Final research report on OTKA K128074

"Catalytic application of heterodonor ligands towards sustainable chemistry"

The modern transition metal complex catalysis is one of the most effective and environmentally friendly methods for the synthesis of organic compounds. The combination of characteristics like high activity and broad tolerance for a number of substrates, substituents and solvents is the basis for the application of such catalysts in organic synthesis. The prediction of the activity and selectivity available by a novel asymmetric transition-metal catalyst still remains a research target. To generate predictive power, it is crucial to shed light on the fundamental interactions that determine catalytic performance. Besides the electronic features, the steric interactions are also widely implicated in effective asymmetric induction. Based on these considerations novel bi- and tridentate heterodonor ligands were synthesized and applied in transition metal catalyzed homogeneous catalytic processes as the main objective of the project. The fine tuning of the ligands' structure enabled the development of highly active and selective catalytic systems as useful tools towards sustainable chemistry.[1]

During the research in the present project the laboratory experiments slightly shifted compared to their scheduled time given in the original research plan. This delay was a consequence of the worldwide pandemic. Similarly, less intense conference appearances can be attributed to Covid-19. As a result, several planned studies could not be performed during the timeframe of the project (eg. the application of ruthenium-catalysts in hydrogenation reactions). These experiments are currently performed and the scientific results will be published in a due course.

1. Synthesis and application of novel catalysts containing bidentate heterodonor ligands

Novel alkane-diyl based heterobidentate P,N (**L1**-**L3**) and S,N (**L4**-**L9**) ligands capable of forming five- and seven-membered chelate rings have been prepared starting from cyclic sulfate esters (**1a** and **c**) or naturally occurring chiral compounds (Figure 1).[2] The S,N type ligands having thioether and secondary amino functionalities represent a particularly important class of compounds due to their unique stereoelectronic features. The electronic heterogeneity of the N- and S-atom and the possibility of the stereoselective coordination for both donor types ensure extremely rich coordinating abilities as well as exceptional catalytic properties.

Furthermore, their synthesis and handling is much simpler then those of phosphines or phosphites, as S,N systems are not sensitive towards oxidation or hydrolysis. The length of the ligands' backbone and the reaction conditions applied strongly affected the stereochemical outcome of the synthesis when using cyclic sulfates as starting materials (Figure 1).

