Themes of PhD dissertation

AMINOCARBONYLATION REACTIONS OF IODOAROMATICS

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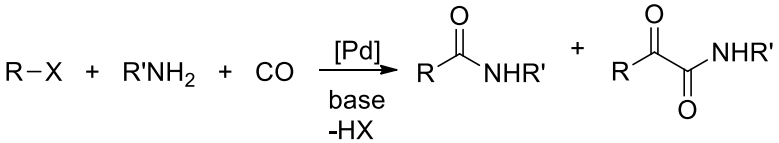
1. Introduction

Discoveries of the 70's in organic chemistry have revolutionized the synthesis of carbon compounds. Application of cross-coupling reactions with transition metal catalysts has started a new era that affected most scientific fields of chemistry. Carbon-carbon cross-coupling is a specific area of organometallic chemistry where carbon monoxide is one of the crucial reagents. Nowadays, CO is considered the most widely used C1 building block. This molecule has the capacity to easily intercalate into metal-carbon (M-C) bond of an organometallic compound even at atmospheric pressure, for example by creating an acyl-palladium complex that is a key intermediate of catalytic cycles of this kind. Depending on the reaction partners of the acyl-metal complex intermediate important synthetic reagents can be created such as carboxylic acids, aldehydes or ketones. Starting materials can be alkenes, alkynes, aryl, alkenyl or vinyl compounds. A great variety of products can be obtained based on the nucleophile used. In case the substrate is reacted with an alcohol, water, or amine in CO atmosphere the product would be ester, carboxylic acid, or amide respectively. Palladium catalysed reactions of aryl halides – where *N*-nucleophiles with various structures are presented – have become essential methods for the synthesis of aromatic amide derivatives.

The subject of this thesis is the investigation of palladium catalysed aminocarbonylation reactions of iodoaromatics using primary and secondary amines as nucleophiles in homogeneous catalytic reactions resulting in amides as final products. This method is suitable for the selective one-step formation of an amide group without the preliminary use of any protective group at mild reaction conditions (low pressure and temperature). Aryl halides as substrates have been reacted with various *N*-nucleophiles in CO atmosphere in the presence of catalytic amount of palladium complex. During the reactions, the leaving group (X) is formally substituted by the nucleophilic reagent attached to one or two inserted molecules of CO. The reactions can be carried out at 50-140 °C and 1-60 bar CO pressure. It is worth noting that stoichiometric amount of base is required that is crucial for the regeneration of the catalyst to form palladium(0) species of key importance in the activation of the substrates (R-X) (Scheme 1).



Scheme 1. General scheme of aminocarbonylation reactions

2. Aims of the thesis

- Aminocarbonylation reactions resulting in ring-closure products in intramolecular carbonylations: investigation of the effect of substrate and amine structure on selectivity and reaction rate.
- Investigation of the effect of functional groups at positions 5 and 7 of indole derivatives on the reaction rate and chemoselectivity of aminocarbonylation.
- Investigation of electron-donating and -withdrawing substituents on the reaction rate and chemoselectivity of aminocarbonylation.
- Investigation of the effect of normal-chain and branched amines furthermore various catalysts on chemoselectivity in case of *para*-substituted iodobenzenes.
- Investigation of the influence of reaction conditions (CO pressure, reaction time, *N*-nucleophile) on reactivity and chemoselectivity.
- Isolation and full analytical characterization of new compounds prepared by aminocarbonylation.
- Applicability of a new environmentally benign solvent in aminocarbonylation.

3. Experimental methods

All laboratory experiments were carried out using inert Schlenk-technique and autoclaves for high pressure experiments. The latest one is a 100 cm^3 stainless steel device capable to withstand 10-40 bar pressure that was applied for the experiments. Conversion and composition of the reaction mixture of aminocarbonylation were determined by GC-MS. The following spectroscopic methods were used for identification and analysis: GC-MS, IR, ^{1}H- and ^{13}C-NMR spectroscopy, and elemental analysis.

4. Thesis points

As the aim of this doctoral thesis several iodoaromatic model compounds have been subjected to palladium catalysed aminocarbonylation in the presence of *N*-nucleophiles (primary and secondary amines) (Figure 2/a), amino acid methyl esters (Figure 2/b) and hydrazines (Figure 2/c) at different CO pressure (1-40 bar). The catalytically active palladium(0)-complex has been synthesised *in situ* from palladium(II) acetate with triphenyl phosphine.

