

UNIVERSITY OF PÉCS

Doctoral School of Chemistry

**INSERTION REACTIONS OF CARBON MONOXIDE AND
CARBON MONOXIDE ANALOGUES:
THEORETICAL AND SYNTHETIC STUDY**

PhD thesis

Noémi Pálinkás

Supervisor:

Dr. Tamás Kégl

Senior Research Fellow



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1. Introduction

The reactions, which based on the application of organometallic compounds, are important in synthetic organic chemistry. Organometallic reagents in homogeneous catalytic reactions open the possibility for synthetic applications which had not been feasible in the classical ways. One prominent example for homogeneous catalytic transformations is the activation of small molecules by insertion into metal-carbon bond.

The most important field of application of the carbonyl complexes is the carbonyl group insertion into organic molecules leading to the formation of new carbon-carbon or carbon-heteroatom bonds. Carbonyl compounds and carboxylic acid derivatives can be produced with carbon monoxide insertion in laboratory or in industrial processes. In this way, important intermediates or products of the pharmaceutical, paint and pesticide industries can be synthesised.

The molecules, which contain the amidine functional group, are remarkable in several fields in the synthetic organic chemistry and are of special importance in the production of biologically active products. Regarding the biological importance of nucleobases, it is not surprising, that amidine-based compounds can be considered as basic elements of pharmaceutical chemistry and the above mentioned structure occurs in numerous agents.

Recently, transition metal complexes of heterocumulene molecules were investigated widely in recent decades and it was determined that carbon dioxide, sulfur dioxide and carbonyl sulfide can be activated by transition metals. These molecules can react in insertion, dimerisation and disproportionation reactions.

Unraveling the coordination features of small molecules can lead us to invaluable knowledge paving the way for the development of effective catalytic systems with high activity and selectivity. Theoretical methods are especially suitable to describe the donor-acceptor interactions as well as steric and electronic properties of various ligands in transition metal complexes.

2. Aims

- The synthesis, isolation and characterization of novel compounds via palladium catalysed alkyl-isonitrile insertion reaction.
- Investigation of the effect of the reaction conditions (nature and quantity of alkyl-isonitrile, bases, substrates, monodentate and bidentate phosphine ligands) on reactivity and chemoselectivity.
- Imidoylative reaction of 4-substituted iodobenzenes in order to investigate the effect of the substituent on reactivity and selectivity.
- Studying the coordination behaviour of sulfur-containing small molecules and the electronic structure of their transition metal complexes of catalytic importance.
- Determination of the mechanism and elementary steps of the aminocarbonylation reaction by means of quantum chemical computations.
- Exploring the relationship between the rate of oxidative addition and the Hammett substituent constant.

3. Methods

3.1. Synthetic methods

Parallel reactors were applied for the synthetic work. The mixture of the substrate, catalyst and additional reactants were dissolved under argon, then the reaction was conducted at 105 °C for 72 hours. The products were purified by column chromatography, then were characterized by advanced instrumental methods (GC-MS, IR, ¹H NMR, ¹³C NMR.)

3.1. Theoretical methods

The energy and geometry calculations of the mechanism of aminocarbonylation reaction were carried out with the ORCA 4.0.1 software package with solvation correction and M06//B97-D3 model chemistry was employed with the def2-TZVP basis set for iodine and palladium, and with the def2-SVP basis set for the other atoms. The Bader analysis was implemented with AIMAll software, while the NBO

analysis was done with GENNBO 5.0 program. The ETS-NOCV calculations were done with ADF 2012, the NCI calculations were done with NCIPLOT program.

The structure of the $M(\text{PH}_3)_2(\text{CE}^1\text{E}^2)$ -type complexes were calculated with the PBPBE functional in combination with the def2-TZVP basis set.

