

UNIVERSITY OF PÉCS

Doctoral School of Chemistry

**Palladium-catalysed aminocarbonylation reactions of iodoarenes
and iodoalkenes**

PhD Thesis

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1. Introduction

The transition metal-catalysed homogeneous catalytic reactions, as a substantial part of organo-transition metal chemistry, after an unbelievable expansion in the last few decades, reached the stage of general application in synthetic organic chemistry. Since the early discovery of cobalt-catalysed hydroformylation in 1939, the application of transition metals for synthetic purposes has become general in academic research and has found several applications in industry as well. The recognition of the carbon-metal bonding properties and the mechanistic understanding of the basic catalytic reactions, as well as the definition of the scope and limitations have rendered many of the transition metal catalysed reactions the most efficient solution to practical problems. In many recent reviews organo-transition metals are considered as the most important source of truly new reactions. Due to their favorable yield and exceptional chemo-, regio- and enantioselectivity, nowadays only rarely can we encounter with modern synthetic reactions of importance without some forms of organometallic homogenous catalysis. Many general treatises and reviews, as well as increasing number of research papers, some of them listed also in my thesis, demonstrate the increasing role of transition metals in the field of organometallic synthesis.

Several objections (expensive reagents, reactions of no industrial importance, *etc.*) to the wide application of homogeneous catalysis were taken in the first decades after discovery. Overcoming the fear of novel type of reactants and a myth of using transition metal complexes in a different way than 'classical' organic reagents, some of these systems are used routinely nowadays in several organic syntheses or as a tool for the functionalization of various skeletons of practical importance.

There is an increasing interest in developing new strategies to introduce functional groups into specific positions of various skeletons. The enhanced selectivities, well-defined mechanism, and the applicability of standard techniques are the main features which make the homogeneous catalytic reactions attractive also in the synthesis of carboxylic acid derivatives such as carboxamides and esters. Not only primary publications but several reviews have shown the strength of homogeneous catalytic carbonylations in the synthesis of both simple 'model compounds' and backbones of practical (biological, pharmacological, *etc.*) importance.

The palladium-catalysed aminocarbonylation of aryl/alkenyl-halides in the presence of various *N*-nucleophiles, resulting in the corresponding amide derivatives, is of special synthetic importance. Hundreds of examples have shown its synthetic potential. The

aminocarbonylation of aryl-halides have become an indispensable tool for the synthesis of amides of unprecedented structures. Similar to the aryl halides, iodo- and bromoalkenes of various structure also readily undergo aminocarbonylations resulting in α,β -unsaturated amides. The major difference to the corresponding aromatic substrates lies in the lack of double carbon monoxide insertion and the formation of 2-ketocarboxamides were reported using this methodology.

In general, in the palladium-catalysed aminocarbonylation reaction aryl/alkenyl derivatives are treated with an appropriate *N*-nucleophile in a carbon monoxide atmosphere in the presence of a catalytic amount of a palladium complex, whereby, the leaving group X is formally replaced by the nucleophile with incorporation of one or two molecules of carbon monoxide. Typically, the reactions take place at 50-140 °C and 1-60 bar of carbon monoxide, and require a stoichiometric amount of base to regenerate the catalyst (**Figure 1**).