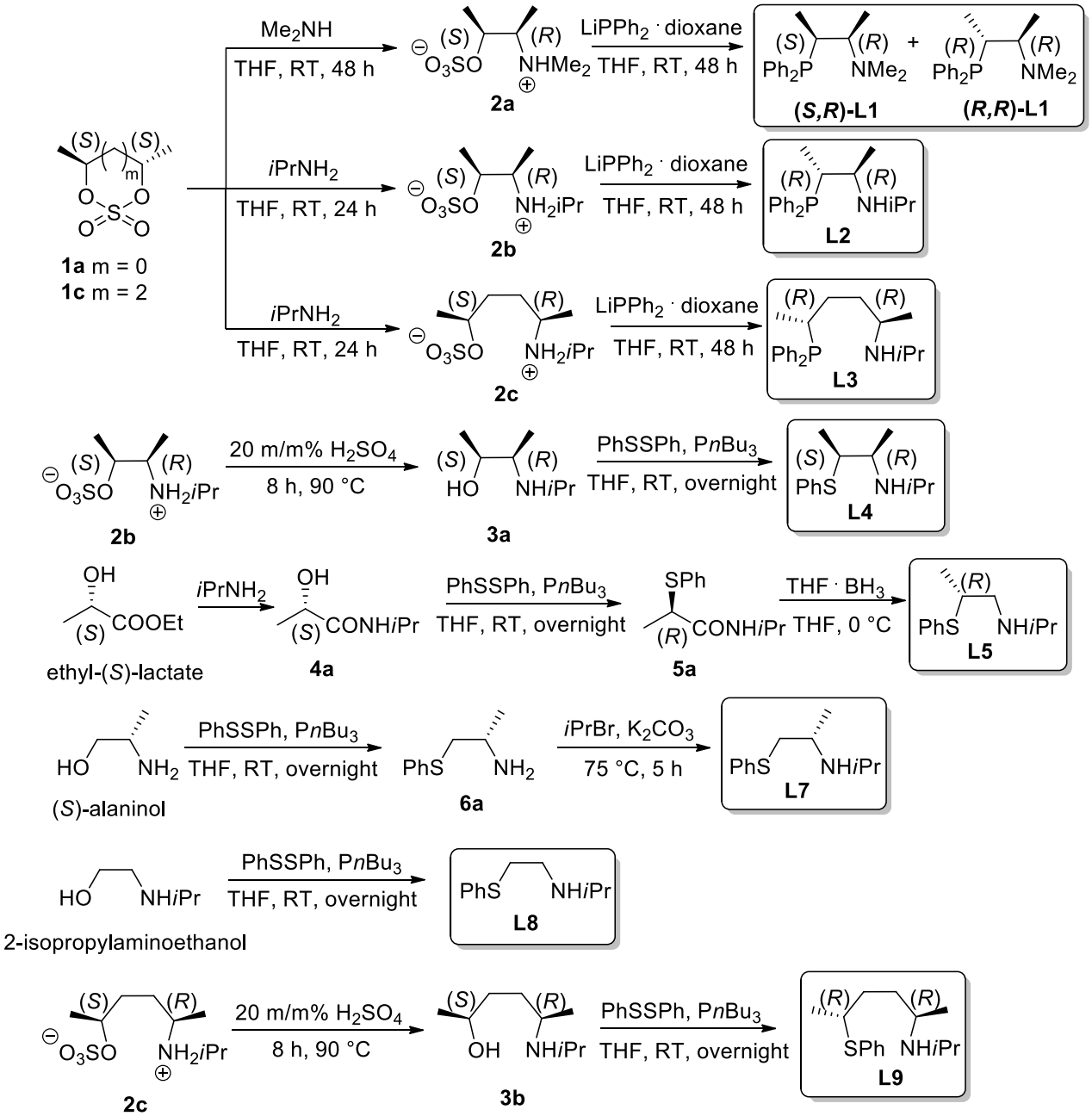


Figure 1 Synthesis of P,N and S,N type bidentate ligands **L1-L9**

Palladium(II)-complexes of the new ligands were characterized by 1D and 2D NMR spectroscopy in solution and in several cases by X-ray crystallography in the solid phase. The structural versatility of the ligands enabled the straightforward comparison of the

stereoselectivity of their coordination as a function of their tether length, backbone substitution pattern, donor sets (S,N vs. P,N) and relative carbon atom configuration in their backbone. The catalytic features of the novel compounds were investigated in asymmetric allylic alkylation of 1,3-diphenylallyl-2-acetate (**S1**) with dimethyl malonate as a model reaction where the tether length of the ligand proved to be a crucial factor in determining the enantioselectivity (Figure 2).

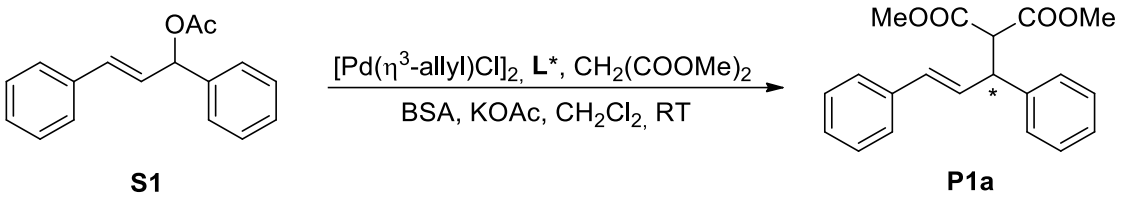


Figure 2. Asymmetric allylic alkylation of 1,3-diphenylallyl-2-acetate with dimethyl malonate

Our synthetic protocol starting from cyclic sulfate esters enabled the synthesis of phosphine-aminoalcohol type chiral ligands (**L10**-**12**) have been synthesized in two simple steps using cyclic sulfates ((*S*,*S*)- and (*R*,*R*)-**1b**) (Figure 3).[3] The coordination behavior of **L10**-**12** having stereochemically labile nitrogen donor to the square planar Pd(II) center was investigated by X-ray crystallography, 1D and 2D NMR methods and by DFT calculations. In the solid state of complex [Pd(**L10**)Cl_2] an intramolecular hydrogen bond could be observed between the OH-moiety and one of the Cl co-ligands, while intermolecular hydrogen bonds were detected in the case of [Pd(**L11**)Cl_2] between the same functionalities. In the dichloromethane solution of the complexes the hydrogen bond was identified as a crucial factor in determining ring conformation and nitrogen configuration. Ligand **L10** coordinated stereoselectively to the metal in [Pd(**L10**)Cl_2] leading to a complex having a single conformationally rigid six-membered chelate and a configurationally fixed N-donor. In contrast, coordination of ligands **L11** and **L12** resulted in the formation of a mixture of isomers with different chelate conformation and nitrogen configuration. The ligands were utilized in Pd-catalyzed asymmetric allylic alkylation where high enantioselectivities (ees up to 96%) and activities could be obtained (Figure 2).

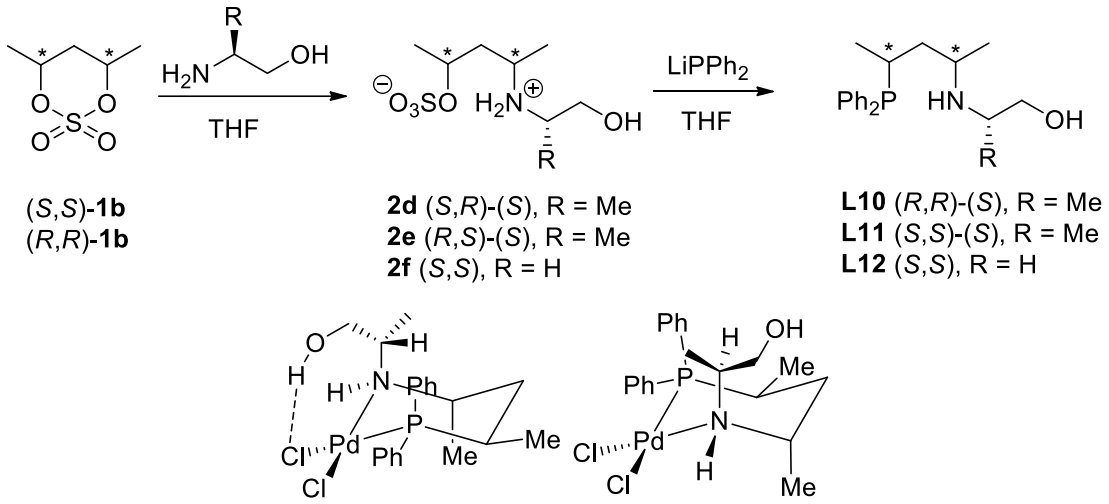


Figure 3. Synthesis (top) and coordination chemistry (bottom left: **L10**, bottom right: **L11**) of chiral phosphine-aminoalcohol ligands

