated by quantum chemical calculations. The results showed that the formation of the cyclic alkoxyphosphonium salt diastereomers [(*S*)-**6** or (*R*)-**6**] goes through a nearly identical low transition state, and there is only a slight energetic difference between the formation of the two diastereomers. On the contrary, the transition state is higher, and the difference between the two diastereomers is also much higher for acyclic organophosphorus derivatives. Thus, the lack of high diastereoselectivity for the cyclic phosphine oxides could be interpreted on the basis of these calculations.



Scheme 2.

A novel preparation of 1-substituted-3-methyl-3-phospholene boranes[3,5]

The cyclic chlorophosphonium salts (**5**), which can be prepared in the reaction of 3-phospholene oxides (**4**) and oxalyl chloride are reactive intermediates. They react readily with $LiBH_4$ to furnish the corresponding 3-methyl-3-phospholene boranes (**9**) in a yield of 58-85%. This two-step reaction is a silane-free deoxygenation and a borane complex formation protocol for 3-phospholene oxides (**4**). Interestingly, it was found that the double bond of the cyclic chlorophosphonium salt (**5**) may rearrange, which allowed us to synthesize a 2-phospholene borane and a *P*-oxide derivative (**11** and **12**) (Scheme 3).

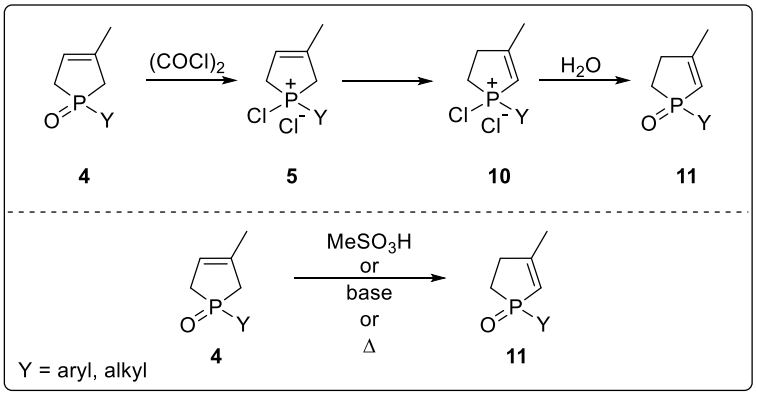


Scheme 3.

Efficient preparation of 2-phospholene oxides by the isomerization of 3-phospholene oxides[12,14]

During the preparation of the cyclic chlorophosphonium salts (**5**), a side-reaction was observed. The chloro-3-phospholenium chlorides (**5**) rearranged to the corresponding 2-phospholenium salt (**10**) upon prolonged reaction times. This side-reaction prompted us to investigate in detail the isomerization of the 3-phospholene oxides (**4**) to 2-phospholene oxides (**11**) in addition to our originally submitted workplan. Considering the phospholenes, the position of the double bond (2- or 3-phospholenes) offers different possibilities for functionalization to obtain a *P*-heterocycle with the desired substitution pattern and potential bioactivity. In the literature, the number of synthetic methods for 2-phospholene-derivatives (**11**) is limited.

In our work, four different methods were outlined to prepare 2-phospholene oxides (**11**) from 3-phospholene oxides (**4**). Complete isomerization took place either via the formation of chlorophospholenium salts (**5→10**), or by heating the 3-phospholene oxides (**4**) in the presence of methanesulfonic acid. A series of 1-substituted-3-methyl-2-phospholene oxides (**11**) were prepared by both methods. It was also shown that the isomerization may occur to some extent in the presence of inorganic bases, or at elevated temperatures without using any reagent. However, the isomerization remained incomplete under these conditions. It was found that methyl group(s) at positon 3 or 4 in the *P*-heterocyclic ring hinder the isomerization in all reaction pathways investigated. The mechanisms of the rearrangement of the cyclic chlorophosphonium salts (**5→10**), the acid- or base-mediated, as well as thermal isomerizations were elucidated by quantum chemical calculations. The results justified why a given isomerization pathway leads to an equilibrium or proceeds until completion.