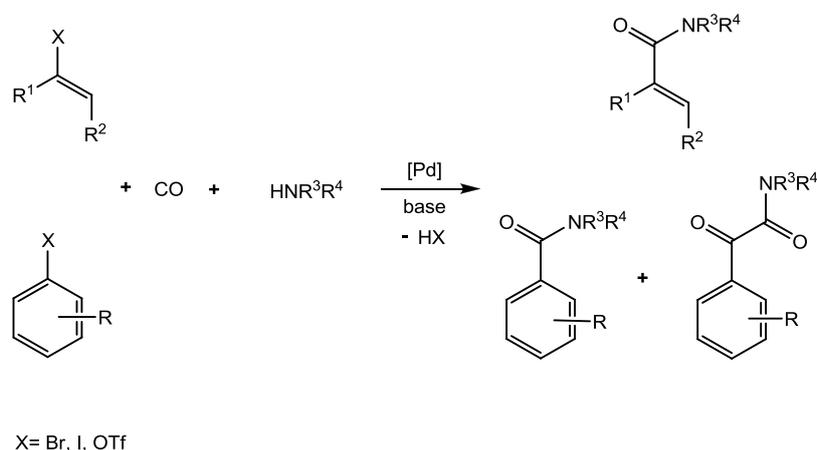


Figure 1. General scheme of the aminocarbonylation of aryl/alkenyl-halides

In spite of the overwhelming literature of transition metal catalysed carbonylations, several fine details including structure — reactivity relations and mechanistic details are still unexplored. These facts have prompted me to investigate the palladium-catalysed aminocarbonylation of several model compounds such as iodoarenes and iodoalkenes.

2. Aims

- The investigation of palladium-catalysed aminocarbonylation of iodoarenes and iodoalkenes in the presence of various amines.
- The investigation of the relations of the structure-reactivity and the structure-selectivity (chemo- and regioselectivity).
- The investigation of the influence of the reaction conditions (CO pressure, temperature, *N*-nucleophile) on reactivity and chemoselectivity.
- The verification of the elemental steps of the catalytic cycle of aminocarbonylation reaction.
- Synthesis of new carboxamide derivatives with practical importance in the presence of *N,O*-dimethylhydroxylamine and diethyl α -aminobenzylphosphonate.
- The isolation and full characterization (IR, GC-MS, ^1H -NMR, ^{13}C -NMR) of all products.

3. Methods

Standard inert Schlenk-technique and high-pressure autoclave method was used. The experiments involving high pressure (10-80 bar) were performed in a 100 cm³ stainless steel autoclave.

The conversions and the product distributions were determined by using GC/MS. The products were identified by GC-MS, IR, ^1H - and ^{13}C -NMR measurements and element (C, H, N) analyses.

4. Results

In my experiments palladium-catalysed aminocarbonylation of several iodoarenes and iodoalkenes with various *N*-nucleophiles (simple primary and secondary amines (**Figure 2. / a**), amino acid methyl esters (**Figure 2. / b**) and amines with more complex structure (**Figure 2. / c**) was carried out under different carbon monoxide pressure (1-80 bar). The highly active palladium(0) catalyst formed *in situ* from palladium acetate and triphenylphosphine in the reaction mixture.

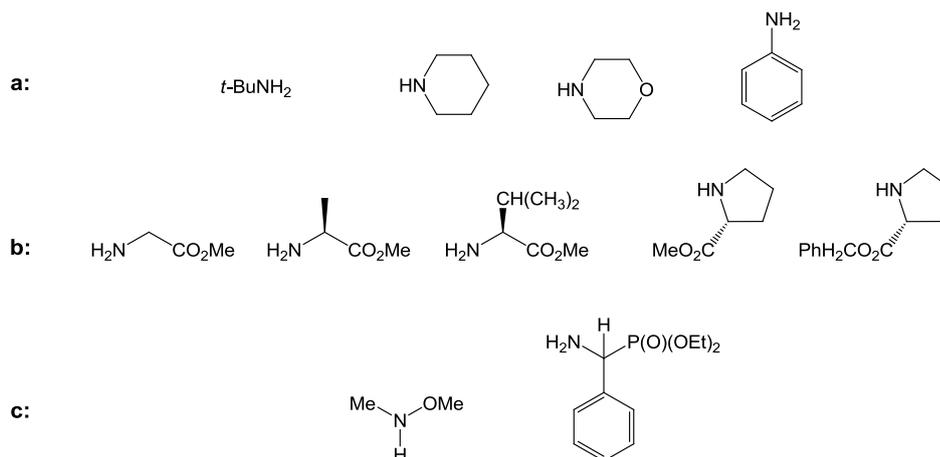


Figure 2. Structure of the amine nucleophiles used in aminocarbonylation

My results and observations are summarized as follows:

1. It was proved during the aminocarbonylation reactions of 2-iodoanisole, that the reactivity of this iodoarene substrate was not influenced by the methoxy group in the *ortho*-position, using *N*-nucleophiles with different structure (**Figure 3.**). It was established that the carboxamide/2-ketocarboxamide ratio can be regulated by the carbon monoxide pressure.