We have synthesized new thioether-phosphite type ligands (**L13-15**) possessing axially chiral biaryl moiety (Figure 4).[4] The [Rh(COD)(**L13-15**)]BF_4 type complexes of the ligands (where COD = (*Z*,*Z*)-cycloocta-1,5-diene) provided a good opportunity to investigate the stereo-directing effect of the biaryl unit, the electronic properties of the ligands as well as the dynamic processes of the compounds in solution. Based on our NMR studies it can be assumed that the exocyclic terminal biaryl moiety is able to efficiently control the stereoselective coordination of the stereogenic sulfur atom. The mechanism of a dynamic process, i.e. the selective exchange of olefinic protons in the coordinated COD ligand, has been substantiated by the comparison of the thioether-phosphite complexes to their phosphine-phosphite analogues. It has been found that the selective exchange occurs via three-coordinate T-shaped intermediates formed by the dissociation of the Rh-S bond. In situ NMR studies and catalytic experiments provided firm evidence that thioether-phosphites and phosphine-phosphites have very distinct coordination properties at higher than 1:1 ligand-to-metal molar ratio. In the latter case the formation of *bis*-chelate species can be observed, while in the case of thioether-phosphites *bis*-monodentate coordination is preferred due to the hemilability of the P,S ligand. The Rh-complexes were applied in the asymmetric hydrogenation of dehydroaminoacid and itaconic acid esters.

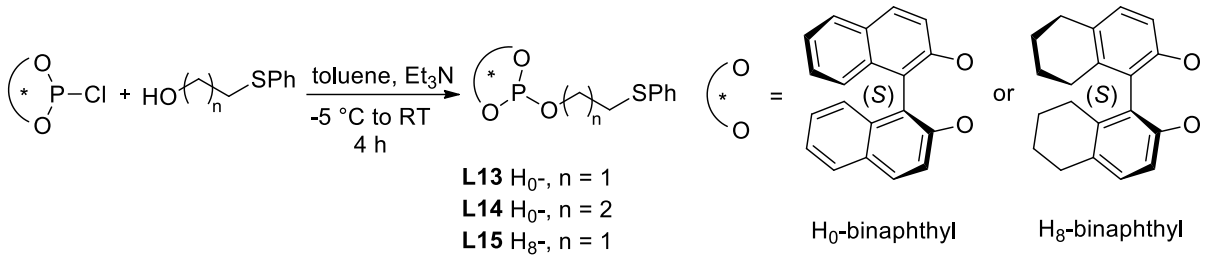


Figure 4. Synthesis of axially chiral thioether-phosphite ligands

Six novel alkane-diyl based thioether-aminophosphine type chiral ligands (**L16-21**) with have been synthesized (Figure 5).[5] The ligands were synthesized in the simple coupling of the corresponding thioether-amines and chlorophosphines. The thioether-amines were synthesized starting from cyclic sulfate esters (precursors of **L17-21**) or form naturally occurring chiral compounds (**L5**, Figure 1). The modular structure of the ligands and the new methodologies developed for their preparation enabled the systematic variation of their tether length, the substitution pattern of the backbone as well as the P-, N- and S-substituents. The ligands proved to be highly effective in Pd-catalyzed asymmetric allylic etherification reactions providing the products in high yields (up to 95%) and with good enantioselectivities (up to 86%) using unprecedentedly low (0.2 mol%) loadings of the chiral Pd-catalyst (Figure 6).

