UNIVERSITY OF PANNONIA

SYNTHESIS, COORDINATION CHEMISTRY AND CATALYTIC APPLICATION OF NOVEL CHIRAL AMINOALKYL-PHOSPHINE LIGANDS

THESIS OF THE DOCTORAL (PhD) DISSERTATION

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I. Introduction and objectives

A large number of naturally occurring organic compounds is composed of chiral molecules. A chiral molecule is not identical with its mirror image as they cannot be superimposed onto each other. The two structures related as non-superimposable mirror images form a pair of enantiomers. Although scalar physical properties of the enantiomers are identical, but their behavior is different towards chiral reagents. Consequently, the selective synthesis of the enantiomers of biologically active chiral compounds (e.g. active pharmaceutical ingredients, pesticides) has high significance.

There are several methods for the preparation of enantiomerically pure compounds. Amongst these possibilities, transition metal catalyzed asymmetric synthesis can be mentioned as one of the most powerful methodologies. In this case, the catalyst is a transition metal complex containing an optically pure chiral ligand, so the chiral information can be transferred from the catalyst to the substrate. Chiral bidentate ligands with C_1 symmetry represent a unique type of stereoselectors due to their ability to desymmetrize the transition metal complex both sterically and electronically. Chiral phosphine-amine (P,N) type compounds belong to a more specific class of C_1 symmetry heterodonor ligands. These compounds contain two donoratoms of remarkably distinct electronic properties: while phosphorus has both σ-donor and π-acceptor ability, nitrogen exhibits good σ-donor properties. Additionally, the introduction of a stereogenic nitrogen in a phosphine-amine ligand may further increase the catalytic efficiency of the transition metal catalyst. In this case, the configuration of the nitrogen is fixed upon coordination and the stereogenic donoratom directly attached to the metal is expected to ensure more efficient transfer of chirality.

The main objectives of my PhD studies were the synthesis of chiral alkane-diyl based phosphine-amine ligands having stereogenic nitrogen donor and their application in palladium-catalyzed asymmetric allylic substitution reactions. The catalytic reactions enabled the stereoselective formation of carbon-carbon and carbon-nitrogen bonds and therefore the preparation of synthetically useful chiral building blocks. The additional aim of the work was the synthesis of the palladium complexes of the novel ligands and their analysis by NMR spectroscopy, X-ray diffraction method and theoretical calculations. The purpose of these studies was the identification of structure-reactivity relationships of the newly developed catalysts.

II. Experimental methods

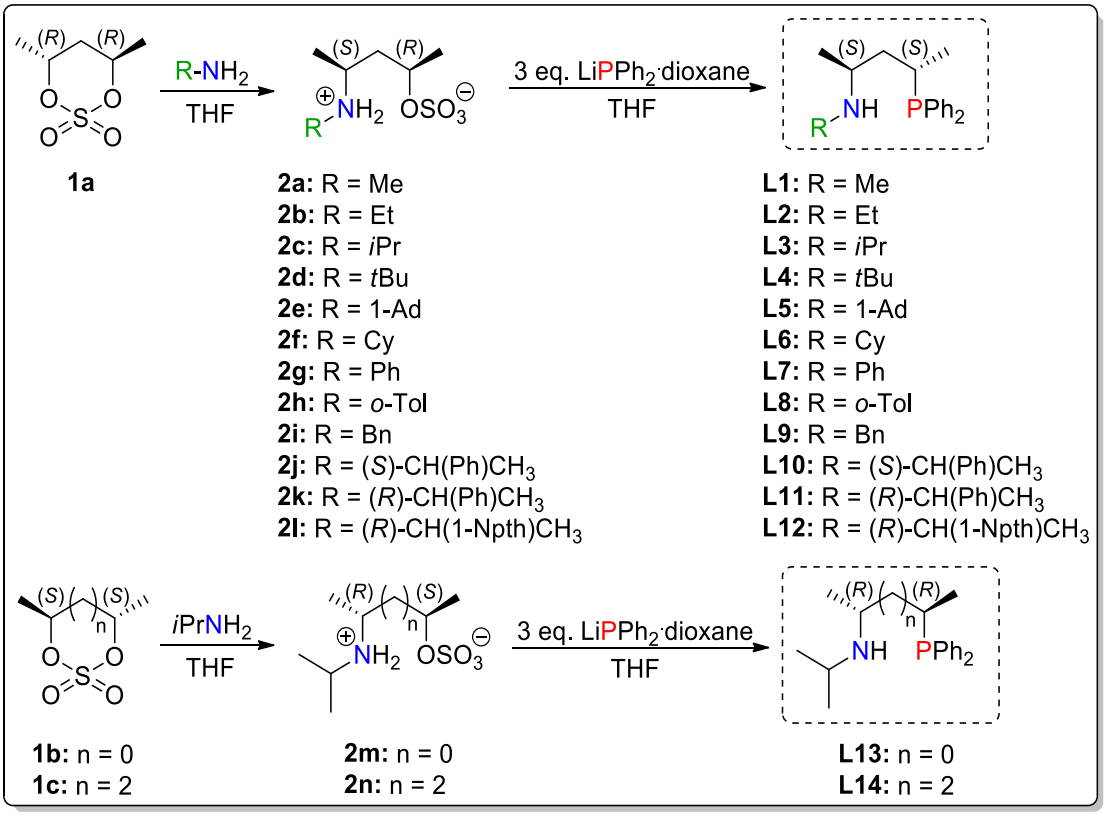
The synthetic and catalytic work was performed under an inert atmosphere using Schlenk-techniques. The solvents used were purified by standard literature methods.