4. Theses

1. Amidines and ketimin-amidines were obtained in insertion reactions of *tert*-butyl isonitrile with aryl halogenide in the presence of various palladium-phosphine complexes. The double insertion products (ketimin-amidines) were formed in higher proportion by using both monodentate and bidentate ligands.
2. New compounds were synthesized by using *para*-substituted iodobenzenes under similar conditions as above (**Figure 1**). Higher conversion was achieved by applying electron withdrawing groups in 4-position. It can be stated, that no linear correlation between chemoselectivity and Hammett *para* constant can be observed.

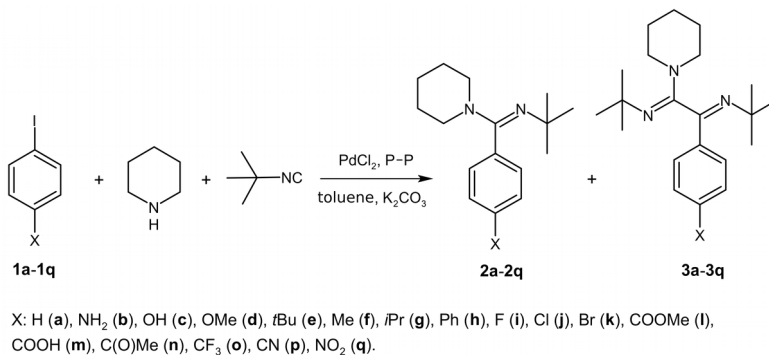


Figure 1: Reactions of *para*-substituted iodobenzenes with *tert*-butyl isonitrile and piperidine in the presence of 'in situ' formed Pd(0) complex

- The computational investigation on the catalyst systems containing bidentate phosphine ligands revealed that the conversion increases with the increase of the bite angle and decreases with the partial charge of palladium.
- According to theoretical chemical calculations, the $M(\text{PH}_3)_2(\text{CE}^1\text{E}^2)$ ($\text{E}^1, \text{E}^2 = \text{O}, \text{S}; \text{M} = \text{Ni}, \text{Pd}, \text{Pt}$) complexes possess $\eta^2\text{-}(\text{E}^1, \text{C})$ coordination and planar structure (**Figure 2**). The metal-carbon bond lengths are the shortest in case of nickel complexes, and the longest in the palladium-containing complexes. Moreover, the E^1CE^2 bond angles are the least in palladium-complexes and the biggest in case of nickel-containing complexes.

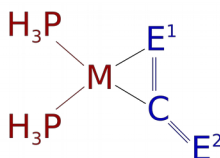


Figure 2: Structure of $M(\text{PH}_3)_2(\eta^2\text{-L})$ complexes

- The computational calculations unraveling the donation and back donation in complexes shown in **Figure 2**, reveal that beside the $\pi_{\text{E}^1\text{-C}}$ orbital the C-E^1 σ bond is also involved in the donating interaction, albeit to a lesser extent. The dominant back donation interactions takes place between the d orbital of the metal and the π^* antibonding orbital of the ligand. Furthermore, a minor back donating interaction originates from the donor electron pair of phosphorous.
- The M06//B97-D3; SMD (DMF) combination of functionals was chosen for computing the mechanism of the aminocarbonylation reaction. The theoretical results were in agreement with the experimental data. The complexes, which may play a role in the mechanism, were determined considering all possible ligand dissociation and ligand exchange steps, starting from the $\text{Pd}(\text{PPh}_3)_4$ complex. The Gibbs activation and reaction free energies were investigated in case of oxidation addition of iodobenzene with all complexes. It could be

concluded that the $\text{Pd}(\text{PPh}_3)_2$ and the $\text{Pd}(\text{PPh}_3)(\text{CO})$ are the most probable species as active catalysts.

7. The oxidative addition of *para*-substituted iodobenzenes was investigated (**Figure 3**), and it was established that the Gibbs free energy of activation, and the electrostatic potential at the nucleus of palladium show linear correlation with the *para* Hammett constants of the substituents in 4-position.

