Final Report

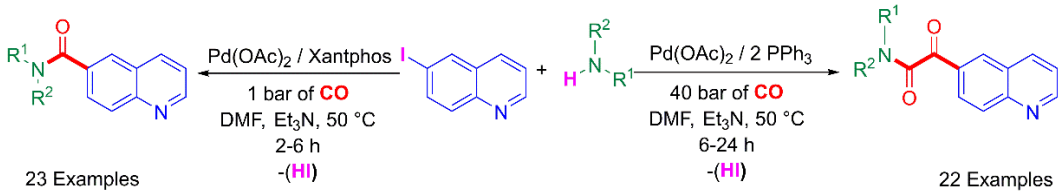
Palladium-catalyzed aminocarbonylation reaction: a highly efficient synthetic tool for the synthesis of amides of biological importance

The palladium-catalyzed aminocarbonylation has a great synthetic relevance producing carboxamides under mild reaction conditions. Under optimized conditions, iodo-(hetero)arene and iodo-alkene substrates with various primary and secondary amines in carbon monoxide atmosphere provide amides of biological or practical importance. This three-component process has outstanding importance since such carboxamides could be produced by using this method, which are not available via conventional organic synthetic pathways. Furthermore, there is a possibility to form 2-keto-carboxamide type derivatives, caused by double carbon monoxide insertion, under high-pressure conditions making this carbonylative transformation even more precious. Considering the above-mentioned facts, during my postdoctoral fellowship, my goal was to investigate palladium-catalyzed aminocarbonylation in detail and to produce carboxamides of biological or practical relevance in selective manner. The results reached in the research project can be divided into three different parts which will be discussed below.

I. Investigation of palladium-catalyzed aminocarbonylation of iodo-heteroarenes.

a) Palladium-catalyzed aminocarbonylation of 6-iodoquinoline.[1]

In this work, the quinoline skeleton was functionalized at position 6 via palladium-catalyzed aminocarbonylation in the presence of amines of various structures providing several 6-carboxamido- and 6-glyoxylamido-quinolines (**Scheme 1**). The selectivity of the reaction was strikingly influenced by the ligand and the carbon monoxide pressure used during the reactions.



Scheme 1. Palladium-catalyzed aminocarbonylation of 6-iodoquinoline.

It was shown, that the aminocarbonylation of 6-iodoquinoline provides more than 82% selectivity for the target double carbonylated derivatives in almost all cases under 40 bar of carbon monoxide pressure in the presence of $Pd(OAc)_2$ / 2 PPh_3 catalyst. In some cases, the selectivity towards quinoline-6-glyoxylamides was decreased (28-66%) due to the steric hindrance of some amine nucleophiles (e.g. valine and phenylglycine methyl ester, 4-(ethylaminomethyl)pyridine). It has to be noted, that a primary aromatic amine aniline provided the 6-(*N*-phenylcarboxamido)quinoline product exclusively and the ketoamide was not detected by GC-MS analysis. The 22 novel 6-glyoxylamido-quinoline derivatives synthesized in the aminocarbonylation of 6-iodoquinoline substrate were isolated and fully characterized. In this way, a novel one-pot synthetic approach of valuable 6-glyoxylamido-quinolines was developed, whose synthesis is quite difficult with conventional organic synthetic methods.

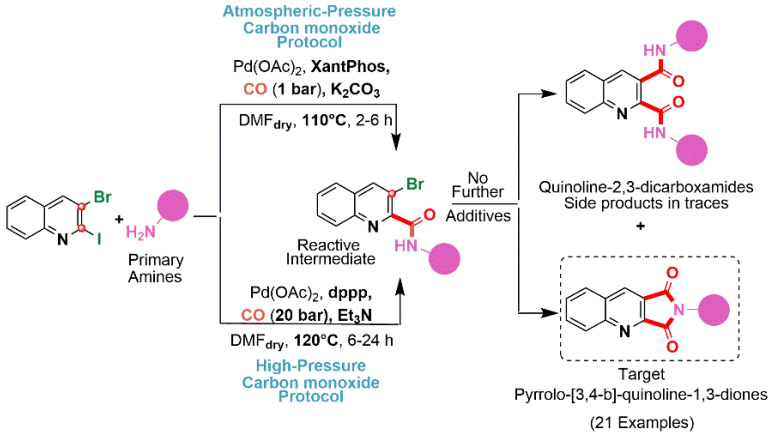
When the bidentate XantPhos was used instead of triphenylphosphine under atmospheric carbon monoxide pressure, the synthesis of quinoline-6-carboxamides was