The synthetic reactions were monitored by thin layer chromatography (TLC). The conversion and enantioselectivity of the catalytic reactions were determined by high pressure liquid chromatography (HPLC) using chiral columns, the regioselectivity of the reactions was established by ^{1}H NMR spectroscopy. Several products were purified by column chromatography.

The products of synthetic and catalytic reactions were analyzed by mass spectroscopy (ESI-MS), infrared (IR) and ^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H\}$, ^{1}H-^{1}H COSY, ^{1}H-^{1}H NOESY NMR techniques and in some cases by X-ray crystallography.

III. New scientific results

1. Ten novel (**L2**, **L5**-**L8**, **L10**-**L14**) aminoalkyl-phosphine (P,N) type ligands with stereogenic nitrogen was prepared. The synthesis of these compounds was carried out by a simple two-step method enables the preparation of versatile P,N type compounds, that differ in the nitrogen substituent (**L1**-**L12**) and the length of P,N backbone (**L13** and **L14**). The structure of the new compounds was investigated by nuclear magnetic resonance and mass spectroscopic methods. [1-4]



2. It was established that the [Pd(**L**)Cl_2] complexes of pentane-2,4-diyl based ligands **L1**, **L2**, **L3**, **L9** and **L10** form six-member chelate rings with chair conformation. It has been recognized that the coordination of ligands **L1** and **L2** having sterically less demanding N-methyl and N-ethyl group, respectively, results in the formation of an isomeric mixture. In contrast to these, the coordination of ligands **L3**, **L9** and **L10** with bulkier *i*Pr-, Bn- and (*S*)-phenyl-ethyl substituents, respectively, occurs stereoselectively with respect to the configuration of the nitrogen and the conformation of the chelate ring. [1,2] It has been proven that changing the length of alkane-diyl backbone also leads to the formation of isomerically related palladium species. In the case of ligand **L13** with butane-2,3-diyl backbone the two five-membered chelates have opposite nitrogen configuration, the coordination of hexane-2,4-diyl based ligand **L14** results in the formation of multiple complex species.

