Final report on the results of the project (OTKA 113177)

Principal investigator: L. Kollár

(University of Pécs)

As it was described in the submitted proposal, the main objective of the research carried out in the past 5 years was the *investigation some of the factors determining enantioselectivity* in various carbonylation reactions (e.g., hydroformylation, aminocarbonylation).

Two main aims of the research proposal were declared.

A) To get a deeper insight into the structure of transition metal-complexes (primarily platinum, palladium complexes) showing carbonylation activities, detailed coordination chemistry studies by analytical and possibly, by computational means.

B) The catalytic and mechanistic details of two carbonylation reactions, such as platinum-catalysed hydroformylation and palladium-catalysed aminocarbonylation (alkoxy/aryloxycarbonylation), were planned.

In addition to the above described plans, several further closely related topics have been investigated by the financial support of the project. For instance, various types of enantioselective and 'normal' carbonylations were studied, carbonylative functionalization of several basic skeletons was investigated focusing on structure-reactivity and structure-selectivity relations.

In accordance with the interim reports submitted yearly, the report is divided into three subchapters A) coordination chemistry, model reactions; B) computational studies, mechanistic details; C) Carbonylations of synthetic importance).

A) Coordination chemistry studies, catalytic investigations with model substrates

A1)

Novel chiral phospholene oxides and their reduced phospholenes were synthesised: Their corresponding Pt-complexes were tested in enantioselective hydroformylation [1]. Similar palladium(II) complexes of 1-substituted-3-phospholene ligands were prepared and evaluated as catalysts in hydroalkoxycarbonylation.[2]

A similar strategy was used in case of a P,N,P (potentially) terdentate ligand family [3]. The coordination chemistry of platinum-diphosphine-tin(II)chloride systems as well as the 'green aspects' of enantioselective hydroformylation were investigated by using gamma-valerolactone (GVL) as environmentally benign solvent [4]. This biomass-derived solvent was also used in rhodium-catalysed asymmetric hydroformylation. Rhodium-phosphine 'in situ' catalysts proved to be highly active providing good branched regioselectivities in the hydroformylation of 4-substituted styrenes as substrates. [5]

The substituent effect on the reversal of enantioselectivity, i.e., strong dependence of enantioselectivity on temperature in the asymmetric hydroformylation of 2- and 4-substituted styrenes with $PtCl_2$[(R)-BINAP] + $SnCl_2$ 'in situ' catalyst has been investigated [6] The efficiency of a similar system under 'green conditions' was proved by hydroformylation reactions in gamma-valerolactone, a biomass-derived solvent [7] The catalyst stucture-regioseelctivity correlations were investigated in platinum-catalysed hydroformylation of styrene using platinum(II)-1-phenyl-1,2,3,6-tetrahydrophosphinine 'pre-formed' catalyst [8]. The primary products of hydroformylation were transformed to unsaturated ketones in tandem hydroformylation/aldol condensation reactions. [9]

Novel platinum(II)–monophospha-crown ether complexes were synthesized and tested in hydroformylation. Basic coordination chemistry and elementary reactions, such as tin(II) chloride insertion and addition of further phosphine ligands were investigated. [10] In cooperation with researchers of the Technical University of Budapest (P. Huszthy) the investigation of the chiral analogues of the above P-crowns is in progress.

Enantioselective hydroaryloxycarbonylation of styrene model substrates were carried out using 4-substituted phenols as *O*-nucleophiles. [11] Cyclohydroaryloxycarbonylation of 2-allylphenol derivatives using formic acid as carbon monoxide source was performed and six-membered chiral lactones in up to 50% ee were synthesised for the first time. [12]

A2)

Efforts have been made towards the palladium-catalysed aminocarbonylation of racemic BINOL-ditriflate in order to investigate the potential of kinetic resolution. Surprisingly, neither mono- nor dicarboxamide formation was observed. However, the 'opposite' reaction, that is, using axially chiral binaphthyl-based diamine (2,2'-diamino-1,1'-binaphthyl) as *N*-nucleophile in the aminocarbonylation of simple iodoaromatics and iodoalkenes resulted in the formation of the corresponding carboxamides possessing an axial element of chirality. For the first time, kinetic resolution was also observed using standard chiral diphosphines such as (*R*,*R*)-DIOP, (*S*,*S*)-BDPP, (*S*,*S*)-CHIRAPHOS, *etc*.) [13].