also achieved via palladium-catalyzed aminocarbonylation. Under these conditions, the reactions showed extremely high chemoselectivity giving exclusively the desired monocarbonylated products.

The molecular structure of some products (*N*-cyclohexylquinoline-6-carboxamide, *N*-phenylquinoline-6-carboxamide, and *N*-decyl-2-oxo-2-(quinolin-6-yl)acetamide) was unambiguously supported by single-crystal X-ray diffraction study. The novel 2-ketocarboxamides and carboxamides, synthesized and isolated in this work, could have biological and practical relevance. The perfect selectivity toward the target compounds and the good isolated yields make these reactions of synthetic importance.

b) Palladium-catalyzed aminocarbonylation of 3-bromo-2-iodoquinoline.[2]

In this work, the Pd-catalyzed aminocarbonylation of 3-bromo-2-iodoquinoline was investigated in the presence of various primary amines. (**Scheme 2**).



Scheme 2. Synthesis of *N*-substituted pyrrolo[3,4-b]quinoline-1,3-diones under aminocarbonylation conditions.

A detailed optimization study revealed that the reaction conditions have a great influence on the selectivity toward the target pyrroloquinolinediones. Under atmospheric conditions, the $Pd(OAc)_2$ / XantPhos catalyst was the most effective using K_2CO_3 at 110 °C. Moreover, in the presence of $Pd(OAc)_2$ / dppp catalyst, the reaction selectively provided the target ring closed product under 20 bar of carbon monoxide pressure using Et_3N at 120 °C. It has to be mentioned, that in some cases the quinoline-2,3-dicarboxamide type side products were also isolated in low yields, and fully characterized giving a new and non-described quinoline-2,3-dicarboxamide scaffold. The formation of the products was explained by a proposed mechanism based on the well-known elementary steps of the catalytic cycle of aminocarbonylation. In this way, a panoply of novel *N*-substituted pyrrolo[3,4-b]quinoline-1,3-diones were synthesized by simple one-step palladium-catalyzed carbonylative cyclization of 3-bromo-2-iodoquinoline with a large variety of primary amines.

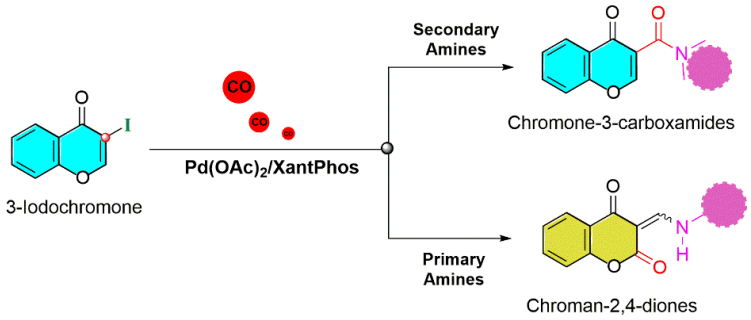
It has to be also emphasized, that an unexpected and interesting racemization was perceived during the synthesis of some pyrroloquinolinediones even though enantiopure L-amino acid methyl esters were used as *N*-nucleophiles reaction partners, which process was justified by single crystal X-ray diffraction study, and the measurements of the specific rotations of these compounds. Although in-depth investigations of the

stereochemical and mechanistic features of the synthesis have not yet been carried out, these preliminary results indicate that a possible palladium-promoted-interconversion between enantiomers of the first-stage formed *N*-(3-bromoquinoline)-2-acetyl-α-amino acid methyl esters could happen, as it is described by Beller's group, for similar *N*-acetyl α-amino acids.