3. It has been shown that the coordination of ligands with sterically congested (*R*)-phenyl-ethyl (**L11**) and (*R*)-naphthyl-ethyl (**L11**) substituents led to the formation of dinuclear palladium-complexes with a 12-membered ring instead of the expected six-membered chelates. Both nitrogen donors coordinate stereoselectively in these C_2 symmetry

compounds. It has been observed that both the 12-membered dinuclear complex and the six-membered chelate form in the case of the coordination of ligand **L4** with N-*t*Bu substituent. [4]

4. A straightforward correlation has been observed between the steric demand of the nitrogen substituent and the geometry of the chelate ring in [Pd(**L**)Cl_2] complexes of ligands **L2**, **L3**, **L9** and **L10** based on X-ray diffraction and NMR studies as well as on theoretical calculations. It has been recognized that increasing the steric bulk of the axially positioned nitrogen substituent results in the more pronounced distortion of the six-membered chelate ring. [2]

5. The [Pd(η^3-PhCHCHCHPh)(**L**)]BF_4 type complexes of ligands **L1**, **L2**, **L3**, **L9** and **L10** were prepared. It has been shown that the steric bulk of the nitrogen substituent affects the stereoselectivity of coordination, the geometry of the chelate ring, the ratio of the *exo* and *endo* isomers and the spatial orientation of diphenylallyl group. [1,2]

6. The phosphine-amine ligands were successfully applied in palladium-catalyzed asymmetric allylic substitution reactions of C-nucleophiles and substrates containing allylic leaving group. It has been proven that the nitrogen substituent of the ligand strongly affects the selectivity of the catalytic reaction. Sterically more demanding nitrogen substituents provided higher optical yield (96% *ee*) that can mainly be attributed to the stereoselective coordination. [1-3]

7. It has been recognized that the bidentate ligands can also be applied effectively in palladium-catalyzed allylic amination reactions. It has been proven that the structure of the amine and the amount of the solvent have a significant effect on the activity and selectivity. Reactions with cyclic amines under solvent-free conditions took place with outstanding activity (TOF > 12.000 1/h). [3]

IV. Significance of the scientific results

The primary aim of my PhD research is the synthesis of simple, chiral phosphine-amine-type ligands with alkane-diyl-based skeleton and their catalytic application in palladium-

catalyzed asymmetric substitution reactions. As a unique feature, the ligands contain a stereolabile nitrogen atom that enables the N-coordination to the transition metal in a stereoselective manner. It is noteworthy, that in the case of certain nitrogen substituents the coordination occurred stereoselectively resulting in the formation of a single isomer. This phenomenon explains the high enantioselectivities achieved in the catalytic reactions and underlines the significance of the stereoselective coordination as a useful strategy in successful chiral ligand design. Our ligands can be used in the asymmetric allylic substitution reactions of various 1,3-diaryl-allyl- and cycloalkenyl-acetate-type substrates with C-nucleophiles (e.g. malonates, β-diketones). The products of the catalytic reactions can be optically pure chiral building blocks of potentially biologically active compounds (e.g. pharmaceuticals, herbicides and perfume components). In addition, the scientific knowledge gained during the research can provide an excellent basis for the development of further high-performance chiral catalytic systems.

V. Scientific publications, presentations and posters

Publications serving as the basis of the dissertation

1. **Zsófia Császár**, Gergely Farkas, Attila Bényei, György Lendvay, Imre Tóth, József Bakos
   Stereoselective coordination: a six-membered P,N-chelate tailored for asymmetric allylic alkylation
   Dalton Transactions, **2015**, *44*, 16352-16360.

   IF: 4.177

2. Gergely Farkas, **Zsófia Császár**, Kristóf Stágel, Evelin Nemes, Szabolcs Balogh, Imre Tóth, Attila Bényei, György Lendvay, József Bakos
   Efficient stereochemical communication in phosphine-amine palladium-complexes: exploration of N-substituent effects in coordination chemistry and catalysis
   Journal of Organometallic Chemistry, **2017**, *846*, 129-140.

   IF: 1.978

3. **Zsófia Császár**, Patrik Imre, Szabolcs Balogh, Attila Bényei, Gergely Farkas, József Bakos
   Aminoalkyl-phosphine (P,N) ligands with pentane-2,4-diyl backbone in asymmetric allylic substitution reactions
   Monatshefte für Chemie - Chemical Monthly, **2017**, *148*, 2069-2077.