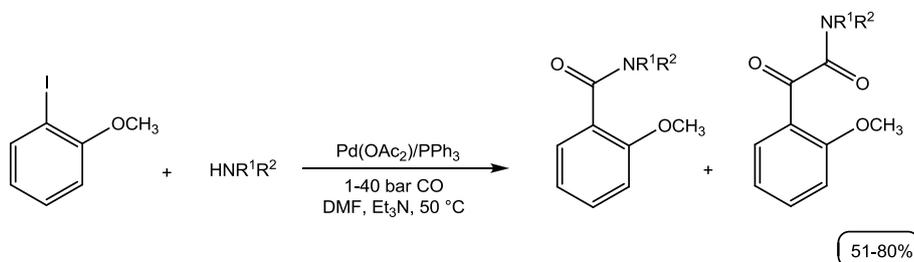


Figure 3. Aminocarbonylation of 2-iodoanisole

2. The aminocarbonylation of 1,8-diiodonaphthalene was carried out. While the application of secondary amines resulted in the formation of 1,8-dicarboxamides, the primary amines provided the corresponding *N*-substituted 1,8-naphthalimides in good yields (69-82%) in a chemoselective reaction (**Figure 4**).

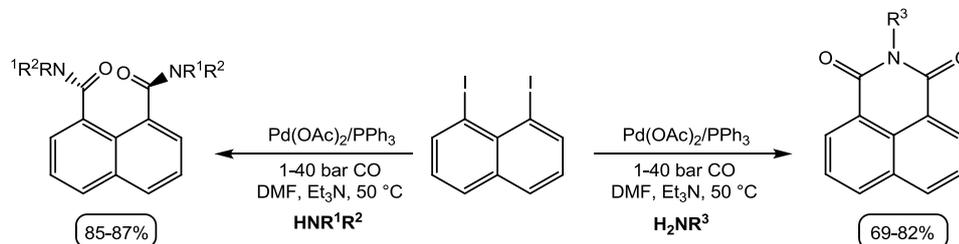


Figure 4. Aminocarbonylation of 1,8-diiodonaphthalene in the presence of primary and secondary amines

3. The systematic investigation of iodo-*N*-heteroaromatic substrates in aminocarbonylation revealed that the corresponding carboxamides can be synthesised in chemoselective reaction using 2-iodo-heteroaromatic compounds (2-iodopyridine, iodopyrazine) as substrates (**Figure 5**).

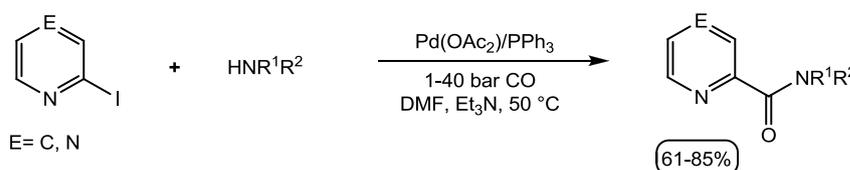


Figure 5. Aminocarbonylation of 2-iodopyridine and iodopyrazine

Structures of the possible catalytic intermediates which could be responsible for the selective formation of carboxamides and, in the same time, could be responsible for the lack of double carbon monoxide insertion were suggested. 3-Iodopyridine tends to undergo double carbon monoxide insertion and the mixture of carboxamides and 2-ketocarboxamides were obtained in the whole pressure range. *N*-Substituted nicotinamides with potential biological importance were synthesised using this methodology.

4. By using 5-chloro-7-iodo-8-hydroxy-quinoline and 5,7-diiodo-8-hydroxy-quinoline substrates under aminocarbonylation conditions, selective hydrogenolysis of the iodoarene functionality took place. It was established that the phenolic OH group induce the hydrogenolysis and the amines served as the H-source. It is worth noting that the above reaction is always accompanied by the direct carbonylation of the

amine resulting in the corresponding urea-type compound $((R'R''N)_2CO)$ (**Figure 6**).