In summary, the high efficiency, the broad scope of amines with various structures, and the good to excellent isolated yields (up to 82%) make this synthetic route one of the prominent alternative pathways to pyrroloquinolinediones.

c) Palladium-catalyzed carbonylation reactions of 3-iodochromone.[3]

In this study, the palladium-catalyzed transformations of 3-iodochromone were investigated under aminocarbonylation conditions (**Scheme 3**). It was shown, after a detailed optimization study that the corresponding chromone-3-carboxamide was formed selectively under appropriate reaction conditions ($Pd(OAc)_2$ / XantPhos catalyst, DMF, Et_3N, 1 bar of CO, 50°C) in the presence of *N*,*O*-dimethylhydroxylamine.



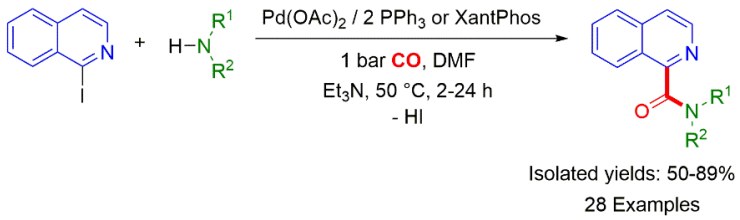
Scheme 3. Palladium-catalyzed carbonylative transformations of 3-iodochromone.

To extend the scope of the chromone-3-carboxamide family, further 7 secondary amines were used as nucleophiles providing exclusively the target compounds in high yields. Using primary amines in the reactions under the above-mentioned conditions, a strikingly different phenomenon was observed: 3-functionalized chromane-2,4-diones were formed as main carbonylative products instead of the chromone-3-carboxamide type derivatives. In this case, the tendency of 3-iodochromone substrate to undergo ANRORC (*A*ddition of the *N*ucleophile, *R*ing *O*pening, and *R*ing *C*losure) rearrangement with *N*-nucleophiles, was crucial to shift the reaction toward an unprecedented chemoselective carbonylative transformation, where a late-stage carbonyl insertion is favored concomitantly to the last ring-closure step. The proposed aza-Michael addition/ring-opening/intramolecular aryloxycarbonylation sequence showed compatibility with primary amines providing a novel synthetic approach to access chroman-2,4-dione framework. The formation of the 3-functionalized-chromane-2,4-dione products was rationalized by a proposed mechanism based on the well-known elementary steps catalytic cycle of aminocarbonylation. The isolation and characterization (NMR, IR, HRMS) of the new carbonylated derivatives of various structures were also accomplished. Furthermore, the solid-state structures of one chromone-3-carboxamide and one chroman-2,4-dione were undoubtedly established by single-crystal XRD analysis.

In conclusion, various practically important chromone-3-carboxamides and chroman-2,4-diones were prepared, starting from 3-iodochromone, under palladium-catalyzed aminocarbonylation conditions.

d) Synthesis of isoquinoline-1-carboxamides via Pd-catalyzed aminocarbonylation.[4]

In this research, the palladium-catalyzed aminocarbonylation process of 1-iodoisoquinoline was accomplished under mild reaction conditions (1 bar of CO, 50 °C) in DMF (**Scheme 4**).



Scheme 4. High yielding palladium-catalyzed aminocarbonylation of 1-isoquinoline.