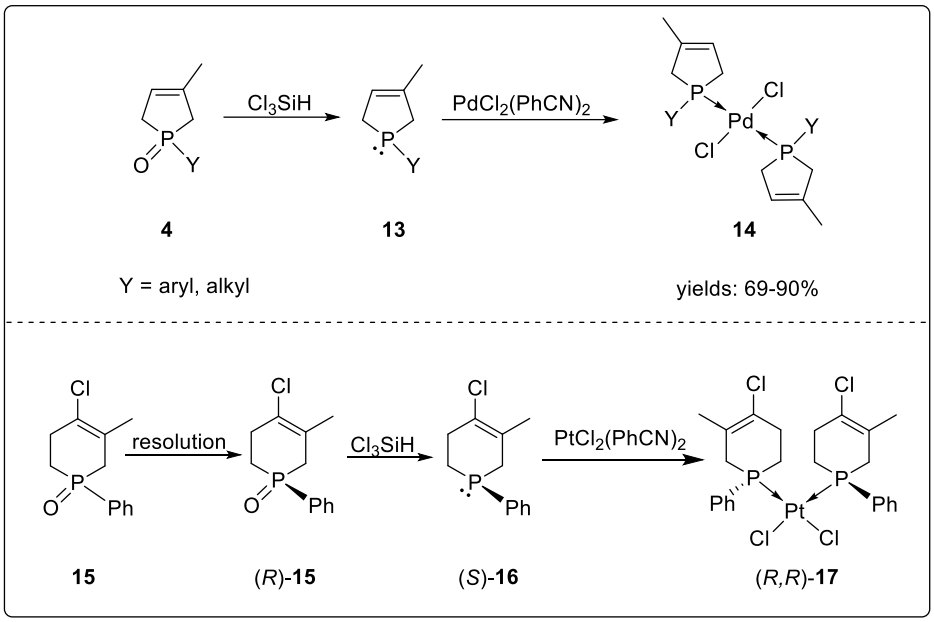


Scheme 4.

Synthesis of the transition metal complexes of P-heterocycles[1,12,14]

A series of palladium complexes incorporating 1-substituted-3-methyl-3-phospholene ligands (**14**) was synthesized and characterized. Starting from racemic 3-phospholene oxides (**4**), the $PdCl_2$(phospholene)$_2$-type complexes (**14**) were made available as a mixture of homochiral and meso forms. An optically active Pd-complex incorporating (*S*)-1-propyl-3-methyl-3-phospholene ligand (**13**) was also prepared (Scheme 5). One phenyl- and the *i*-pentyl-substituted palladium complex (**14**) were tested as catalysts in hydroalkoxycarbonylation of styrene using various *O*-nucleophiles by Dr. Péter Pongrácz and Prof. László Kollár. The *i*-pentyl-derivative showed higher activity and selectivity towards the linear derivative. However, the overall activity of these $PdCl_2$(phospholene)$_2$-type complexes (**14**) was rather low.

As an addition to the original workplan submitted, the platinum complex of a six-membered *P*-heterocycle (**17**) was synthesized in racemic and optically active form, and these complexes were utilized in enantioselective hydroformylation by Dr. Péter Pongrácz and Prof. László Kollár. The six-membered heterocyclic 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine oxide (**15**) was made available in enantiopure form by resolution. The intermediate diastereomeric complex was investigated by XRD spectroscopy. The racemic and optically active tetrahydrophosphinine oxide [(*R*)-**15**] were converted to the corresponding platinum complexes [(*R*,*R*)-**17**] after deoxygenation of the cyclic *P*-oxides by trichlorosilane (Scheme 5). The platinum complexes – in the presence of $SnCl_2$ – showed high catalytic activity in the hydroformylation of styrene. The catalytic system showed high chemo- and moderate regioselectivity towards the branched product, the 2-phenylpropanal. Applying optically active platinum complex of phenyl-tetrahydrophosphinine [(*R*,*R*)-**17**] in the enantioselective hydroformylation of styrene, the 2-phenylpropanal was obtained with ee-s up to 29%.



