

UNIVERSITY OF PÉCS

Doctoral School of Chemistry

**Palladium-catalyzed carbonylation in the presence of *N*-heterocyclic amines
as nucleophilic agents**

PhD Thesis

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Introduction

The investigation of transition metal complexes in homogeneous catalytic reactions run back over several decades. First, Wilkinson and his coworkers published their results on catalytic hydrogenation with rhodium complexes, drawing the attention to the importance of transition metal complexes. In the '70s, by the discovery of cross-coupling reactions new pathways were opened to form new carbon-carbon and carbon-heteroatom bonds which are hardly available in conventional reactions. The Nobel Prize in Chemistry in 2010, awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki, shed even more light to palladium-catalyzed reactions.

The wide-spread use of homogeneous catalytic reactions is due to their favourable properties compared to those of heterogeneous reactions. Among others, they are active under milder reaction conditions (lower reaction temperature and pressure). The reaction mechanism of homogeneous catalytic reactions can be cleared-up easier due to the application of efficient instrumental analytical means. The structure of the catalyst can be modified by facile ligand exchange reactions in the coordination sphere of the central metal ('tailor-made catalyst').

To form an efficient catalyst, it is necessary to activate the reactant molecules as weakly bonded ligands in addition to ligands bonded tightly to the central metal ion. Apart from the temperature and pressure, the solvent, the transition metal and ligands as well as the reactants themselves influence substantially the selectivities (chemo-, regio-, enantioselectivity). By the right choice of the reaction conditions and catalyst the target product could be synthesized without formation of the side-products. Not only economical reasons but green chemistry issues also support these efforts.

The major disadvantages of using homogeneous catalytic reactions are the high cost of the catalyst as well as the tardiness in the separation of products and catalyst. To reduce these difficulties, either the heterogenization of the catalyst or the application of novel alternative solvents (ionic liquid, perfluoroalkanes) are necessary. These new solvents enable the recirculation of the catalyst, their application may result in facile separation of the product and catalyst, and importantly, due to their low tension, emission to the atmosphere can be reduced.

Carbonylative reactions, involving carbon monoxide as C1 building block, form one of the most important group of homogeneous catalytic reactions. In the presence of several transition metal complexes, carbon monoxide is apt to insert into metal-carbon bond to form the corresponding metal-acyl complex even under atmospheric CO pressure. These acyl

complexes are key catalytic intermediates in the transition metal catalyzed synthesis of aldehydes, ketones, carboxylic acids or their derivatives.

The carbonylation reactions of aryl or alkenyl halides (triflates) can be classified according to the nucleophile. The use of water, alcohol, amine or hydrazine nucleophile results in hydroxycarbonylation, alkoxycarbonylation, aminocarbonylation or hydrazinocarbonylation, respectively. In case of using unsaturated substrates, generally alkenes, the name of the reactions is preceded by hydro- (*e.g.* hydroalkoxycarbonylation).

Carboxamides are widely used in various fields, spanning from pharmaceutical chemistry to the production of plastics. Some of these compounds of practical importance can be synthesized in aminocarbonylation reaction. Although palladium-catalyzed aminocarbonylation is known from the middle of the '70s, there are several details to discover regarding both reaction mechanism and synthetic applications. Among the transition metal catalysts showing aminocarbonylation activity, palladium complexes are still the most widely used ones due to their functional group tolerance and good activity toward carbon-carbon and carbon-nitrogen bond formation.

1. Aims

- Synthesis of new *N*-heteroaromatic model compounds and their derivatives of practical importance using palladium-catalyzed aminocarbonylation reactions.
- Investigation of the relationships between structure-reactivity and structure-selectivity (chemo- and regioselectivity) for the applied model substrates.
- Study of the effect of reaction conditions (temperature, carbon monoxide pressure) on reactivity and chemoselectivity.
- Investigation of the effect of the *N*-nucleophiles used on the reaction.
- Isolation and complete analytical characterization of the prepared compounds.
- Crystallization of the isolated compounds. Determination of the X-ray structure of successfully crystallized derivatives.