   IF: 1.323

4. **Zsófia Császár**, Kristóf Stágel, Szabolcs Balogh, Attila Bényei, György Lendvay, Gergely Farkas, József Bakos
   Steric effects enforce double stereoselective N-coordination in twelve-membered binuclear palladium(II)-complexes containing chiral bridging aminoalkyl-phosphine ligands
   Journal of Organometallic Chemistry, **2018**, *855*, 59-62.
   IF: 2.091

Presentations and posters serving as the basis of the dissertation

5. Gergely Farkas, **Zsófia Császár**, Attila Bényei, György Lendvay, Imre Tóth, József Bakos
   Stereoselective coordination as a promising strategy in effective catalyst design
   3rd International Symposium on the Soai Reaction and Related Topic, Felsőmocsolád, 2-5 September 2015

6. **Zsófia Császár**, Gergely Farkas, József Bakos
   Sztereogén nitrogénatommal rendelkező foszfin-amin ligandumok koordinációs és katalitikus tulajdonságainak vizsgálata
   XXXVIII. Kémiai Előadói Napok, Szeged, 26-28 October 2015

7. Gergely Farkas, Imre Tóth, **Zsófia Császár**, Kristóf Stágel, Attila Bényei, György Lendvay, József Bakos
   N-Substituent Effects of Chiral Pentane-2,4-diyl Based P,N Ligands on the Coordination Chemistry and Enantioselectivity in Palladium-Catalyzed Asymmetric Allylic Alkylations
   XX. International Symposium on Homogeneous Catalysis, Kyoto, Japan, 10-15 July 2016

8. **Zsófia Császár**, Gergely Farkas, Attila Bényei, György Lendvay, Imre Tóth, József Bakos
   Aminoalkyl-phosphine ligands with stereogenic nitrogen donor atom: synthesis, coordination chemistry and application in catalysis
   XXXIX. Kémiai Előadói Napok, Szeged, 17-19 October 2016

9. **Zsófia Császár**, Kristóf Stágel, Evelin Nemes, Szabolcs Balogh, Imre Tóth, Attila Bényei, György Lendvay, Gergely Farkas, József Bakos
   Structure elucidation of Pd complexes of P,N heterobidentate ligands bearing 2,4-pentanediyl backbone
   Magnetic Moments in Central Europe, Budapest, 8-12 March 2017

10. **Zsófia Császár**, Gergely Farkas, Kristóf Stágel, Szabolcs Balogh, Imre Tóth, Attila Bényei, György Lendvay, József Bakos
    N-Substituent effects in transition metal phosphine-amine complexes
    EuCheMS International Organometallic Conference XXII, Netherlands, Amsterdam, 9-13 July 2017

11. Gergely Farkas, **Zsófia Császár**, László Szi-Ferenc, Máté Miklós Major, Szabolcs Balogh, József Bakos
    Versatile aminoalkyl-phosphine ligands: synthesis, coordination chemistry and catalytic application
    22nd International Conference on Phosphorus Chemistry, Budapest, 8-13 July 2018

12. **Zsófia Császár**, László Szi-Ferenc, Gergely Farkas, József Bakos
    CH_2-Linkage effects in P-N and PN-P ligand systems
    22nd International Conference on Phosphorus Chemistry, Budapest, 8-13 July 2018

Publications related to the topic of the dissertation

13. Gergely Farkas, **Zsófia Császár**, Szabolcs Balogh, Imre Tóth, József Bakos
    Synthesis of hemilabile P,N ligands with pentane-2,4-diyl backbone
    Tetrahedron Letters, **2014**, *55*, 4120-4122.
    IF: 2.391

14. László Szi-Ferenc, **Zsófia Császár**, György Lendvay, Attila Bényei, Szabolcs Balogh, Balázs Nánási, Gergely Farkas, József Bakos
    Synthesis of zwitterionic phosphapalladacycles: unusual reactivity pattern of six-membered P,N-chelates
    Organometallics, **2018**, *37*, 2203-2206.
    IF: 4.051

15. László Szi-Ferenc, **Zsófia Császár**, Attila Bényei, József Bakos, Gergely Farkas
    Application of zwitterionic phosphapalladacycles in aqueous phase Suzuki-Miyaura coupling
    Phosphorus, Sulfur, and Silicon and the Related Elements, **2019**, *194*, 569-570.
    IF: 0.674

16. Máté Miklós Major, **Zsófia Császár**, Attila Bényei, Szabolcs Balogh, József Bakos, Gergely Farkas
    Backbone effects in the synthesis, coordination chemistry and catalytic properties of new chiral heterobidentate ligands with P,N and S,N donor sets
    Journal of Organometallic Chemistry, **2020**, *921*, 121332.