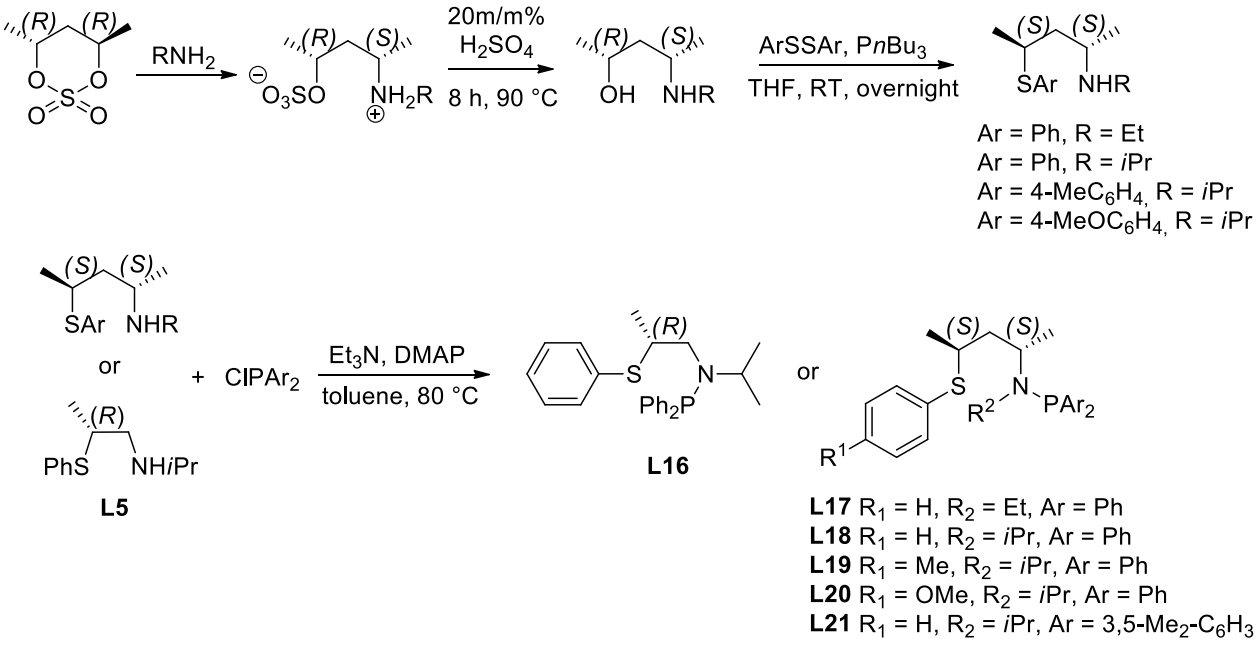
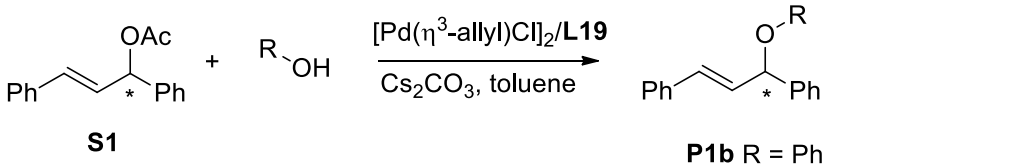


Figure 5. Synthesis of thioether-aminophosphine type chiral ligands **L16-21**

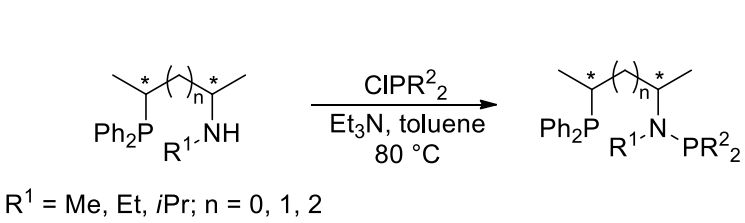
Based on these findings, a new scalable protocol has been developed for the preparation of chiral allylic ethers (eg. **P1b-l**). Furthermore, the Pd(II) coordination chemistry of the ligands was thoroughly investigated by 1D and 2D NMR methods as well as by X-ray crystallography with special attention to the conformation of the chelate ring and the stereoselectivity of the sulfur coordination. Based on these studies, the main factors determining activity and selectivity of the catalytic system have been identified.



P1b R = Ph
P1c R = p-$MeOC_6H_4$
P1d R = p-ClC_6H_4
P1e R = p-BrC_6H_4
P1f R = p-$CF_3C_6H_4$
P1g R = 2-picolyl
P1h R = 2-thiophenylmethyl
P1i R = 2-furfuryl
P1j R = allyl
P1k R = Et
P1l R = Me

Figure 6. Pd-catalyzed symmetric allylic etherification using thioether-aminophosphine type chiral ligand

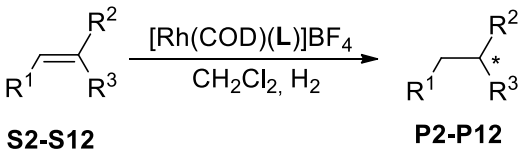
A highly modular synthetic approach suitable for the preparation of phosphine-aminophosphine ligands (**L22-L27**) has been developed (Figure 7).[6] The new ligands were prepared in the reaction of an aminophosphine type compounds with the corresponding chlorophosphine and the yield of the reaction proved to be strongly dependent on the steric congestion around the secondary amine functionality. The coordination chemistry of the ligands was studied by the NMR and IR analysis of their [Rh(COD)(**L**)]BF_4 and [$Rh(CO)_2$(**L**)]BF_4 type complexes, respectively. It has been observed that the size of the chelate ring (6- vs. 7-membered) and the N-substituent do not significantly influence the electronic properties of the metal. Furthermore, the N-substituent seems to have no effect on the ring conformation either, that is assumed to be determined primarily by the planar arrangement of the homochiral pentane-2,4-backbone.



L22 (*S,S*), R^1 = Me, R^2 = Ph, n = 1
L23 (*S,S*), R^1 = Et, R^2 = Ph, n = 1
L24 (*S,S*), R^1 = *i*Pr, R^2 = Ph, n = 1
L25 (*S,S*), R^1 = Me, R^2 = Cy, n = 1
L26 (*R,R*), R^1 = *i*Pr, R^2 = Ph, n = 0
L27 (*R,R*), R^1 = *i*Pr, R^2 = Ph, n = 2

Figure 7. Synthesis of phosphine-aminophosphine type chiral ligands

The novel Rh-complexes were tested in the asymmetric hydrogenation of a broad range of prochiral substrates including dimethyl itaconate (**S2**), dehydroaminoacid derivatives (**S3-6**) and α,β-unsaturated enol ester phosphonates (**S7-12**) (Figure 8). For substituted acetamidocinnamic acid esters ee's up to 98% could be obtained by using pentane-2,4-diyl based systems to produce valuable chiral building blocks (**P2-P12**). In the case of phosphonate esters containing a sterically more demanding tetrahedral P(V) moiety catalysts with less bulky N-substituents provided outstanding enantioselectivities (up to 97%).