2. Methods

Standard inert Schlenk-technique and high pressure autoclave technique was used. The experiments, carried out under high carbon monoxide pressure (40 bar) carbon monoxide, were performed in a 100 cm³ stainless steel autoclave.

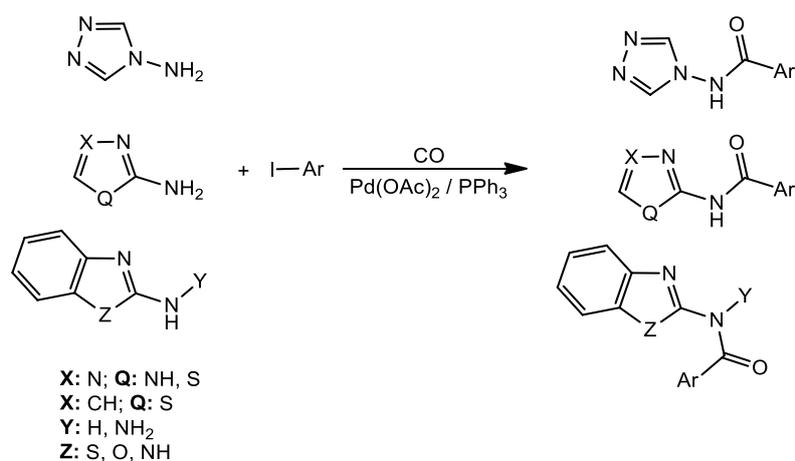
The conversions and the product distributions were determined by using GC. The products were identified by GC-MS, IR, ¹H-, ¹⁹F- and ¹³C-NMR and X-ray diffraction.

3. Thesis

In my PhD Thesis, the palladium-catalyzed aminocarbonylation reactions of heteroaromatic *N*-nucleophiles in the presence of simple iodoaromatics and iodoalkenes are presented. The generally used Pd(0)-PPh₃ catalyst system was prepared 'in situ' from Pd(OAc)₂ precursor and PPh₃.

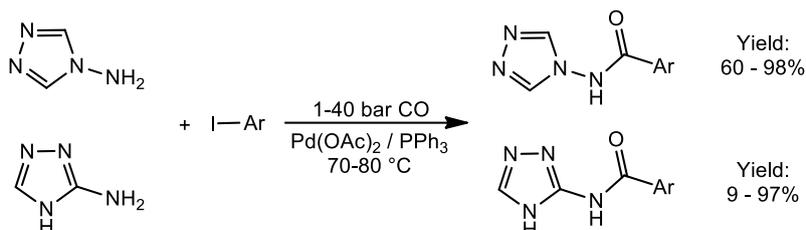
The most important result are summarized below.

1. In the aminocarbonylation reactions of various aryl iodides with the nucleophiles below, carboxamides were formed only by the insertion of single carbon monoxide. I successfully prepared and isolated 127 carboxamides, of which 103 are new compounds. 19 compounds were successfully crystallized, of which 10 were characterized by X-ray diffraction as well.



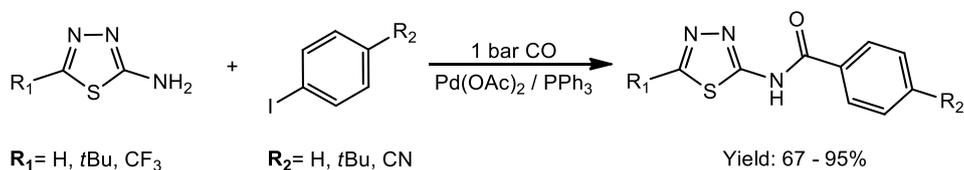
Scheme 1. Aminocarbonylation of aryl iodides in the presence of *N*-heteroaromatic nucleophiles.