Diastereoselective aminocarbonylation was carried out using iodobornene (racemic and enantiomerically pure) substrate and 2,2'-diamino-1,1'-binaphthalene (BINAM) (racemic and enantiomerically pure) nucleophile in the presence of chiral diphosphines as above. All possible diastereoisomers were isolated in analytically pure form [14].

Various 4-substituted iodobenzenes were investigated in palladium-catalysed aminocarbonylation reactions with special focus on the chemoselectivity (i.e., the ratio of carboxamide and 2-ketocarboxamide product formed in simple and double carbon monoxide insertion, respectively). [15] The catalytic features of the same reaction were investigated in gamma-valerolactone as well. [16].

A3)

Regarding the electronic structure, a close analogue to carbon monoxide, *tert*-butylisocyanide, was efficiently applied in palladium-catalysed reaction in the presence of various primary and secondary amines as N-nucleophiles. The synthesis of amidines was carried out via isonitrile insertion. Although several isocyanides with various steric and electronic properties were tested, unfortunately, the reaction seems to be restricted to alkyl isocyanides, and especially to *tert*-butylisocyanide. [17] The unexpected 'communication' of four reaction centres was observed in case of tetraiodo-cavitands. Recently, the influence of base additives on the selectivity of palladium-catalysed aminocarbonylation was investigated in a highly selective functionalization of a cavitand scaffold. [18]

A4)

The reaction conditions were modified in order to get highly selective transition metal catalysts being active under 'green' conditions, *i.e.*, to carry out environmentally benign catalytic reactions. Palladium and copper catalysts immobilised on ionic liquids or ionic liquid polymer/silica hybrid material were used in double carbonylation of iodoarenes [19] and azide-alkyne cycloaddition reactions. [20]

Additionally, biomass-derived gamma-valerolactone (GVL)-based ionic liquids were used as alternative media for Ulmann-type coupling reactions. [21] As a potential surrogate of carbon monoxide, paraformaldehyde was tested in rhodium-catalysed aryloxycarbonylation of iodo-aromatics by using 4-substituted phenols as *O*-nucleophiles. [22] Palladium-catalysed carbonylations of alkyl and alkenyl halides with formic acid as carbonyl source was carried ot. In this way, α,β-unsaturated carboxylic acids and esters were synthesised. [23]

B) Mechanistic studies, computational chemistry

Efforts have been made in order to get a deeper insight into the mechanism of carbonylation reactions by means of computational chemistry. Theoretical studies on the nature of Pt-Sn bond revealed that the electron-withdrawing feature of the trichlorostannato ligand, formed in the 'carbene-like' insertion of tin(II) chloride into the Pt-Cl bond, is by far not as characteristic as previous

investigations suggested. [24] The nature of the metal-ligand interactions in complexes $M(PH_3)_2$(eta-2-L) (M=Ni, Pd, Pt; L=CO_2, COS, CS_2): was investigated. [25] This theoretical study is aimed at introducing CS as C1 building block into alkene and aryl halide substrates in standard transition metal catalysed reactions. Viable pathways for the oxidative addition of iodobenzene to palladium(0)-triphenylphosphine-carbonyl complexes were studied. [26] As a next step, the investigation of the whole catalytic cycle of palladium-catalysed aminocarbonylation is in progress. [27] Mechanistic investigations were carried out regarding the palladium-catalysed aminocarbonylation reactions with special focus on the oxidative addition step of the iodoaromatic substrate. [28]

Computational characterization of bidentate P-donor ligands, as well as direct comparison to Tolman's electronic parameters were carried out and it was found that the model compounds $RhH(CO)(L_2)$ are suitable for the description of the Lewis-basic properties as well as the trans influence of the ligands. [29]

C) Carbonylations as key-reactions ('tools') in selective syntheses

C1)

Palladium-catalysed reactions, with special focus on carbonylations (aminocarbonylation, alkoxycarbonylation, hydroalkoxycarbonylation, *etc*.), have been widely applied in synthesis. Simple novel heterocyclic compounds, potentially applicable as synthetic building blocks, were synthesised in highly efficient reactions [30-32]. Based on the structure-reactivity (structure-selectivity) relations, obtained by simple model compounds, several high-yielding reactions were performed on the steroidal skeleton [33, 34]. As potential further substrates of catalytic transformations, 16-arylidene steroids were synthesized in Claisen-Schmidt condensation. [35]