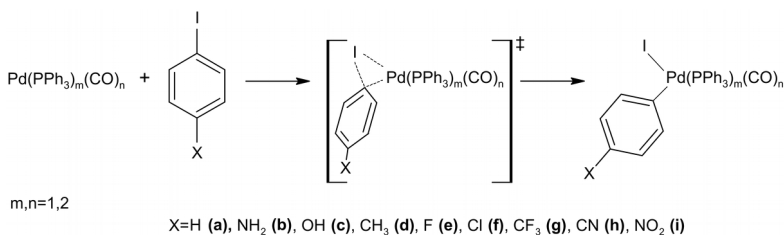


Figure 3: Oxidative addition of *para*-substituted iodobenzenes

8. The oxidative addition is followed by carbon monoxide insertion, which was found to take place with a small energy barrier. The most plausible pathways leading to amide derivatives were investigated: mechanisms with formation of hydride-complex, furthermore with nucleophilic attack. The formation of 2-ketocarboxamide occurs through the carbamoyl complex. The expected product is formed by the coupling of the acyl and carbamoyl ligands during reductive elimination.

5. Publications related to the PhD thesis:

1. N. Pálincás, L. Kollár, T. Kégl: Nature of the Metal-Ligand Interactions in Complexes $\text{M}(\text{PH}_3)_2(\eta^2\text{-L})$ ($\text{M}=\text{Ni}, \text{Pd}, \text{Pt}$; $\text{L}=\text{CO}_2, \text{COS}, \text{CS}_2$): A Theoretical Study. *Chemistry Select*, **2017**, 5740-5750.
2. N. Pálincás, L. Kollár, T. Kégl: Mechanism of the Oxidative Addition of Iodobenzene to Palladium(0)-Triphenylphosphine-Carbonyl complexes: a Theoretical Study. *Dalton Trans.*, **2017**, 46, 15789-15802.

3. N. Pálincás, L. Kollár, T. Kégl: Palladium-Catalyzed Synthesis of Amidines via *tert*-Butyl Isocyanide Insertion. *ACS Omega*, **2018**, 3, 16118–16126.

6. Other Publications:

1. P. Ács, A. Takács, M. Kiss, N. Pálincás, S. Mahó, L. Kollár: Systematic investigation on the synthesis of androstane-based 3-, 11-, 17- carboxamides via palladium-catalyzed aminocarbonylation. *Steroids*, **2011**, 76, 280-290.
2. M. Kiss, N. Pálincás, A. Takács, S. Mahó, L. Kollár: A systematic approach to the synthesis of androstane-based 3,17-dicarboxamides (homo- and mixed dicarboxamides) via palladium-catalyzed aminocarbonylation. *Steroids*, **2013**, 78, 693-699.
3. T. R. Kégl, N. Pálincás, L. Kollár, T. Kégl: Computational Characterization of Bidentate P-Donor Ligands: Direct Comparison to Tolman's Electronic Parameters. *Molecules*, **2018**, 23, 3176-3187.

7. Conferences related to the PhD thesis:

- N. Pálincás, L. Kollár, T. Kégl: Jódbenzol palládium(0)-trifenilfoszfín- karbonil komplexekre történő oxidatív addíciójának vizsgálata elméleti kémiai számításokkal, Vegyészkonferencia; Hajdúszoboszló, poszter szekció, 2017. 06. 19-21.
- N. Pálincás, L. Kollár, T. Kégl: Investigation of isonitril insertion in palladium catalyzed carbonylation reactions, 23rd International Conference on Chemistry; Deva (Romania), 2017. 10. 25-28.
- N. Pálincás, L. Kollár, T. Kégl: Amidinek előállítása palládium-katalizált reakciókban, MTA Szervetlen és Fémorganikus Kémiai Munkabizottsági Ülés; 2017. 12. 15.
- N. Pálincás, L. Kollár, T. Kégl: Palladium-Catalyzed Synthesis of Amidines via *tert*-Butyl Isocyanide Insertion, 24rd International Conference on Chemistry; Sovata (Romania) poster session, 2018. 10. 24-27.