2. In the case of aminotriazoles, a higher-than-usual reaction temperature is necessary to complete the reaction, and in some cases the application of increasing CO pressure is beneficial. The presence of hydroxyl and nitro groups in 4-amino-4*H*-1,2,4-triazole resulted in side reactions. In both cases, a polymeric by-products were formed. In the case of amitrole, a poorly soluble precipitate with palladium was formed. The precipitate includes 1/3 and 1/2 palladium/triazole complexes.



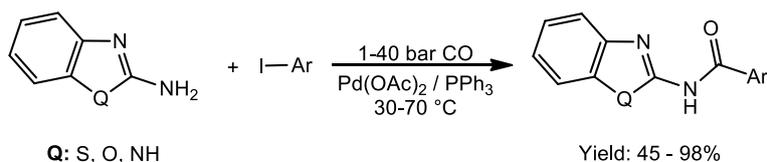
Scheme 2. Aminocarbonylation of aryl iodides in the presence of aminotriazoles.

3. The reactions of 2-aminothiadiazoles and aryl iodides show more moderate reactivity with the substituted starting materials. Reactivity is significantly reduced when both the nucleophile and the aryl iodide are substituted.



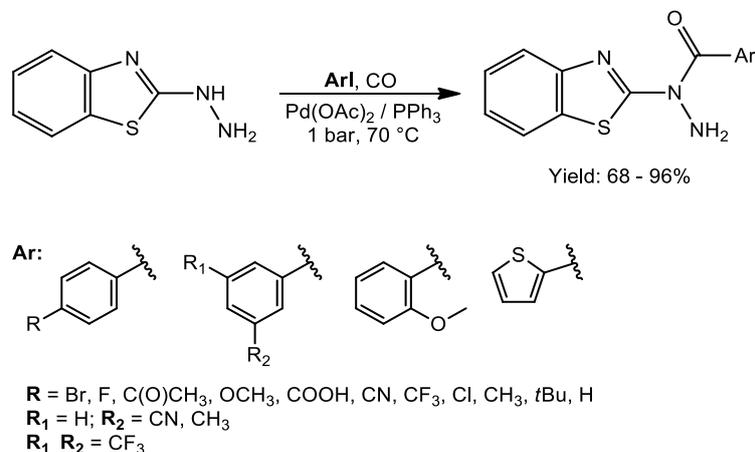
Scheme 3. Aminocarbonylation of aryl iodides in the presence of 5-substituted-2-amino-1,3,4-thiadiazoles.

4. In the aminocarbonylation of aryl iodides with condensed ring heteroaromatic amines, the use of high CO pressure resulted in faster product formation. The products of 2-aminobenzimidazole and 2-aminobenzoxazole acted as inhibitors in the reaction.



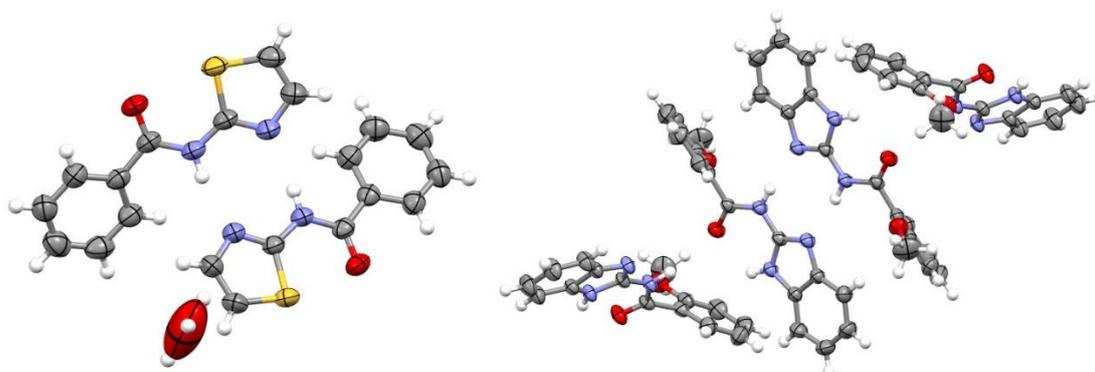
Scheme 4. Aminocarbonylation of aryl iodides in the presence of condensed ring heteroaromatic amines.