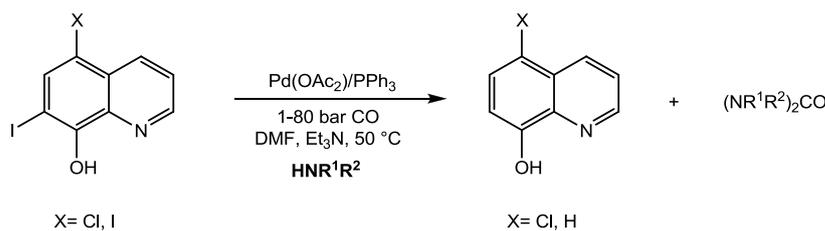


Figure 6. Dehydroiodination of 8-hydroxyquinoline derivatives under aminocarbonylation conditions

- No dehydroiodination of the 8-protected derivatives of the above mentioned 8-hydroxyquinoline compounds was detected under aminocarbonylation conditions. The oxidative addition of the iodoarene functionality was occurred exclusively by using the alkoxyquinoline derivatives containing both iodo- and chloroarene moieties. In this case the highly selective formation of 5-carboxamido-7-chloro-8-alkoxyquinolines was observed. 5-Carboxamido-7-iodo-8-benzyloxyquinolines, potential building blocks for further synthesis, were synthesised in high-yielding palladium-catalysed regioselective aminocarbonylation of 5,7-diiodo-8-benzyloxyquinoline (**Figure 7**).

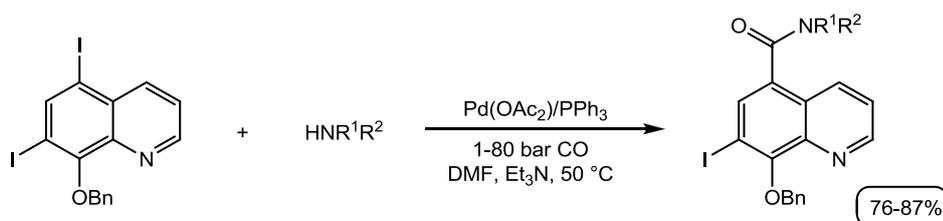


Figure 7. Regioselective aminocarbonylation of 5,7-diiodo-8-benzyloxyquinoline

- Aminocarbonylation of different substrates in the presence of functionalised amines (diethyl α -aminobenzyl-phosphonate) as *N*-nucleophile was carried out. It was established that the reactivity was not reduced by the phosphonate functionality. Although the iodoaromatics provided the mixture of carboxamides (86-98%) and 2-ketocarboxamides (2-14%), in the aminocarbonylation of various iodoaromatics and iodoalkenes the corresponding carboxamides with practical importance were obtained in high isolated yields (72-82%).

7. The palladium-catalysed aminocarbonylation of iodoarenes and iodoalkenes in the presence of *N,O*-dimethylhydroxylamine as the *N*-nucleophile was carried out. The reaction was highly chemoselective (>92%) yielding the expected Weinreb amides. In this way, a high-yielding, simple method for the synthesis of these widely used synthetic building blocks is provided (**Figure 8**).

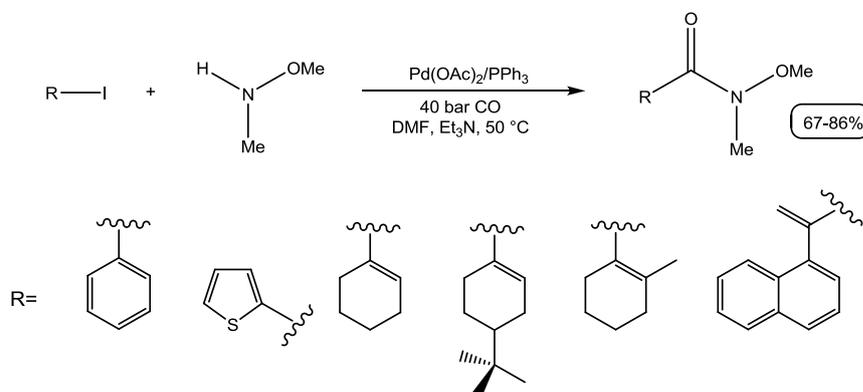


Figure 8. The synthesis of Weinreb amides in aminocarbonylation reaction

8. Although the systematic investigation on the aminocarbonylation of simple iodoarene and iodoalkene substrates ('model compounds') was the main goal of my PhD thesis, more than 60 new compounds, including a number of synthetic building blocks, were synthesised.