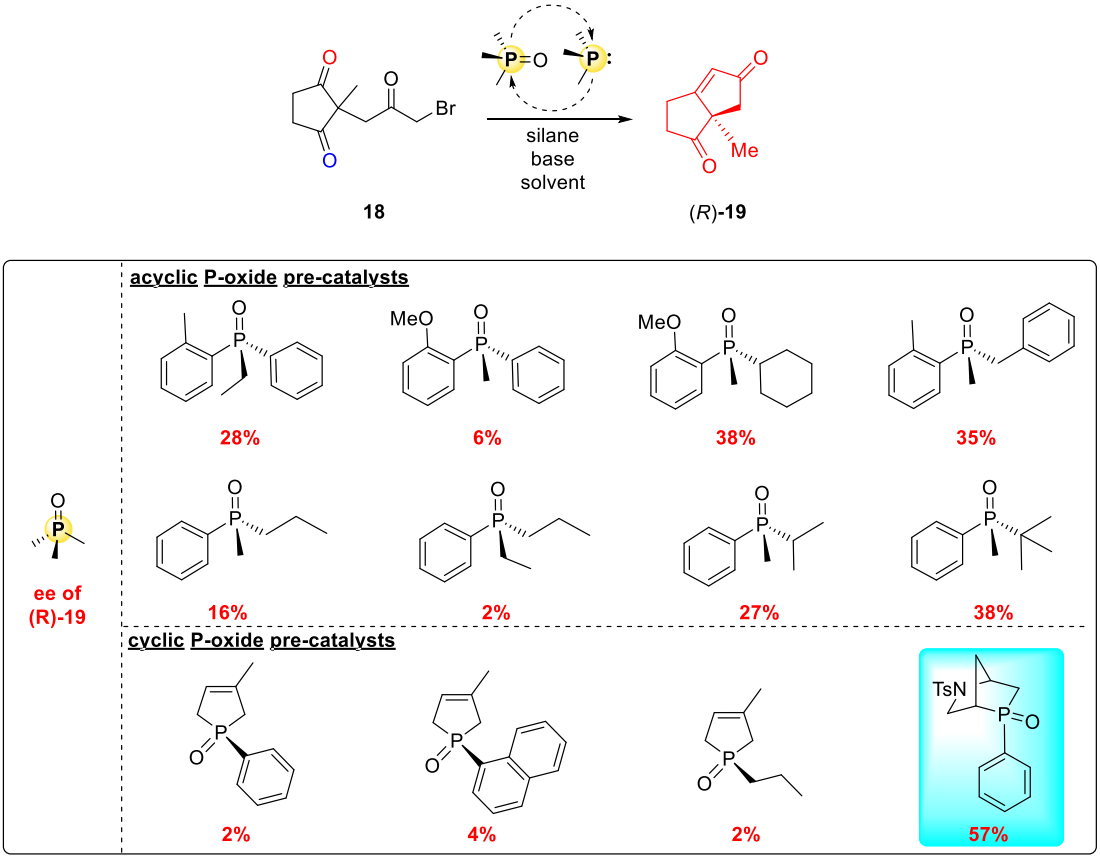
Scheme 5.