5. In the case of 2-hydrazinobenzo[*d*]thiazole, the reaction is regioselective, only the α -nitrogen reacted resulting in the corresponding *N*-acyl product. The use of an excess of iodo aromatics or the increase in carbon monoxide pressure do not affect the selectivity of the reaction.



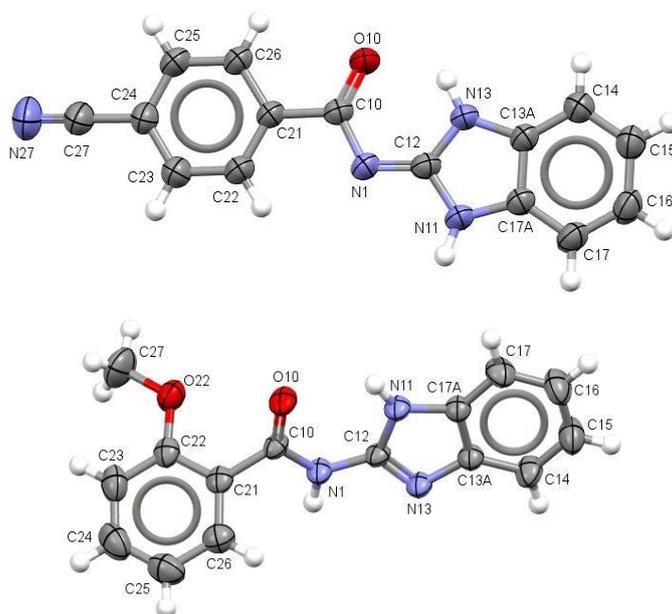
Scheme 5. Hydrazinocarbonylation of aryl iodides in the presence of 2-hydrazino-benzothiazole.

6. Investigating the structure-reactivity relationship of *para*- and *meta*-substituted iodobenzenes, those ones possessing electron-donating group are less reactive than those with electron-withdrawing group. *meta*-Substituted iodobenzenes are more reactive than *para*-substituted ones.
7. The high chemical shift of the NH proton(s) of various products indicated the presence of hydrogen bonds. The NH protons of the 2-methoxyphenyl derivatives participate an intramolecular hydrogen bond indicated by the shape of the signal and by the smaller chemical shift, which is also supported by the X-ray diffraction structures.



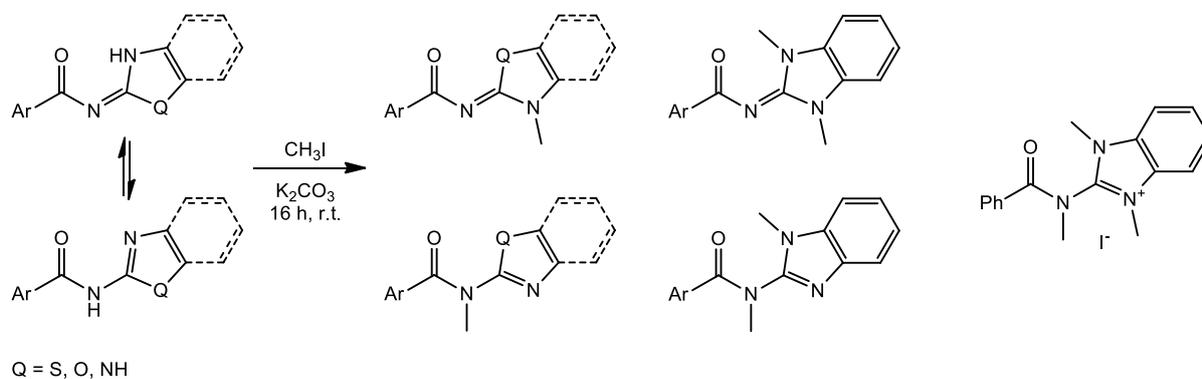
Scheme 6. Hydrogen bonds in the X-ray diffraction structure of crystallized products.