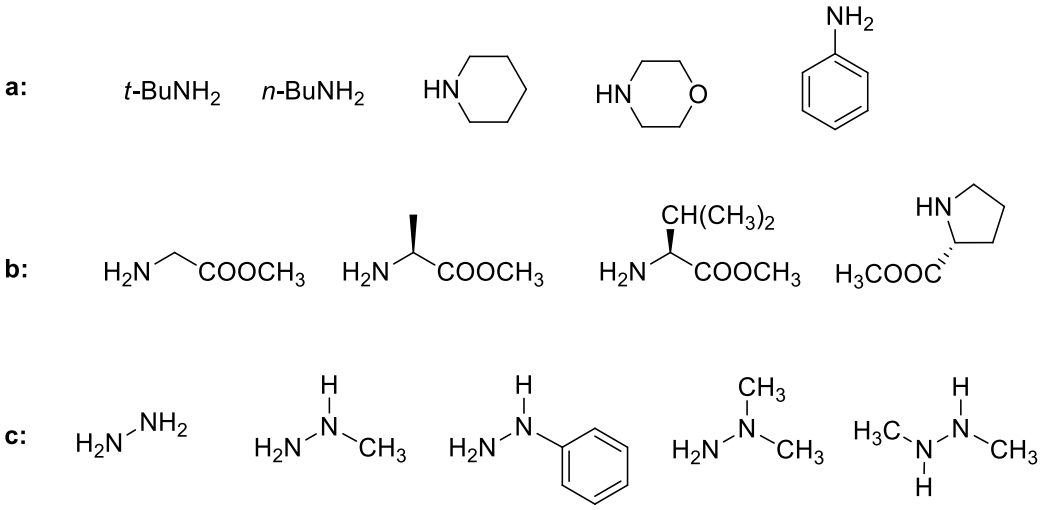


Figure 2. Structures of the *N*-nucleophiles

1. Aminocarbonylation of bifunctional 2-iodobenzyl bromide resulted in the conclusion that the outcome of the reaction is highly amine dependent. Primary amines create ring-closed products (1-isoindoline derivatives – Figure 3) in chemoselective reactions with good yields (75-89%). Using hydrazines as nucleophiles, the intramolecular hydrazinocarbonylation of 2-iodobenzyl bromide occurs. The ring-closure products, 1,2,3,4-tetrahydrophthalazine-1-on derivatives, have been synthesised with good yields (52-85%).

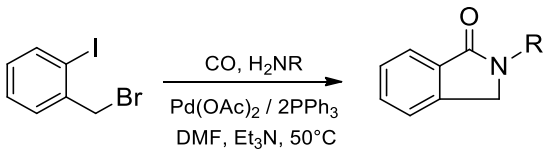


Figure 3. Cycloaminocarbonylation of 2-iodobenzyl bromide in the presence of primary amines

2. Cycloaminocarbonylation of 1,2-diiodobenzene with primary amines has been successfully carried out. The corresponding phthalimide derivative has been isolated in 30-32 % yield (Figure 4). When 1,2-diiodobenzene was hydrazinocarbonylated the main products have been identified as monohydrazides.

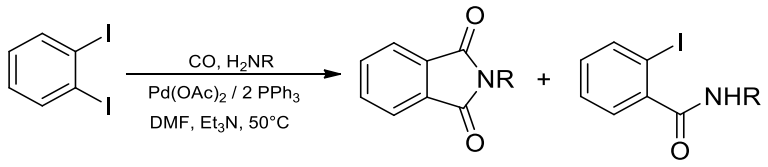


Figure 4. Aminocarbonylation of 1,2-diiodobenzene with primary amines

3. A correlation has been found between the relative position of the iodine substituent and N-atom and the chemoselectivity in the aminocarbonylation reactions of iodoheteroaromatics. Less chemoselectivity was observed during the ketoamide-indole derivative formation from the aminocarbonylation of 5-iodoindole (Figure 5) than from 5-bromo-7-iodoindole. Strictly monoinsertion of CO has been observed to aniline with both substrates creating amide type products.

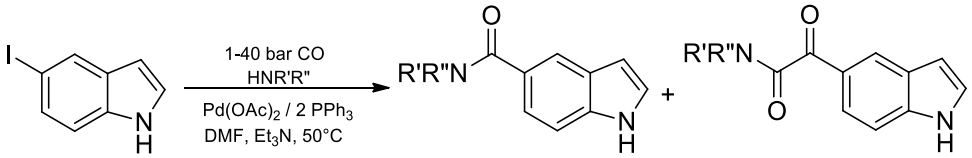


Figure 5. Aminocarbonylation of 5-iodoindole

Suzuki-coupling has been carried out on 5-bromo-7-ketoamidoindole derivatives and the corresponding product, 5-phenyl-7-ketoamidoindole, has been obtained with full conversion (Figure 6).