S2 R^1 = H; R^2 = CH_2COOMe; R^3 = COOMe
S3 R^1 = Ph; R^2 = COOMe; R^3 = NHCOMe
S4 R^1 = H; R^2 = COOMe; R^3 = NHCOMe
S5 R^1 = 4-MeO-C_6H_4; R^2 = COOMe; R^3 = NHCOMe
S6 R^1 = 2-MeO-C_6H_4; R^2 = COOMe; R^3 = NHCOMe
S7 R^1 = H; R^2 = $P(O)(OMe)_2$; R^3 = OBz
S8 R^1 = Et; R^2 = $P(O)(OMe)_2$; R^3 = OBz
S9 R^1 = *n*Bu; R^2 = $P(O)(OMe)_2$; R^3 = OBz
S10 R^1 = *i*Pr; R^2 = $P(O)(OMe)_2$; R^3 = OBz
S11 R^1 = Ph; R^2 = $P(O)(OMe)_2$; R^3 = OBz
S12 R^1 = 4-MeO-C_6H_4; R^2 = $P(O)(OMe)_2$; R^3 = OBz

Figure 8. Asymmetric hydrogenation of the C=C double bond in several prochiral substrates

We have synthesized novel six-membered zwitterionic palladacycles with formal negative charge on the metal center and positive charge on the chiral ligand in the unprecedented reaction of [Pd(COD)Cl_2] and the corresponding P,N ligand in the presence of 1 molar equivalent of benzoquinone. The novel zwitterionic complexes were tested in aqueous phase asymmetric Suzuki-Miyaura coupling (Figure 9). The novel catalysts provided good activity, but no enantioselectivity in the reaction of 1-iodo-2-methoxynaphthalene and 1-naphthylboronic acid. In the next set of experiments the utilization of P,N ligated Pd-complexes is planned to be utilized and non-aqueous solvents are planned to be applied.

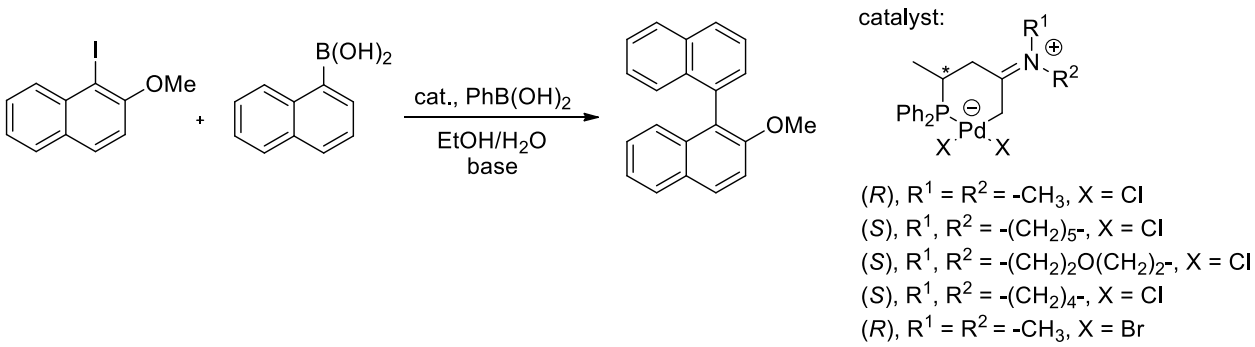


Figure 9. Aqueous-phase asymmetric Suzuki-Miyaura coupling catalyzed by zwitterionic phosphapalladacycles

The synthesis of covalently anchored chiral P,N ligands according to Figure 10 was originally proposed. The ring opening of the cyclic sulfate by the amino functionalities of the corresponding resin (JandaJel-NH_2) could successfully be accomplished according to solid phase NMR spectra. However, in the next step the reaction with $LiPPh_2$ could not be realized in different solvents and at different temperatures. The phosphide is assumed to react with other functions of the support. Later, according to another immobilization strategy, the P,N ligand with secondary and primary amino functionality was used as nucleophile to the ring opening of the oxirane rings of the solid support Eupergit-C©. Unfortunately, the ring opening provided a very complex mixture of products due to the fact the phosphine also took part in the ring opening as a nucleophile. Our further efforts to covalently anchor chiral ligands to solid support failed.

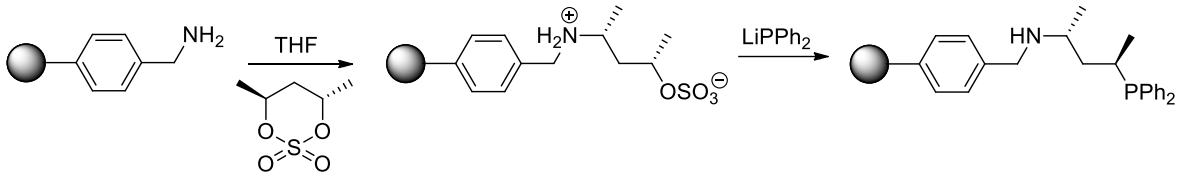


Figure 10. Proposed reaction route leading to covalently anchored P,N ligands

2. Synthesis and application of novel catalysts containing chiral tridentate ligands

A novel, highly modular approach has been developed for the synthesis of new chiral P,N,N ligands **L28-L33** starting from the corresponding sulfate esters **1a-b** (Figure 11).[7] The reaction occurs smoothly with complete inversion at the stereogenic centers trough aminoalkyl-sulfates, as intermediates. This two-step reaction sequence is a nice example for the extension of the synthetic strategy starting from cyclic sulfates to the preparation of tridentate ligands.