8. Based on the ^1H and ^{13}C NMR spectra of the benzimidazole derivatives, the benzimidazole moiety is symmetrical with the exception of the 2-methoxy derivative. The ring nitrogens are protonated and an exocyclic imine bond is formed, which is confirmed also by X-ray structures.



Scheme 7. X-ray diffraction structures of benzimidazole derivatives.

9. Several methyl derivatives were prepared by the methylation reaction of the isolated products. The aim of these reactions was to exchange the NH proton(s) for a heavy atom(s). The main products were the aromatic ring nitrogen-methylated keto-imine-type compounds. I was able to isolate 11 products from the methylation of 6 compounds, of which 6 compounds were successfully crystallized and their X-ray structure was determined.



Scheme 8. Methylation of isolated products.

4. Publications, conferences:

Publications related to the PhD thesis:

1. **M. Gergely**, B. Boros, L. Kollár:
High-yielding synthesis of *N*-triazolyl carboxamides via palladium-catalysed aminocarbonylation.
Tetrahedron 73 (2017) 6736-6741. **IF: 2,424**
2. **M. Gergely**, L. Kollár:
Aminothiazoles and aminothiadiazaoles as nucleophiles in aminocarbonylation of iodobenzene derivatives.
Tetrahedron 74 (2018) 2030-2040. **IF: 2,493**
3. **M. Gergely**, L. Kollár:
Synthesis of benzamide-benzothiazole conjugates via palladium-catalysed aminocarbonylation (hydrazinocarbonylation).
Tetrahedron 75 (2019) 2027-2036. **IF: 2,289**
4. **M. Gergely**, A. Bényei, L. Kollár:
2-Aminobenzimidazole and -benzoxazole as *N*-nucleophile in palladium-catalysed aminocarbonylation.
Tetrahedron 76 (2020) 131079. **IF: 2,460***

Other publications:

1. **M. Gergely**, L. Kollár:
Aminocarbonylation (hydrazinocarbonylation) of iodoalkenes and iodoarenes.
Tetrahedron 73, (2017), 838-844. **IF: 2,424**
2. **M. Gergely**, A. Takács, L. Kollár:
4-Amino-TEMPO as *N* - Nucleophile in Palladium - Catalyzed Aminocarbonylation.
J. Heterocyclic Chem. 54, (2017), 634-640. **IF: 1,081**
3. **M. Gergely**, R. Farkas, A. Takács, A. Petz, L. Kollár:
Synthesis of *N*-picolyloxycarboxamides via palladium-catalysed aminocarbonylation of iodobenzene and iodoalkenes.

Conferences related to the PhD thesis:

- M. Gergely, L. Kollár: Hydrazinocarbonylation of iodoalkenes and iodoarenes. 16th Tetrahedron Symposium Asia Edition; Melbourne, 2017. 07. 23-27.
- M. Gergely, B. Boros, L. Kollár: High-yielding synthesis of *N*-triazolyl carboxamides via palladium-catalysed aminocarbonylation. 23rd International Conference on Chemistry; Deva (Romania) poster session, 2017. 10. 25-28.
- M. Gergely, L. Kollár: Aminothiazoles and aminothiadiazoles as nucleophiles in aminocarbonylation of iodobenzene derivatives. 24th International Conference on Chemistry; Sovata (Romania), 2018. 10. 24-27.

Other conference:

- M. Gergely, L. Kollár: Synthesis of *N*-picolyloxycarboxamides via palladium-catalysed aminocarbonylation. 15th Tetrahedron Symposium; London, 2014. 06. 23-26.
- M. Gergely, L. Kollár: 4-Amino-TEMPO mint N-nukleofil palládium-katalizált aminokarbonilezési reakcióban, (4-Amino-TEMPO as N-nucleophile in palladium-catalysed aminocarbonylation.) Congress of the Hungarian Chemical Society; Hajdúszoboszló, poster section, 2017. 06. 19-21.