The resorcinarene-based cavitands provided a perfect platform for highly selective homogeneous catalytic reactions such as (3+2)-azid-alkyne cycloaddition reactions [36, 37] and aminocarbonylations. [38] The possible cooperation of the four reaction centres situated on the upper rim of the cavitand, the mechanistic and catalytic investigations is still in the focus of our research. A review on the various aspects of aminocarbonylation has been also published. [39]

The investigations on the synthesis and application of resorcinarene-based cavitands were continued with the aim of providing a host molecule for copper ion [40] and caffeic acid [41] guests. The cavitands forming a rigid 'basket' proved to be excellent platform for mechanistic investigations in highly 'tetra-selective' aminocarbonylation reactions, i.e., for intramolecular narcissistic self-sorting [42].

The synthesis of pyridazine carboxamides [43] and amino-substituted pyridylglyoxylamides [44] was carried out via palladium-catalysed aminocarbonylation. The applicability of some novel *N*-nucleophiles such as 4-amino-TEMPO [45] and 1-aminopyrrolidine derivatives (1,1-disubstituted hydrazine derivatives) [46] were investigated in palladium-catalysed aminocarbonylation (hydrazinocarbonylation) of iodoalkenes and iodoarenes. Potentially applicable synthetic building blocks were synthesised in highly efficient hydroformylation reaction of 4-vinyl-1,3-dioxolan-2-one substrate [47].

C2)

Palladium-catalysed carbonylation reactions, including asymmetric aminocarbonylations were studied. A set of iodoalkenes and iodoaromatics underwent carbonylation using aminoheterocycles [48, 49] and α-phenylethylamine as *N*-nucleophile. [50] In case of the latter chiral amine, the reaction was carried out with chiral iodoalkenes in a diastereoselective manner. In addition to the mixture of diastereoisomers, all possible diastereomers were synthesised as analytically pure ('standard') compound using both substrates and amines in enantiomerically pure form.

The aminocarbonylation of various diiodopyridines resulted in multiple carbonylations, involving single and double CO insertions, providing novel carboxamide and 2-ketocarboxamide structures hardly available via conventional synthetic procedures. [51] The results discussed in our

previous reports enabled to carry out novel synthesis of amino-pregnenolone derivatives [52] and cavitands possessing triazole moieties in the ’arms’ of deepened cavitands. [53]

As a topic of our continuing interest, palladium-catalysed chiral and achiral aminocarbonylations were investigated. Recently, the application of novel N-nucleophiles such as aminothiazoles and aminothiadiazoles [54] and aminolactames [55] were studied using simple iodoaromatics as substrates. In a similar reaction, iodoalkynes served as suitable starting materials for the synthesis of alkynyl amides (‘ynamides’) [56] Oxazol derivatives of various structures were obtained from iodoalkenes via aminocarbonylation–cycloisomerization sequence in one-pot reaction. [57]

Benzamide—benzothiazole conjugates were synthesised via palladium-catalysed aminocarbonylation (hydrazinocarbonylation) [58] The facile, high-yielding synthesis of 5- and 4-carboxamido-1,2,3-triazoles via azide-alkyne cycloaddition–aminocarbonylation sequence was carried out. [59,60].

The uracil ring was aminocarbonylated via palladium-catalysed aminocarbonylation. [61] Pd-catalyzed Sonogashira coupling reactions in gamma-valerolactone-based ionic liquid was performed. [62]. 2-Aminobenzimidazole and -benzoxazole *N*-nucleophiles provided novel-type tautomers in palladium-catalysed aminocarbonylation. Twelve X-ray structures were determined and the compounds were characterised unequivocally [63].