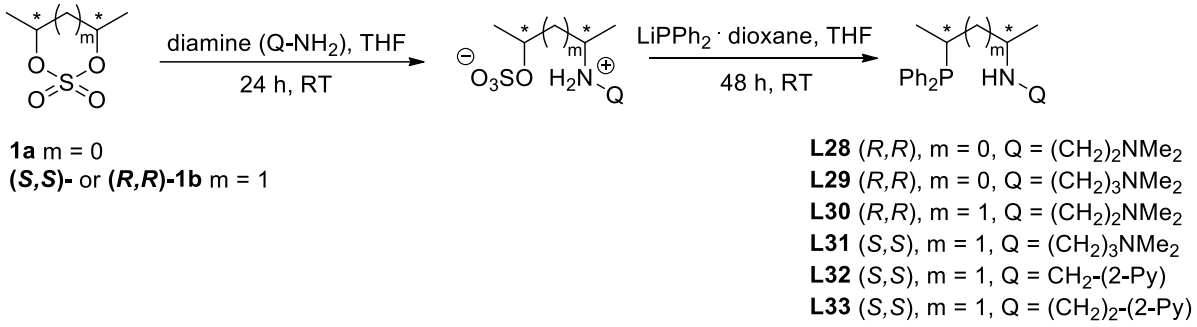


Figure 11. Synthesis of chiral tridentate P,N,N ligands

The novel ligands **L28-L33** were utilized in the iridium-catalyzed chemo- and enantioselective hydrogenation of α,β-unsaturated ketones **S13-19** (Figure 12). The systematic variation of their P-N and N-N backbone led to the conclusion that the activity, chemo- and enantioselectivity in the hydrogenation reactions is highly dependent on the combination of the two bridge lengths. It has been found that a minor change in the ligand's structure, i.e. varying the value of *m* from 1 to 0 (ligand **L31** vs. **L29**, respectively), can switch the chemoselectivity of the reaction, from 80% C=O to 97% C=C selectivity in the case of (*E*)-chalcone as substrate. Additionally, by using ligand **L31** the product allylic alcohols could be obtained with enantioselectivities up to 96%.

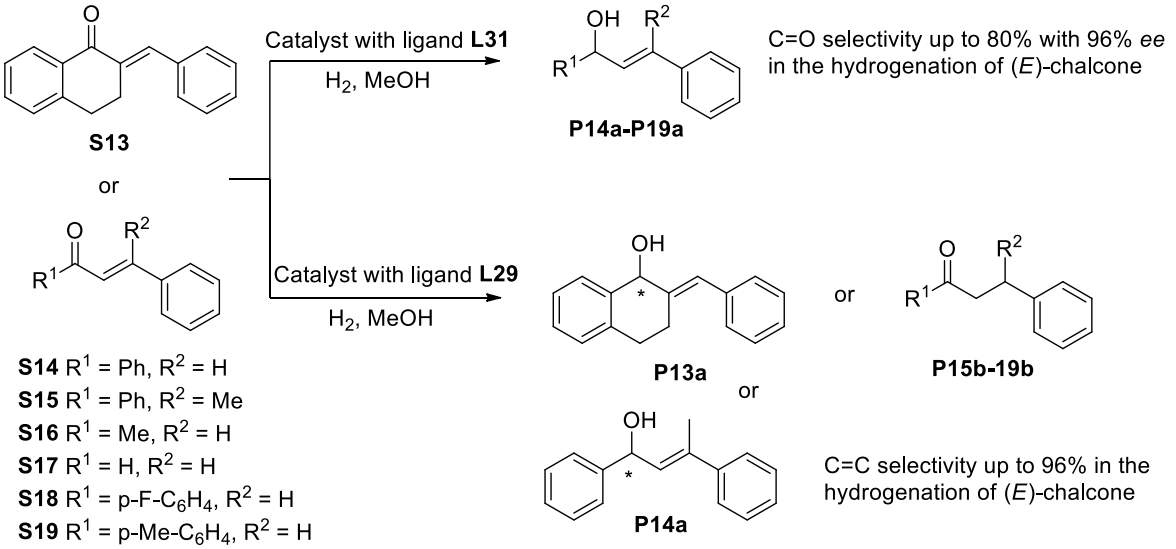


Figure 12. Chemo- and enantioselective hydrogenation of α,β-unsaturated ketones (products from the „**a**" series are formed by C=O hydrogenation, products from the „**b**" series are formed by the saturation of the C=C bond)

Manganese complexes modified by simple alkane-diyl based, potentially tridentate P,N,N (**L28-31**) and bidentate P,N ligands (**L34** and **L35**) have been synthesized and tested in the asymmetric hydrogenation of ketones (Figure 13).[8] It has been demonstrated that only tridentate ligands capable of forming five-membered N-N chelates coordinate in a tridentate fashion. In contrast, potentially tridentate P,N,N type compounds with longer N-N tether length forms mono-chelate complexes.

