

UNIVERSITY OF PÉCS

Doctoral School of Chemistry

Synthesis of alkenyl iodides and their amino- and alkoxy carbonylation reactions in the presence of palladium(0)-triphenylphosphine catalysts

PhD Thesis

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I. Introduction

Due to the diverse research efforts, the transition metal catalysed reactions can be discussed in several ways.

The main features of the transition metal and the modes of coordination are substantially determined by the electronic and steric properties of the ligands attached. The coordination of the molecules entering to the coordination sphere is influenced by the structural and electronic features of the other ligands already bonded. The catalytic activity, the efficiency of the catalyst, the selectivity issues can be rationalised by these peculiarities. The right choice of the ligand can make ideal conditions for the reaction leading to the target compounds.

In addition, the recognition of the structure–reactivity relations, the right selection of the substrates to a given catalyst can also be considered as a precondition of the successful application of a catalytic reaction.

The planning of catalytic reactions in respect to environmental, economical conditions, as well as the mild reaction conditions, the limited amount of the side products, the easy availability of the substrates are further important issues. Regarding syntheses of practical importance, the fundamentals of green chemistry has also to be considered.

In addition to simple model compounds, more complicated ones possessing stereochemically challenging structures can be synthesised via carbonylation reactions.

Among the substrates of the carbonylation reactions the halide derivatives such as aryl and alkenyl halides are thoroughly investigated (*Figure 1*).

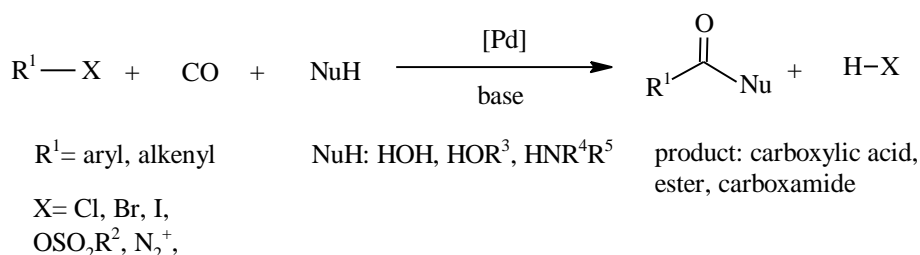


Figure 1. The substrates used in various carbonylation reactions

It is worth noting that the reaction rate of the oxidative addition of the alkenyl iodides to the coordinatively unsaturated transition metal complexes is the largest among alkenyl

halides. Although the strength of the carbon-halide bond is influenced by the structure of the substrate, further simple aryl, heteroaryl and alkenyl halides including more complicated structures such as steroids can be used.

The palladium-catalysed carbonylations of iodoalkenes are widely used reactions in the synthesis of aromatic and unsaturated carboxamides. Carboxamides and esters can be synthesised in the presence of amine and alcohol nucleophiles, respectively. The efficiency and importance of these reactions can be illustrated by the synthesis of both simple building blocks and more complicated compounds of biological significance. The importance of these reactions is that those carboxamides, unavailable in conventional carboxylic acid-carboxylic halide-carboxamide route, can be synthesised from simple starting compounds.

The great variety of the substrates applicable in palladium-catalysed reactions piqued my interest. Therefore, substrates synthesised in a systematic research were tested in aminocarbonylation reaction in order to investigate the catalytic system and the peculiarities of the aminocarbonylation.

II. Aims

- Synthesis of novel and highly reactive iodoalkene substrates with iodo leaving group and their use as synthetic surrogates of the corresponding enol-triflate analogues.
- The investigation of the structure–reactivity relations of the iodoalkene substrates and that of the properties how the catalytic system tolerates the structural peculiarities.
- Homogeneous catalytic synthesis of novel unsaturated carboxylic acid derivatives in the presence of *N*- and *O*-nucleophiles.
- The investigation of the influence of the reaction conditions (CO pressure, reaction time, temperature, *O*- and *N*-nucleophiles) on the product distribution.
- Structural characterization of the synthesized substrates and the prepared carboxylic acid derivatives with various substituents (GC-MS, IR, NMR).

III. Methods

The inert Schlenk-technique was used in the iodination and carbonylation reactions. The autoclave method was used in the high-pressure synthesis. The high-pressure carbonylation reactions were carried out in a 100 ml stainless steel autoclave.

The conversions and the product distributions were analysed by using GC and GC/MS. The characterization of the isolated products was carried out by GC/MS, IR, ¹H- and ¹³C-NMR and elemental analyses.

IV. Results

In this work, substrates for the amino- and alkoxyacylation reactions, via the usual ketone–hydrazone–iodoalkene synthetic route, were synthesised. The Pd(0)/PPh₃-system, used in the carbonylation reactions, have been prepared *in situ* from the catalytic precursor Pd(OAc)₂. The investigation of the carbonylation reactions is focused on the influence of the reaction conditions on the conversion and the product distribution. An emphasis was placed on the prepared substrates from the point of view of the structure and reactivity, and on the conditions effecting chemoselectivity.

The results are as follows:

1. Aromatic model substrates with iodoalkene functionality in the side chain and in the fused ring, as well as aromatic substrates both with iodoaryl and iodoalkenyl functionality were prepared. An iodoalkene with open-chain and a substrate with iodoalkene functionality and with spiro structure were also synthesised with the aim of further testing in aminocarbonylation (*Figure 2*). Excellent yields or yields with practical importance were reached in every reactions.