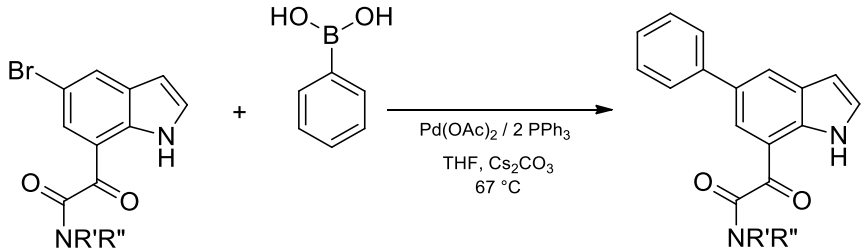


Figure 6. Suzuki-coupling reactions of 5-bromo-7-ketoamidoindoles

4. In the aminocarbonylation of iodobenzene substrates it was found that the *para*-substituent has a straight effect on reaction rate and chemoselectivity (Figure 7). For this, 15 *para*-substituents have been tested with *tert*-butylamine at atmospheric and high CO pressure. Only low conversion can be achieved at atmospheric CO pressure however, the increase in conversion by the increasing Hammett substituent constant (σ) is significant and shows also an increasing tendency at higher (40 bar) CO pressure. Considering selectivity, those substrates possessing electron-donating groups at *para*-position ($-\sigma_p$) gave higher than 70% 2-ketoamide ratio. Substrates with electron-withdrawing groups slightly pushed the selectivity towards amide formation.

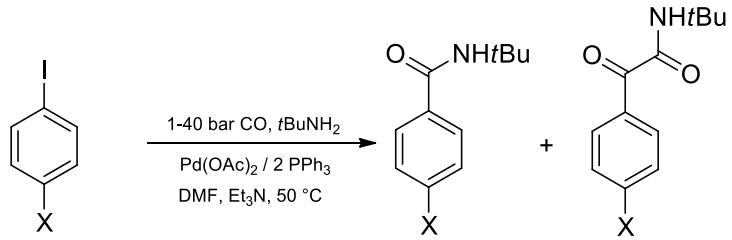


Figure 7. Aminocarbonylation of *para*-substituted iodobenzene derivatives

5. It was found that by using *n*-butylamine the reactivity with better electron-withdrawing groups can be increased. Selectivity shifted firmly to amide formation at positive Hammett substituent constant groups. When aminocarbonylation was carried out with bidentate ligands a similar behaviour of Pd-dppf and Pd-PPh_3 systems was observed. In contrast to these observations, the reaction rate decreased noticeably using XanthPhos ligand and only amide derivatives were detected in chemoselective reactions.

6. Aminocarbonylation of *para*-substituted iodobenzene derivatives in a biomass-based solvent, γ-valerolactone (GVL) was carried out and the solvent effect on reactivity and selectivity was investigated. The reactivity toward ketoamide products decreased substantially accompanied by higher chemoselectivity.

5. Scientific publications, presentations

I. Publications related to the subject of the PhD thesis:

1. **D. Marosvölgyi-Haskó**, T. Kégl, L. Kollár:
Substituent effects in aminocarbonylation of *para*-substituted iodobenzenes.
Tetrahedron 72 (2016) 7509-7516. **IF: 2.645**

2. **D. Marosvölgyi-Haskó**, B. Lengyel, J. M. Tukacs, L. Kollár, L. T. Mika:
Application of ă-Valerolactone as an Alternative Biomass-Based Medium for Aminocarbonylation Reactions.
ChemPlusChem 81 (2016) 1-7. **IF: 2.869**

3. A. Takács, **D. Marosvölgyi-Haskó**, Zs. Kabak-Solt, L. Damas, F. M. S. Rodrigues, R. M. B. Carrilho, M. Pineiro, M. M. Pereira, L. Kollár:
Functionalization of indole at C-5 or C-7 via palladium-catalysed double carbonylation. A facile synthesis of indole ketocarboxamides and carboxamide dimers.
Tetrahedron 72 (2016) 247-256. **IF: 2.645**

4. **D. Marosvölgyi-Haskó**, A. Takács, Zs. Riedl, L. Kollár:
High-yielding synthesis of 1-isoindolinone derivatives via palladium-catalysed cycloaminocarbonylation.
Tetrahedron 67 (2011) 1036-1040. **IF: 3.025**

5. **D. Marosvölgyi-Haskó**, A. Petz, A. Takács, L. Kollár:
Synthesis of tetrahydrophthalazine and phthalamide (phthalimide) derivatives via palladium-catalysed carbonylation of iodoarenes.
Tetrahedron 67 (2011) 9122-9128. **IF: 3.025**

II. <u>Conferences related to the subject of the PhD thesis:</u>

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.

2. 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.