    IF: 2.304

17. **Zsófia Császár**, Máté Miklós Major, József Bakos, Gergely Farkas
    Variációk négy donoratomra (P, N, S, O): a ligandum szerkezetének finomhangolása nagy hatékonyságú katalizátorok előállítására
    Magyar Kémiai Folyóirat, **2021**, *127*, 137-143.

Publications not related to the topic of the dissertation

18. Gergely Farkas, **Zsófia Császár**, Szabolcs Balogh, Áron Szöllősy, Gouygou Maryse, József Bakos
    Phosphine-phosphite ligands in the palladium-catalyzed asymmetric allylic alkylation: Electronic and steric effects
    Catalysis Communications, **2013**, *36*, 94-97.

    IF: 3.32

19. Gergely Farkas, **Zsófia Császár**, Szabolcs Balogh, József Madarász, József Bakos
    A ligandum szerkezetének finomhangolása: út a nagy aktivitású és enantioszelektivitású katalizátorokhoz
    Magyar Kémikusok Lapja, **2014**, *6*, 182-183.

20. **Zsófia Császár**, József Bakos, Gergely Farkas
    Sulfonated phosphine ligands in the ruthenium catalyzed biphasic hydrogenation of unsaturated hydrocarbons
    Catalysis Letters, **2020**, *150*, 2529-2536.

    IF: 2.482

21. **Zsófia Császár**, Eszter Zsófia Szabó, Attila Bényei, József Bakos, Gergely Farkas
    Chelate ring size effects of Ir(P,N,N) complexes: Chemoselectivity switch in the asymmetric hydrogenation of α,β-unsaturated ketones
    Catalysis Communications, **2020**, *146*, 106128.

    IF: 3.626

22. **Zsófia Császár**, Tatjána Juzsakova, Miklós Jakab, Szabolcs Balogh, Ágnes Szegedi, Hanna Solt, Jenő Hancsók, József Bakos, Gergely Farkas
Continuous flow Friedel-Crafts alkylation catalyzed by silica supported phosphotungstic acid: an environmentally benign process
Topics in Catalysis, **2021**, https://doi.org/10.1007/s11244-021-01497-y
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23. **Zsófia Császár**, Regina Kovács, Máté Fonyó, József Simon, Attila Bényei, József Bakos, Gergely Farkas
Testing the role of the backbone length using bidentate and tridentate ligands in manganese-catalyzed asymmetric hydrogenation
Molecular Catalysis, **2022**, *529*, 112531.
IF: 5.089

24. **Zsófia Császár**, Mária Guóth, Evelin Farsang, Attila Bényei, József Bakos, Gergely Farkas
Hydrogen bond-directed coordination of phosphine-amino-alcohol (P,N,OH) ligands: stereochemical considerations and catalytic studies
Inorganica Chimica Acta, **2022**, *543*, 121153.
IF: 3.118

25. Gergely Farkas, **Zsófia Császár**, Evelin Tóth-Farsang, Attila Bényei, József Bakos
Application of alkane-diyl based chiral phosphine-aminophosphine (P-NP) and thioether-aminophosphine (S-NP) ligands in Rh-catalyzed asymmetric hydrogenation
Journal of Organometallic Chemistry, **2023**, *994*, 122723.
IF: 2.345

26. **Zsófia Császár**, Zsanett Eszter Pőrgye, Evelin Tóth-Farsang, Margit Kovács, Attila Bényei, József Bakos, Gergely Farkas
Ruthenium complexes of new chiral phosphine-amine-ether ligands (Ru-PNO) for asymmetric hydrogenation – the role of backbone chirality in pincer ligand design
Applied Organometallic Chemistry, **2024**, *38*, e7379.
IF: 3.773