By using simple primary and secondary amines as well as aliphatic amines containing a (hetero)aromatic moiety (e.g. 2-, 3-, and 4-picolylamines), the $Pd(OAc)_2$ / 2 PPh_3 catalyst was very effective, producing the corresponding isoquinoline-1-carboxamides selectively in short reaction times (2-8 hours). In the presence of less reactive *N*-nucleophiles (e.g. amino acid methyl esters, aromatic amines) or amines having more complex structures (nortropinone, nortropine, and diethyl-(α-aminobenzyl)-phosphonate), the bidentate XantPhos had to be used to convert completely the starting material into the target carboxamides at 50 °C under atmospheric conditions in 8-24 hours. All of the 28 isoquinoline-1-carboxamides, synthesized in this research, were isolated and fully characterized.

Moreover, the aminocarbonylation of 1-iodoisoquinoline was also performed and investigated in three bio-renewable solvents (γ-valerolactone (GVL), ethyl levulinate (EtLev), and 2-methyltetrahydrofurane (2-MeTHF)) under the same reaction conditions as in the case of conventional DMF in the presence of some amines. Performing the reactions in GVL by using 10 nucleophiles chosen from the above group of amines, almost the same conversions were detected after 8 hours as in the conventional solvent. A few reactions were also performed by using cyclopentylamine, piperidine, aniline, and alanine methyl ester in EtLev and 2-MeTHF and it was seen that ethyl levulinate showed similar properties to the GVL, especially in the case of aniline and alanine methyl ester, while the 2-MeTHF was not effective enough to reach comparable conversion to the other two green candidates as well as the DMF.

The identical chemoselectivity and similar reactivity experiences in the case of DMF, GVL, and EtLev justify that the same catalytic cycle could be responsible for the synthesis of target isoquinoline-1-carboxamides in both conventional and green solvents. In this way, a proposed mechanism was given based on the well-known elementary steps of carbonylation.

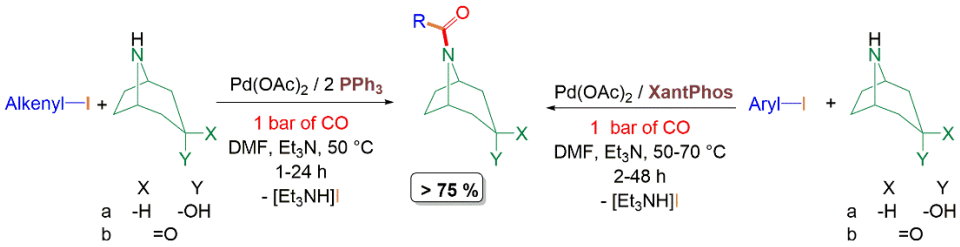
In overall, an effective process was described allowing to produce of a wide range of isoquinline-1-carboxamides in the presence of different amine nucleophiles having various properties. It was also justified that some green solvent (GVL, EtLev) could be

an appropriate reaction medium for this palladium-catalyzed aminocarbonylation of 1-iodoisoquinoline. The mild reaction conditions, the chemospecific reactions, the good to high isolated yields (50-89%), and the applicability of the use of bio-renewable solvent make this reaction of synthetic importance.

II. Using amines having biological importance as nucleophile partners in the palladium-catalyzed aminocarbonylation of iodo-alkenes and iodo-heteroarenes.

a) Nortropane-based compounds as nucleophile reaction partners.[5]

In this study, two nortropane-based derivatives (nortropinone, nortropine) were used as *N*-nucleophiles in palladium-catalyzed aminocarbonylation of several iodoalkenes and iodo-(hetero)arenes (**Scheme 5**).



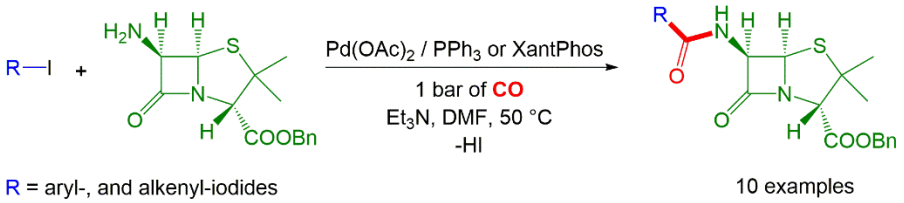
Scheme 5. Synthesis of *N*-acyl nortropanes via palladium-catalyzed aminocarbonylation of aryl-, and alkenyl-iodides.