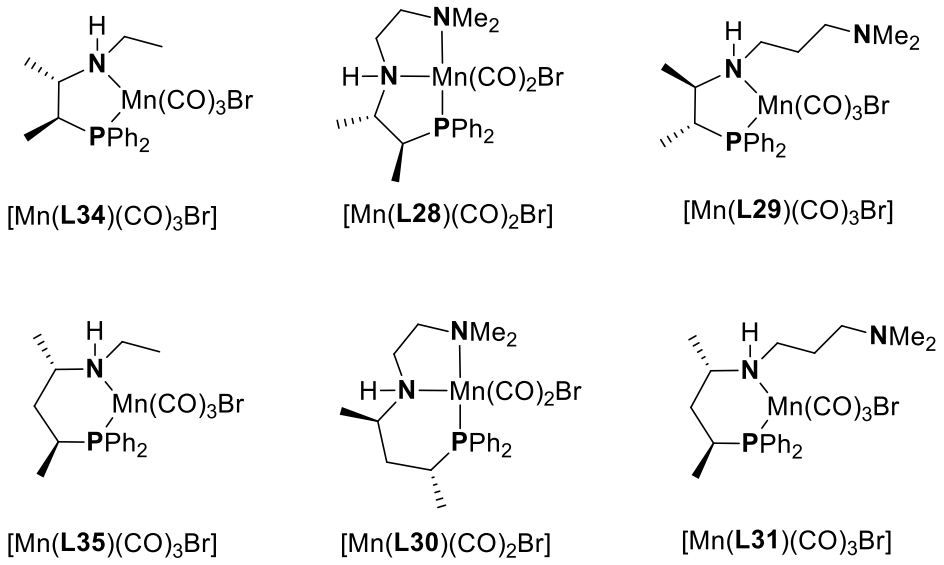
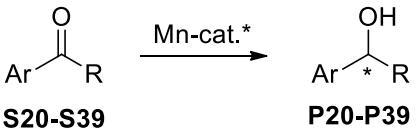


Figure 13. Manganese(I) precatalysts modified by chiral bi- and tridentate ligands

The combined coordination and catalytic studies led to the conclusion that the N-N tether length of the P,N,N type compounds plays a crucial role in determining the chemoselectivity, while the length of the P-N skeleton has been shown to affect the catalytic activity. Mn-catalysts containing P,N,N ligands with the proper tether lengths (m = 0, n = 1) provided high enantioselectivities (up to 95% *ee*) and activities (substrate/catalyst molar ratio = 300, full conversion in 20 h reaction time) in the asymmetric hydrogenation of acetophenone derivatives (Figure 14). The influence of substitution of the acetophenone substrate and the reaction conditions is demonstrated. Based on quantum chemistry calculations, a qualitative model explaining the origin of enantioselectivity is proposed.



S20-S39 **P20-P39**

S20 Ar = Ph, R = Me
S21 Ar = 2-MeO-C_6H_4, R = Me
S22 Ar = 3-MeO-C_6H_4, R = Me
S23 Ar = 4-MeO-C_6H_4, R = Me
S24 Ar = 2,4-$(MeO)_2$-C_6H_3, R = Me
S25 Ar = 4-CF_3-C_6H_4, R = Me
S26 Ar = 3-CF_3-C_6H_4, R = Me
S27 Ar = 3,5-$(CF_3)_2$-C_6H_3, R = Me
S28 Ar = 4-F-C_6H_4, R = Me
S29 Ar = 4-Br-C_6H_4, R = Me
S30 Ar = 4-Cl-C_6H_4, R = Me
S31 Ar = 4-I-C_6H_4, R = Me
S32 Ar = 4-CH_3-C_6H_4, R = Me
S33 Ar = 2,4-Me_2-C_6H_3, R = Me
S34 Ar = 4-*i*Bu-C_6H_4, R = Me
S35 Ar = 1-Npth, R = Me
S36 Ar = 2-Npth, R = Me
S37 Ar = Ph, R = Et
S38 Ar = Ph, R = *n*Pr
S39 Ar = Ph, R = CHCHPh

Figure 14. Asymmetric hydrogenation of ketones catalyzed by chiral Mn-complexes

List of journal articles based on the present project

[1] Z. Császár, M. M. Major, J. Bakos, G. Farkas, Variációk négy donoratomra (P, N, S, O): a ligandum szerkezetének finomhangolása nagy hatékonyságú katalizátorok előállítására, *Magy. Kém. F.*, **2021**, *127*, 137-143. http://doi.org/10.24100/MKF.2021.03-4.137

[2] M. M. Major, Z. Császár, A C. Bényei, S. Balogh, J. Bakos, G. Farkas, Backbone effects in the synthesis, coordination chemistry and catalytic properties of new chiral heterobidentate ligands with P,N and S,N donor sets, *J. Organomet. Chem.*, **2020**, *921*, 121332. https://doi.org/10.1016/j.jorganchem.2020.121332