5. Publications, presentations

I. Publications forming the basis of PhD dissertation

1. **A. Takács**, B.Jakab, A.Petz, and L. Kollár:
Homogeneous catalytic aminocarbonylation of nitrogen-containing iodo-heteroaromatics. Synthesis of *N*-substituted nicotinamide related compounds.
Tetrahedron 63 (2007) 10372-10378. **IF: 2.869**
2. **A. Takács**, P. Ács and L. Kollár:
Facile synthesis of 1,8-naphthalimides in palladium-catalyzed aminocarbonylation of 1,8-diiodo-naphthalene.
Tetrahedron 64 (2008) 983-987. **IF: 2.897**
3. **A. Takács**, A. Petz and L. Kollár:
Palladium-catalyzed aminocarbonylation of iodoarenes and iodoalkenes with aminophosphonate as *N*-nucleophile.
Tetrahedron 64 (2008) 8726-8730. **IF: 2.897**
4. **A. Takács**, A. R. Abreu, A. F. Peixoto, M. Pereira and L. Kollár:
Synthesis of *ortho*-alkoxy-aryl carboxamides via palladium-catalyzed aminocarbonylation.
Synth. Commun. 39 (2009) 1534-1548. **IF: 0.961**
5. **A. Takács**, A. Petz and L. Kollár:
High-yielding synthesis of Weinreb amides via homogeneous catalytic carbonylation of iodoalkenes and iodoarenes.
Tetrahedron 66 (2010) 4479-4483. **IF: 3.011**
6. **A. Takács**, A. Szilágyi, P. Ács, L. Márk, A. F. Peixoto, M. M. Pereira and L. Kollár:
Palladium-catalyzed reactions of 8-hydroxy- and 8-benzyloxy-5,7-diiodoquinoline under aminocarbonylation conditions.
Tetrahedron 67 (2011) 2402-2406. **IF: 3.025**

II. Other publications

1. P. Ács, B. Jakab, **A. Takács** and L. Kollár:
Facile synthesis of 11-carboxamido-androst-4,9(11)-dienes via palladium-catalyzed aminocarbonylation.
Steroids 72 (2007) 627-632. **IF: 2.143**
2. **A. Takács**, A. Petz, B. Jakab and L. Kollár:
Aminocarbonylation of 2-iodothiophene. High-yielding synthesis of thiophen-2-yl-glyoxylamides.
Lett. Org. Chem. 4 (2007) 590-594. **IF: 0.981**

3. **A. Takács**, R. Farkas, A. Petz and L. Kollár:
High-yielding synthesis of 2-aryl-acrylamides via homogeneous catalytic aminocarbonylation of α -iodo-styrene and α, α' -diiodo-1,4-divinylbenzene.
Tetrahedron 64 (2008) 61-66. **IF: 2.897**
4. P. Ács, **A. Takács**, A. Szilágyi, J. Wölfling, G. Schneider and L. Kollár:
The synthesis of 17-alkoxycarbonyl- and 17-carboxamido-13 α -estra-1,3,5(10),16-tetraene derivatives via palladium-catalyzed carbonylation reactions.
Steroids 73 (2008) 669-675. **IF: 2.588**
5. **A. Takács**, P. Ács, R. Farkas, G. Kokotos and L. Kollár:
Homogeneous catalytic aminocarbonylation of 1-iodo-1-dodecene. The facile synthesis of odd-number carboxamides via palladium-catalyzed aminocarbonylation.
Tetrahedron 64 (2008) 9874-9878. **IF: 2.897**
6. P. Ács, **A. Takács**, A. Szilágyi, J. Wölfling, G. Schneider and L. Kollár:
The synthesis of 13 α -androsta-5,16-diene derivatives with carboxylic acid, ester and carboxamido functionalities at position-17 via palladium-catalyzed carbonylation.
Steroids 74 (2009) 419-423. **IF: 2.905**
7. **A. Takács**, R. Farkas, A. Petz and L. Kollár:
Synthesis of 2-naphthylacrylamides and 2-naphthylacrylates via homogeneous catalytic carbonylation of 1-iodo-1-naphthylethene derivatives.
Tetrahedron 65 (2009) 4795-4800. **IF: 3.219**
8. **A. Takács**, P. Ács, Z. Berente, J. Wölfling, Gy. Schneider and L. Kollár:
Novel 13 β - and 13 α -D-homo steroids: 17 α -carboxamido-D-homoestra-1,3,5(10),17-tetraene derivatives via palladium-catalyzed aminocarbonylations.
Steroids 75 (2010) 1075-1081. **IF: 3.106**
9. P. Ács, **A. Takács**, M. Kiss, N. Pálinkás, S. Mahó and L. Kollár:
Systematic investigation on the synthesis of androstane-based 3-, 11- and 17-carboxamides via palladium-catalyzed aminocarbonylation.
Steroids 76 (2011) 280-290. **IF: 2.829**
10. D. Marosvölgyi-Haskó, **A. Takács**, Zs. Riedl and L. Kollár:
High-yielding synthesis of 1-isoindolinone derivatives via palladium-catalyzed cycloaminocarbonylation.
Tetrahedron 67 (2011) 1036-1040. **IF: 3.025**
11. D. Marosvölgyi-Haskó, A. Petz, **A. Takács**, L. Kollár:
Synthesis of tetrahydrophthalazine and phthalamide (phthalimide) derivatives via palladium-catalyzed carbonylation of iodoarenes.
Tetrahedron 67 (2011) 9122-9128. **IF: 3.025**