Utilization of P-stereogenic phosphine oxides as pre-catalysts in an enantioselective catalytic Wittig-reaction[11,17]

The investigation of an asymmetric version of the catalytic *Wittig*-reaction was our main focus, as *P*-stereogenic phosphine oxides were rarely employed in such transformations. Two separate reactions were investigated, an intermolecular version between 4-*t*-butylcyclohexanone and methyl bromoacetate, and an intramolecular variant involving the enantioselective cyclization of 2-(3-bromo-2-oxopropyl)-2-methylcyclopentane-1,3-dione (**18**). Only the intramolecular enantioselective catalytic *Wittig*-reaction was feasible, and the reaction conditions were optimized. We investigated several silanes, activating agents for deoxygenation, bases, solvents, as well as the reaction temperature and time. In order to maximize the enantioselectivity of the reaction, we intended to use as low reaction temperatures as possible. It was found, that the deoxygenation of the phosphine oxides is the rate determining step of this reaction. The deoxygenation of the acyclic phosphine oxides is slow under 100°C, whereas the same reaction proceeds with acceptable rate at 40°C for cyclic phosphine oxides. The *N*,*N*-diisopropylethylamine was the most suitable base, and the toluene or acetonitrile was the best solvent. Several *P*-stereogenic phosphine oxides were tested as pre-catalysts for the intramolecular enantioselective catalytic *Wittig*-reaction, and the

acyclic phosphine oxides were reacted at 100°C, whereas the cyclic derivatives were tested at 40°C.

The optically active methyl-2,3,6,6-tetrahydropentalene-1,5-dione [(*R*)-**19**] were prepared with an ee of 2-38% using acyclic phosphine oxides. Whereas, the ee of (*R*)-**19** was 2-57% when the cyclic derivatives were used. Intriguingly, it was observed that the enantiopurity of the organocatalyst significantly decreased when the reaction temperature was 100°C, which explains the low ee values of (*R*)-**19** obtained with the acyclic phosphine oxide pre-catalysts. According to the literature, each catalytic step involves the retention of *P*-configuration. Thus, the epimerization of the corresponding phosphines at elevated temperature might be the reason for the racemization of the organocatalysts. Interestingly, the additives used to enhance the rate of deoxygenation step, also increased the rate of racemization. The best enantiomeric excess of (*R*)-**19** (ee = 57%) was obtained with the commercially available endo-phenyl-*Kwon*-[2.2.1]-bicyclic-phosphine oxide at 40°C. Considering these results, the application of other members of these cyclic *P*-oxides will be accomplished in the near future to finish this research topic and publication.



Scheme 6.

References:

Full papers, Short Publications and Book Chapters:

[1.] Bagi, P.; Karaghiosoff, K.; Czugler, M.; Hessz, D.; Kállay, M.; Kubinyi, M.; Szilvási, T.; Pongrácz, P.; Kollár, L.; Timári, I.; Kövér, K. E.; Drahos, L.; Fogassy, E.; Keglevich, G., Synthesis, characterization and application of platinum(II) complexes incorporating racemic and optically active 4-chloro-5-methyl-1-phenyl-1,2,3,6-tetrahydrophosphinine ligand, *Heteroatom Chem.* **2016**, *27* (2), 91-101.

[2.] Bagi, P.; Ujj, V.; Czugler, M.; Fogassy, E.; Keglevich, G. Resolution of P-stereogenic P-heterocycles via the formation of diastereomeric molecular and coordination complexes (a review), *Dalton Trans.* **2016**, *45* (5), 1823-1842.

[3.] Herbay, R.; Bagi, P.; Fogassy, E.; Keglevich, G., Preparation of P-heterocyclic phosphine boranes and optically active phosphine oxides via phosphonium salts, *Phosphorus, Sulfur, Silicon Relat. Elem.* **2016**, *191* (11-12), 1656-1657.

[4.] Bagi, P.; Herbay, R.; Juhász, K.; Varga, B.; Fogassy, E.; Keglevich, G. The resolution and application of P-stereogenic phosphine oxides, *Phosphorus. Sulfur. Silicon Relat. Elem.* **2016**, *191* (11-12), 1459-1461.