References

1. P. Bagi, K. Juhász, I. Timári, K. Kövér, M. Kállay, D. Mester, M. Kubinyi, T. Szilvási, P. Pongrácz, L. Kollár, K. Karaghiosoff, M. Czugler, L. Drahos, E. Fogassy, G. Keglevich, *J. Organomet. Chem.* 797 (2015) 140-152.
2. R. Herbay; G. Györke; I. Timári, L. Drahos, P. Pongrácz, L. Kollár, G. Keglevich, P. Bagi, *Curr. Org.. Chem*. 23 (2019) 2873-2879.
3. E. Bálint, A. Tripolszky, E. Jablonkai, Z. Mucsi, P. Pongrácz, L. Kollár, G. Keglevich, *J. Organomet. Chem.* 801 (2016) 111-121.
4. P. Pongrácz, L. Kollár, L. Mika, *Green Chem.* 18 (2016) 842-847.
5. P. Pongrácz, B. Bartal, L. Kollár, L. Mika, *J. Organomet. Chem*. 847 (2017) 140-145.
6. P. Pongrácz, L. Kollár, *J. Organomet. Chem*. 824 (2016) 118-123
7. P. Pongrácz, L. Kollár, L. Mika, *Green Chem*. 18 (2016) 842-847.
8. P. Bagi, K. Karaghiosoff, M. Czugler, D. Hessz, M. Kállay, M. Kubinyi, T. Szilvási, P. Pongrácz, L. Kollár, I. Timári, K. E. Kövér, L. Drahos, E. Fogassy, G. Keglevich, *Heteroatom Chem*. 27 (2016) 91-101.
9. L. Kollár, P. Pongrácz, *J. Organomet. Chem*. 866 (2018) 184-188.
10. P. Pongrácz, H. Szentjóbi, T. Tóth, P. Huszthy, L. Kollár, *Mol. Catal*. 439 (2017) 128-133.
11. P. Pongrácz, A. Abu Seni, L. T. Mika, L. Kollár, *Mol. Catal*. 428 (2017) 15-18.
12. A. Abu Seni, L. Kollár, P. Pongrácz, *Mol. Catal.* 482 (2019) 110673.
13. N. Pálinkás, G. Mikle, L. Kollár, *Tetrahedron* (submitted)
14. G. Mikle, B. Boros, L. Kollár, *Tetrahedron: Asymm*. 27 (2016) 377-383.
15. D. Marosvölgyi-Haskó, T. Kégl, L. Kollár, *Tetrahedron* 72 (2016) 7509-7516.

16. D. Marosvölgyi-Haskó, B. Lengyel, J. M. Tukacs,, L. Kollár, L. Mika, *ChemPlusChem* 81 (2016) 1224–1229.
17. N. Pálinkás, L. Kollár, T. Kégl, *ACS Omega* 3, 2018, 16118−16126.
18. Z. Nagymihály, Z. Csók, L. Kollár, *Mol. Catal.* 44 (2018) 780-785.
19. B. Urbán; P. Szabó; D. Srankó, Gy. Sáfrán, L. Kollár, R. Skoda-Földes, *Mol. Catal.* 445 (2018) 195-205.
20. K. Fehér, E. Nagy, P. Szabó, D. Srankó, Á. Gömöry, L. Kollár, R. Skoda-Földes, *Appl. Organomet. Chem. (*2018) DOI: 10.1002/aoc
21. L. Orha, J. M. Tukacs, B. Gyarmati, A. Szilágyi, L. Kollár, L. T. Mika, *ACS Sustainable Chem. & Engineering.* 6 (2018) 5097-5104.
22. A. Abu Seni, L, Kollár, L. T. Mika, P. Pongrácz, *Mol. Catal*. 457 (2018) 67-73.
23. B. Bartal, G. Mikle, L. Kollár, P. Pongrácz: *Mol. Catal*. 467 (2019) 143−149.
24. T. Papp, L. Kollár, T. Kégl, *J. Comput. Chem*. 38 (2017) 1712-1726.
25. N. Pálinkás, L. Kollár, T. Kégl, *Chem. Select* 2 (2017) 5740-5750.
26. N. Pálinkás, L. Kollár, T. Kégl, *Dalton Trans*. 46 (2017) 15789-15802.
27. N. Pálinkás, L. Kollár, T. Kégl, *Dalton Trans*. (submitted).
28. T.R. Kégl, L. Kollár, T. Kégl, *Adv. Phys. Chem.* Vol. 2015, Article ID 985268,
29. T. R. Kégl,, L. Kollár, T. Kégl, *Molecules* 23 (2018) 3176.
30. A. Takács, D. Marosvölgyi-Haskó, Z. Kabak-Solt, L. Damas, F.M.S. Rodrigues, R.M.B. Carrilho, M. Pineiro, M.M. Pereira, L. Kollár, *Tetrahedron 72* (2016) 247-256.
31. G. Szőke, A. Takács, L. Kollár, *J. Heterocycl. Chem.* 53 (2016) 2020-2024.
32. R. Farkas, A. Petz, L. Kollár, *Monatsh. Chem.* 146 (2015) 1665-1671.
33. E. Szánti-Pintér, J. Wouters, Á. Gömöry, É. Sághy, É. Szőke, Z. Helyes, L. Kollár, R. Skoda-Földes, *Steroids* 104 (2015) 284-293.
34. M. Kiss, S. Mahó, K. Böddi, B. Boros, L. Kollár, *Monatsh. Chem.* 146 (2015) 357-364.
35. D. Ispán, E. Szánti-Pintér, M. Papp, J. Wouters, B. Zsirka, Á. Gömöry, L. Kollár, R. Skoda-Földes, *Eur. J. Org. Chem*. (2018) 3236-3244.
36. T. Z. Jánosi, G. Makkai, T. R. Kégl, P. Mátyus, L. Kollár, J. Erostyák: *J. Fluorescence* 26 (2016) 679-688.
37. Z. Csók, P. Szuroczki, L. Kollár, H. M. Ngo, I. Ledoux-Rak, N. A. M. S. Caturelles, R. Q. Albuquerque, *J. Phys. Chem. C.* 119 (2015) 12608-12615.
38. Z. Nagymihály, L. Kollár, *Tetrahedron* 71 (2015) 2555-2560.
39. M. Kiss, A. Takács, L. Kollár, *Curr. Green Chem.* 2 (2015) 319-338.
40. Z. Czibulya, É. Horváth, Z. Nagymihály, L. Kollár, S. Kunsági-Máté, *Supramol. Chem*. 28 (2016) 582-588.
41. G. Secenji, G. Matisz, Z. Csók, L. Kollár, S. Kunsági-Máté, *Chem. Phys. Lett*. 657 (2016) 60-64.