12. R. M. B. Carrilho, **A. Takács**, M. M. Pereira, L. Kollár
Systematic study on the catalytic synthesis of unsaturated 2-ketocarboxamides: palladium-catalyzed double carbonylation of 1-iodocyclohexene.
Tetrahedron 68 (2012) 204-207. **IF: 2.803**
13. R. Farkas, E. A. Molnár, **A. Takács**, L. Kollár:
High-yielding synthesis of 1-carboxamido-3,4-dihydronaphthalenes via palladium-catalyzed aminocarbonylation.
Tetrahedron 69 (2013) 500-504. **IF: 2.803***
14. R. M. B. Carrilho, Moreno Maria J. S. M., M. M. Pereira, **A. Takács**, L. Kollár:
A new facile synthesis of steroid dimers containing 17,17'-dicarboxamide spacers.
Tetrahedron Lett. 54 (2013) 2763-2765. **IF: 2.397***
15. 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 78 (2013) 693-699. **IF: 2.803***
16. M. Gergely, R. Farkas, **A. Takács**, A. Petz, L. Kollár:
Synthesis of *N*-picolyloxycarboxamides via palladium-catalysed aminocarbonylation of iodobenzene and iodoalkenes.
Tetrahedron 70 (2014) 218-224. **IF: 2.803***

III. Presentations and posters forming the basis of PhD dissertation

1. L. Kollár, A. Petz, D. Haskó-Marosvölgyi, **A. Takács**:
Palladium-Catalysed Aminocarbonylation of Iodoarenes and Iodoalkenes.
24th Int. Conf. Organomet. Chem. (ICOMC-24)
Taipei (Taiwan), 17-23 July, 2010.

IV. Other presentations

1. **A. Takács**, R. Farkas, A. Szilágyi, L. Kollár:
Activation of Carbon Monoxide: Palladium-catalysed Carbonylations of 1-Iodo-1-aryl-ethenes.
18th Eur. Conf. Organomet. Chem. (EuCOMC-XVIII)
Gothenburg (Sweden), 22-25 June, 2009.
2. **A. Takács**, D. Marosvölgyi-Haskó, Zs. Riedl, L. Kollár:
High-yielding synthesis of *N*-heterocycles via palladium-catalysed cycloaminocarbonylation.
19th Eur. Conf. Organomet. Chem. (EuCOMC-XIX)
Toulouse (France), 03-07 July, 2011.

3. N. Pálincás, P. Ács, M. Kiss, **A. Takács**, S. Mahó, L. Kollár:
Systematic investigation on the synthesis of androstane-based 3-, 11- and 17-
carboxamides via palladium- catalysed aminocarbonylation.
19th Eur. Conf. Organomet. Chem. (EuCOMC-XIX)
Toulouse (France), 03-07 July, 2011.