[5.] Herbay, R.; Bagi, P.; Mucsi, Z.; Mátravölgyi, B.; Drahos, L.; Fogassy, E.; Keglevich, G. A novel preparation of chlorophospholenium chlorides and their application in the synthesis of phospholene boranes, *Tetrahedron Lett.* **2017**, *58* (5), 458-461.

[6.] Bagi, P.; Varga, B.; Szilágyi, A.; Karaghiosoff, K.; Czugler, M.; Fogassy, E.; Keglevich, G. The resolution of acyclic P-stereogenic phosphine oxides via the formation of diastereomeric complexes: a case study on ethyl-(2-methylphenyl)-phenylphosphine oxide *Chirality* **2018**, *30* (4), 509-522.

[7.] Bagi, P.; Juhász, K.; Kállay, M.; Hessz, D.; Kubinyi, M.; Fogassy, E.; Keglevich G. Preparation of enantiopure 1-isopentyl-3-methyl-3-phospholene 1-oxide via the formation of diastereomeric complexes *Heteroatom Chem.* **2018**, *29* (1), e21411.

[8.] Bagi, P.; Herbay, R. Resolution of phosphine oxides in Keglevich, G. (Ed.) *Organophosphorus Chemistry – Novel Developments* **2018**, pp. 66-90.

[9.] Bagi, P.; Herbay, R.; Ábrányi-Balogh, P.; Mátravölgyi, B.; Fogassy, E.; Keglevich, G. Dynamic kinetic resolution of 1-substituted-3-methyl-3-phospholene oxides via the formation of diastereomeric alkoxyphospholenium salts *Tetrahedron* **2018**, *74* (40), 5850-5857.

[10.] Varga, B.; Csizovszky, A.; Bagi, P.; Fogassy, E.; Keglevich, G. Resolution of acyclic phosphine oxides with TADDOL- and tartaric acid derivatives *Phosphorus, Sulfur, Silicon Relat. Elem.* **2019**, *194* (4-6), 556-557.

[11.] Bagi, P.; Herbay, R.; Varga, B.; Fersch, D.; Fogassy, E.; Keglevich, G. The preparation and application of optically active organophosphorus compounds *Phosphorus, Sulfur, Silicon Relat. Elem.* **2019**, *194* (4-6), 591-594.

[12.] Herbay, R.; Péczka, N.; Györke, G.; Bagi, P.; Fogassy, E.; Keglevich, G. Isomerization and application of phospholene oxides *Phosphorus, Sulfur, Silicon Relat. Elem.* **2019**, *194* (4-6), 610-613.

Manuscripts under evaluation

[13.] Bagi, P.; Herbay, R.; Györke, G.; Pongrácz, P.; Kollár, L.; Timári, I.; Drahos, L.; Keglevich, G. Preparation of palladium(II) complexes of 1-substituted-3-phospholene ligands and their evaluation as catalysts in hydroalkoxycarbonylation *Curr. Org. Chem.* **2019**. *revision submitted*

[14.] Bagi, P.; Herbay, R.; Péczka, N.; Mucsi, Z.; Timari, I.; Keglevich, G. Efficient preparation of 2-phospholene oxides by the isomerization of 3-phospholene oxides *Asian J. Org. Chem.* **2019**. *submitted*

[15.] Varga, B.; Herbay, R.; Székely, G.; Holczbauer, T.; Madarász, J.; Mátravölgyi, B.; Fogassy, E.; Keglevich, G.; Bagi, P. Scalable enantiomeric separation of dialkyl-arylphosphine oxides based on host-guest complexation with TADDOL-derivatives, and their recovery *Separation and Purification Technology* **2019**. *submitted*

Manuscripts before submission

[16.] Varga, B.; Bagi, P. Coordination mediated enantiomeric separation of dialkyl-arylphosphine oxides with the Ca^{2+}-salts of tartaric acid derivatives

[17.] Péczka, N.; Herbay, R.; Juhász K.; Györke, G.; Varga B.; Bagi, P.; Application of *P*-stereogenic phosphine oxides in enantioselective *Wittig*-reaction to prepare optically active *bis-nor-Wieland–Miescher* ketone

Presentations:

[1.] Bagi, P.; Herbay, R.; Juhász, K.; Varga, B.; Fogassy, E.; Keglevich G. *The resolution and application of P-stereogenic phosphine oxides*, 21th International Conference on Phosphorus Chemistry, Kazan, June 5-10, 2016.