[3] Z. Császár, M. Guóth, E. Farsang, A. C. Bényei, J. Bakos, G. Farkas, Hydrogen bond-directed coordination phosphine-amino-alcohol (P,N,OH) ligands: Stereochemical considerations and catalytic studies, *Inorg. Chim. Acta*, **2022**, *543*, 121153. https://doi.org/10.1016/j.ica.2022.121153

[4] M. M. Major, S. Balogh, J. Simon, J. Bakos, G. Farkas, New chiral thioether-phosphite ligands and their rhodium-coordination chemistry: steric and electronic properties, dynamic processes and application in catalysis, *J. Coord. Chem.*, **2021**, *74*, 1311-1322. https://doi.org/10.1080/00958972.2021.1892086

[5] M. M. Major, M. Guóth, S. Balogh, J. Simon, A. C. Bényei, J. Bakos, G. Farkas, Novel Pd (PN, S)-complexes: Highly active catalysts designed for asymmetric allylic etherification, Mol. Catal., 2021, 512, 111763. https://doi.org/10.1016/j.mcat.2021.111763

[6] G. Farkas, Z. Császár, E. Tóth-Farsang, A. C. Bényei, J. Bakos, Application of alkane-diyl based chiral phosphine-aminophosphine (P-NP) and thioether-aminophosphine (S-NP) ligands in Rh-catalyzed asymmetric hydrogenation, *J. Organomet. Chem.*, **2023**, the paper is accepted with minor revision, submitted to the journal.

[7] Z. Császár, E. Z. Szabó, A. C. Bényei, J. Bakos, G. Farkas, Chelate ring size effects of Ir (P, N, N) complexes: Chemoselectivity switch in the asymmetric hydrogenation of α, β-unsaturated ketones, *Catal. Commun.*, **2020**, *146*, 106128. https://doi.org/10.1016/j.catcom.2020.106128

[8] Z. Császár, R. Kovács, M. Fonyó, J. Simon, A. C. Bényei, G. Lendvay, J. Bakos, G. Farkas, Testing the role of the backbone length using bidentate and tridentate ligands in manganese-catalyzed asymmetric hydrogenation, *Mol. Catal.*, **2022**, *529*, 112531. https://doi.org/10.1016/j.mcat.2022.112531

List of conference appearances based on the project

Major, M. M., Rövid, G., Bakos, J., Farkas, G.: Királis ligandumok szintézise optikailag aktív, természetes vegyületek felhasználásával, XLI. Kémiai Előadói Napok, Szeged, Book of Abstracts p. 145-146., 2018

Major, M. M., Rövid, G., Lendvay, G., Bényei, A., Bakos, J., Farkas, G.: Királis tioéter-amin ligandumok szintézise és katalitikus tulajdonságainak vizsgálata, XXIV. Nemzetközi Vegyészkonferencia, Szovátafürdő, Románia, p. 35., 2018

Farkas, G., Császár, Z., Bényei, A., Lendvay, G., Bakos, J.: Palladium- and ruthenium-complexes of chiral tridentate P,N,O-ligands and their application in catalysis, 5th EuChemS Inorganic Chemistry Conference, Moscow, Book of Abstracts, p. 221., 2019

Major, M. M.,Rövid, G., Lendvay, G., Balogh, S., Bényei, A., Bakos, J., Farkas G.: Királis, kéntartalmú heterodonor ligandumok szintézise, koordinációs és katalitikus tulajdonságai, 53. Komplexkémiai Kollokvium, Velence, Book of Abstracts, E-15., 2019

Major, M. M., Guóth, M., Balogh, S., Bényei, A., Bakos, J., Farkas, G.: Királis kéntartalmú katalizátorok fejlesztése, Pannon Egyetem, Mérnöki Kari Tudományos Konferencia, Veszprém, 2020

Major, M. M., Kovács, R., Guóth, M., Balogh, S., Bényei, A., Bakos, J., Farkas, G.: Új háromfogú kéntartalmú ligandumok szintézise és alkalmazása ruténium-katalizált hidrogénezési reakciókban, XXVI. Nemzetközi Vegyészkonferencia, 2020

PhD dissertation based on the present project

Major, M. M.: Királis tioéterek szintézise és katalitikus tulajdonságainak vizsgálata, PhD értekezés, 2022

BSc and MSc thesis related to the project

Svélecz Richárd: Királis háromfogú ligandumok előállítása és katalitikus alkalmazása, 2018, Eredménye: Közepes (Supervisors: Bakos József, Farkas Gergely) (BSc thesis)

Szabó Eszter Zsófia: Királis háromfogú ligandumok alkalmazása α,β-telítetlen ketonok aszimmetrikus hidrogénezési reakciójában, 2020, Eredménye: Jeles (Supervisors: Császár Zsófia, Farkas Gergely) (BSc thesis)

Guóth Mária: Tioéter-aminofoszfin ligandumok alkalmazása allil-éterek palládium-katalizált enantioszelektív szintézisében, 2022 (Supervisors: Major Máté Miklós, Farkas Gergely) (BSc thesis)

Kovács Regina: Prokirális ketonok mangán-katalizált aszimmetrikus hidrogénezése, 2022 (Supervisors: Császár Zsófia, Farkas Gergely) (MSc thesis)

Pőrgye Zsanett Eszter: Királis háromfogú ligandumok alkalmazása ketonok aszimmetrikus hidrogénezési reakciójában, védés várható időpontja: 2023 (Supervisors: Császár Zsófia, Farkas Gergely) (BSc thesis)