In the presence of simple iodoalkenes (1-iodocyclohexene, 4-*tert*-butyl-1-iodocyclohexene, *trans*-1-iodo-1-octene), as well as biologically important skeletons possessing iodoalkene functionality (2-iodobornene, 17-iodo-androst-16-ene), the target carboxamide derivatives were produced exclusively under atmospheric carbon monoxide pressure at 50 °C by using $Pd(OAc)_2$ / 2 PPh_3 catalysts. Performing the reactions with iodobenzene, lower reactivity was observed than in the case of iodoalkene substrates using the above-mentioned catalysts. Thus, increased carbon monoxide pressure (40 bar) was used to improve the conversion of this reaction. However, the conversion was still not complete after 48 hours of reaction time, but the chemoselectivity was shifted toward the corresponding 2-ketocarboxamide formed due to the double CO insertion. Additionally, by changing the triphenylphosphine to the bidentate XantPhos, the target carboxamide was formed selectively under mild reaction conditions (1 bar of CO, 50-70 °C). Using these optimized reaction conditions, we were able to synthesize various *N*-acylnortropane derivatives in the presence of some iodo-(hetero)arenes in palladium-catalyzed aminocarbonylation reactions. The new carboxamide derivatives were isolated in moderate to good yields (51-92%) and they were fully characterized.

In summary, it can be stated, that the palladium-catalyzed aminocarbonylation provides an efficient tool for the 'acylation' of amines possessing biologically important skeletons. It is based on the good acylating ability of the palladium(II)-acyl species formed during the catalytic cycle of the aminocarbonylation. In this way, important carboxamides could be synthesized, that cannot be produced by using conventional organic synthetic methods.

b) Using 6-aminopenicillanic acid as a nucleophile reagent in palladium-catalyzed aminocarbonylation.

The 6-aminopenicillanic acid (6-APA) is a valuable amine nucleophile, because it has biological importance, so producing its *N*-acyl derivatives in a one-pot homogeneous carbonylation process under mild conditions could have great synthetic importance (**Scheme 6**).

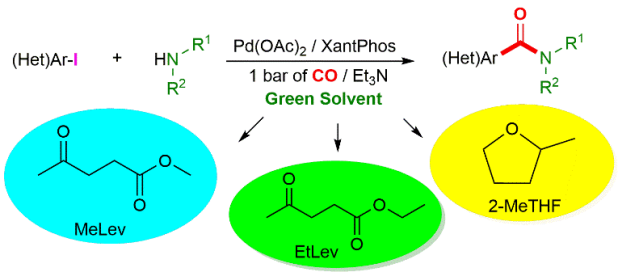


Scheme 6. Synthesis of new penicillin families via palladium-catalyzed aminocarbonylation.

In this work, first, the benzylation of the carboxylic functionality was performed to avoid solubility problems caused by the salt formation in the presence of the base. Using the benzyl ester of the 6-aminopenicillanic acid as a nucleophile reagent, an optimization study was performed using simple iodoalkene and iodoarene substrates. Under appropriate conditions ($Pd(OAc)_2$ / 2 PPh_3 or XantPhos, 1 bar of CO, 50 °C, DMF, Et_3N) several iodoalkenes (1-iodocyclohexene, 4-*tert*-butyl-1-iodo-cyclohexene, *trans*-1-iodo-1-octene, 2-iodobornene, 17-iodo-androsta-16-ene) and iodo(hetero)arenes (iodobenzene, 2- and 3-iodopyridine, 2-iodothiophene) were successfully used to synthesize the corresponding *N*-acyl derivatives of the 6-APA. Furthermore, some *para*-substituted iodobenzene substrates (e.g. 4-iodobenzonitrile, 4-iodotoluene, etc.) were also applied to investigate the substituent effect on the reactions. In this way, an efficient synthetic process has been developed for the synthesis of novel penicillin families, which could have biological importance.