42. Z. Nagymihály, N. A. M. S. Caturello, A. Takátsy, L. Kollár, R. Q. Albuquerque, Z. Csók, *J. Org. Chem.* 82 (2017) 390-396.
43. G. Szőke, A. Takács, L. Kollár, *J. Heterocycl. Chem*. 53 (2016) 2020-2024.
44. G. Szőke, A. Takács, Z. Berente, A. Petz, L. Kollár, *Tetrahedron* 72 (2016) 3063-3067.
45. M. Gergely, A. Takács, L. Kollár, *J. Heterocyclic Chem*. 54 (2017) 634-640.
46. M. Gergely, L. Kollár, *Tetrahedron* 73 (2017) 838-843.
47. P. Pongrácz, L. Kollár, *J. Heterocyclic Chem*. 54 (2017) 1430-1436.
48. M. Gergely, L. Kollár, *Tetrahedron* 73 (2017) 838-844.
49. M. Gergely, B: Boros, L. Kollár, *Tetrahedron* 73 (2017) 6736-6741.
50. G. Mikle, B. Boros, L. Kollár, *Tetrahedron: Asymm*. 28 (2017) 1733-1738.
51. A. Takács, G. M. Varga, J. Kardos, L. Kollár, *Tetrahedron* 73 (2017) 2131-2138.
52. E. Szánti-Pintér, L. Maksó, Á. Gömöry, J. Wouters, B. E. Herman, M. Szécsi, L. Kollár, R. Skoda-Földes, *Steroids* 123 (2017) 61-66.
53. T. Kégl, G. Csekő, G. Mikle, A. Takátsy, T. Kégl, L. Kollár, *ChemistrySelect* 2 (2017) 8337-8345.
54. M. Gergely, L. Kollár, *Tetrahedron* 74 (2018) 2030-2040.
55. A. Takács, L Kollár, *Tetrahedron* 74 (2018) 6116-6128.
56. P. Szuroczki, B. Boros, L. Kollár, *Tetrahedron* 74 (2018) 6129-6136.
57. P. Szuroczki, G. Mikle, L. Kollár, *Mol. Catal.* 452 (2018) 68-74.
58. M. Gergely, L. Kollár, *Tetrahedron* 75 (2019) 2027−2036.
59. P. Szuroczki, J. Sámson, L. Kollár, *ChemistrySelect* 4 (2019) 5527-5530.
60. P. Szuroczki, L. Kollár, *ChemistrySelect* 5 (2020) 448-451.
61. A. Takács, M. G. Varga, Á. Dörnyei, L. Kollár, *Tetrahedron* 75 (2019) 4632-4639.
62. L. Orha, J. M. Tukacs, L. Kollár, L. T. Mika. *Beilstein J. Org. Chem.* 15 (2019) 2907-2913.
63. M. Gergely, L. Kollár, *Tetrahedron* 75 (2019) 2027−2036.