[2.] Herbay, R.; Bagi, P.; Fogassy, E.; Keglevich, G. *Preparation of P-heterocyclic phosphine boranes and optically active phosphine oxides via phosphonium salts*, 21th International Conference on Phosphorus Chemistry, Kazan, June 5-10, 2016.

[3.] Bagi, P.; Herbay, R.; Varga, B.; Nagy, P.; Juhász, K.; Fogassy, E.; Keglevich G. *Novel preparation and application of P-chiral phosphine oxides*, 14th European Workshop on Phosphorus Chemistry, Cluj-Napoca, March 20-22, 2017.

[4.] Herbay, R.; Bagi, P.; Fogassy, E.; Keglevich, G. *Dynamic resolution of P-heterocyclic phosphine oxides via covalent diastereomeric intermediates*, 14th European Workshop on Phosphorus Chemistry, Cluj-Napoca, March 20-22, 2017.

[5.] Bagi, P.; Herbay, R.; Varga, B.; Nagy, P.; Vincze, D.; Juhász, K.; Fogassy, E.; Keglevich, G. *Optikailag aktív foszfor sztereogén centrumot tartalmazó foszforvegyületek előállítása*, Vegyészkonferencia 2017, Hajdúszoboszló, June 19-21, 2017.

[6.] Herbay, R.; Bagi, P.; Péczka, N.; Keglevich, G.; Fogassy, E. *Foszfolén-oxidok dinamikus rezolválása kovalens diasztereomer képzésen keresztül*, Vegyészkonferencia 2017, Hajdúszoboszló, June 19-21, 2017.

[7.] Bagi, P.; Herbay, R.; Varga, B.; Keglevich G. *Preparation and utilization of chiral organophosphorus compounds*, 15th European Workshop on Phosphorus Chemistry, Uppsala, March 14-16, 2018.

[8.] Herbay, R.; Péczka, N.; Bagi, P.; Fogassy, E.; Keglevich, G. *Investigation of the isomerization of phospholene oxides*, 15th European Workshop on Phosphorus Chemistry, Uppsala, March 14-16, 2018.

[9.] Varga, B.; Bagi, P.; Fogassy, E.; Keglevich, G. *The preparation of optically active acyclic phosphine oxides by resolution*, 15th European Workshop on Phosphorus Chemistry, Uppsala, March 14-16, 2018.

[10.] Bagi, P.; Herbay, R.; Varga, B.; Fogassy, E.; Keglevich, G. *Preparation and application of optically active organophosporus compounds*, 22nd International Conference on Phosphorus Chemistry, Budapest, July 8-13, 2018.

[11.] Herbay, R.; Péczka, N.; Györke, G.; Bagi, P.; Fogassy, E.; Keglevich G. *Isomerization and application of phospholene oxides*, 22nd International Conference on Phosphorus Chemistry, Budapest, July 8-13, 2018.

[12.] Varga, B.; Bagi, P.; Fogassy, E.; Keglevich, G. *Resolution of acyclic phosphine oxides with TADDOL- and tartaric acid derivatives*, 22nd International Conference on Phosphorus Chemistry, Budapest, July 8-13, 2018.

[13.] Varga, B.; Bagi, P.; Szemesi, P.; Pauló, J.; Vincze, D.; Nagy, P.; Fogassy, E.; Keglevich, G. *Resolution of P-stereogenic H-phosphinates and secondary phosphine oxides with TADDOL-derivatives*, 16th European Workshop on Phosphorus Chemistry, Bristol, April 24-26, 2019.