III. Testing of some biomass-derived solvent as possible reaction media in palladium-catalyzed aminocarbonylation.[6]

In this research, methyl levulinate (MeLev), ethyl levulinate (EtLev), and 2-methyltetrahydrofuran (2-MeTHF) as bio-derived hemicellulose-based solvents were applied as green alternatives in palladium-catalyzed aminocarbonylation reactions. Iodobenzene and morpholine were used in the optimization reactions under different conditions such as temperatures, pressures, and ligands. It was shown that the XantPhos ligand had a great influence on conversion (98 %) and chemoselectivity (100 % carboxamide) compared with the monodentate PPh_3 (**Scheme 7**).



Scheme7. Palladium-catalyzed aminocarbonylation in biomass-derived solvents.

With the optimized conditions in our hand, we extended the scope of substrates with 19 candidates (various *para*-, *ortho*-, and *meta*-substituted iodobenzene derivatives, and iodo-heteroarenes), as well as 8 different primary and secondary amine nucleophiles. It was unambiguously proved, that the ‚alkyl levulinate'-type solvents are much more effective than the 2-MeTHF. According to our results, it was justified that methyl and ethyl levulinate could be used as an alternative solvent for palladium-catalyzed aminocarbonylation reactions, opening a greener procedure for this synthetically relevant transformation.

In my postdoctoral fellowship, it was justified that palladium-catalyzed aminocarbonylation is a highly efficient tool for the selective synthesis of various carboxamides under mild reaction conditions. The synthetic routes, described during the research project, are applicable to produce such important amides that are not available by using conventional synthetic methods. Furthermore, it has also been established that the palladium(II)-acyl intermediate, formed in the catalytic cycle, could be considered a good 'acylating-agent' providing the opportunity to use amines with biological importance as nucleophile reagent during the aminocarbonylation process. Finally, new biomass-derived solvents were successfully used as an alternative reaction medium in palladium-catalyzed aminocarbonylation, allowing the possibility to replace the conventional fossil-based organic solvents.

References:

1. Chniti S; Kollár L.; Bényei A.; Takács A. Highly selective synthesis of 6-glyoxylamidoquinoline derivatives via palladium-catalyzed aminocarbonylation. *Molecules* **2022**, *27*, 4.
2. Chniti S; Kollár L.; Bényei A.; Dörnyei Á.; Takács A. Highly Chemoselective One-Step Synthesis of Novel *N*-Substituted-Pyrrolo[3,4-b]quinoline-1,3-diones via Palladium-Catalyzed Aminocarbonylation/Carbonylative Cyclisation Sequence. *Eur. J. Org. Chem.* **2023**, *26*, 1-11.
3. Chniti S; Pongrácz P.; Kollár L.; Bényei A.; Dörnyei Á.; Takács A. Synthesis of Chroman-2,4-diones via Ring-Opening/Ring-Closing Reaction Involving Palladium-Catalyzed Intramolecular Aryloxycarbonylation. *Accepted in J. Org. Chem., Manuscript in Press* **2024.**
4. Uzunlu N., Zugó A., Kollár L., Dörnyei Á., Takács A. Synthesis of Isoquinoline-1-Carboxamides via Palladium-Catalyzed Aminocarbonylation. *This research was presented as a poster in the Tetrahedron Symposium in 2023. This work will be submitted in February 2024 to Tetrahedron journal.*
5. Kollár L.; Erdélyi Á.; Rasheed H.; Takács A. Selective Synthesis of N-Acylnortropane Derivatives in Palladium-Catalysed Aminocarbonylation. *Molecules* **2021**, *26*, 1813.
6. Uzunlu N., Pongrácz P., Kollár L., Takács A. Alkyl Levulinates and 2-Methyltetrahydrofuran: Possible Biomass-Based Solvents in Palladium-Catalyzed Aminocarbonylation. *Molecules* **2023**, *28*, 442.

Pécs, 30 October 2023

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