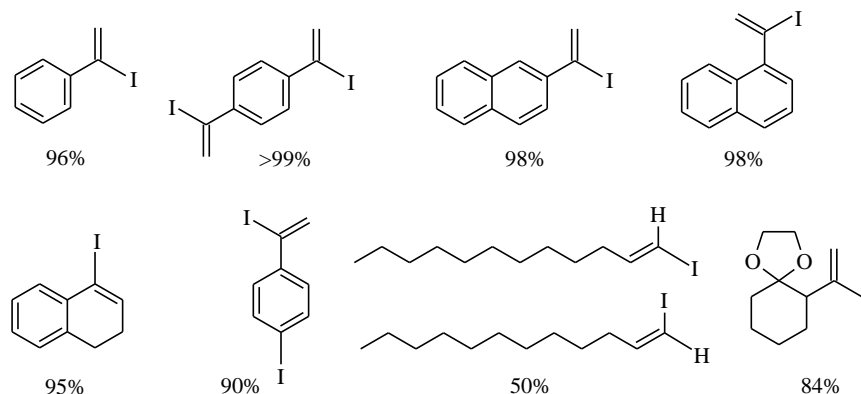


Figure 2. The structure of the prepared iodoalkenyl substrates

2. It was established that α -iodostyrene and α,α' -diiodo-1,4-divinylbenzene are perfect substrates in aminocarbonylation. All of the resulting *N*-substituted 2-phenylacrylamides have been obtained with practically complete conversion (*Figure 3*). Even the arylamine and the sterically hindered secondary amines provided excellent isolated yields in case of the α -iodostyrene. In case of the α,α' -diiodo-1,4-divinylbenzene only the aniline nucleophile has shown decreased reactivity, which

could be explained by its lower basicity. It is worth noting that both at atmospheric and elevated carbon monoxide pressure the corresponding carboxamide derivatives were obtained exclusively. That is, double carbonylation was not observed, so the reaction can be considered as completely chemoselective.

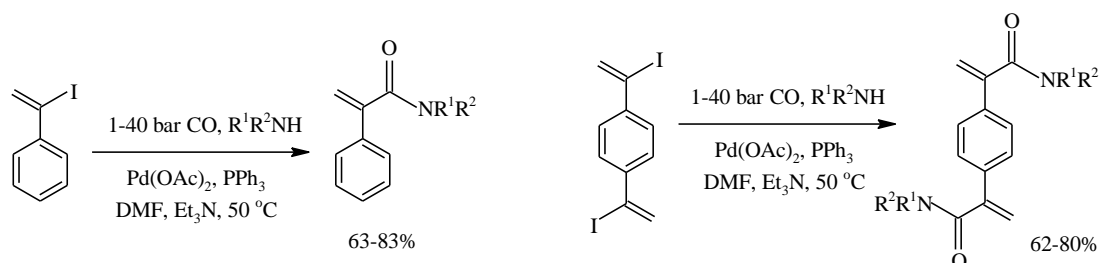


Figure 3. The aminocarbonylation reactions of α -iodostyrene and α, α' -diiodo-1,4-divinylbenzene

- Complete conversions were observed also with 1-(1'-iodovinyl)naphthalene and 2-(1'-iodovinyl)naphthalene. The carboxamide products were obtained with high isolated yields at atmospheric CO pressure (Figure 4). The formation of ketocarboxamides was not observed even with these substrates. High reactivities were shown with the only exception of aniline. Increased reactivities were observed also in alkoxy carbonylation resulting in ester derivatives.

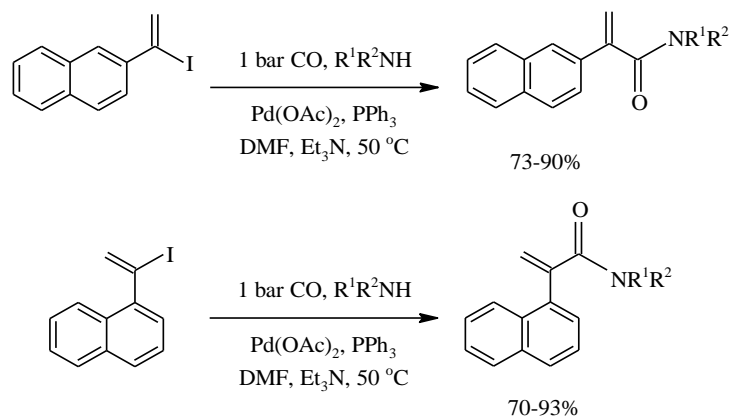


Figure 4. The aminocarbonylation reactions of 1'-iodovinyl naphthalene derivatives

- It was established that 1-iodo-3,4-dihydronaphthalene features an even higher reactivity related to the above iodoalkene substrates. Excellent isolated yields were obtained with all *N*-nucleophiles including aniline (Figure 5). Especially the latter nucleophile gave unexpectedly high yields related to those ones obtained with other substrates. The high

reactivity can be explained by the fast oxidative addition of the sterically less hindered substrate resulting in the palladium(II)-alkenyl intermediate.

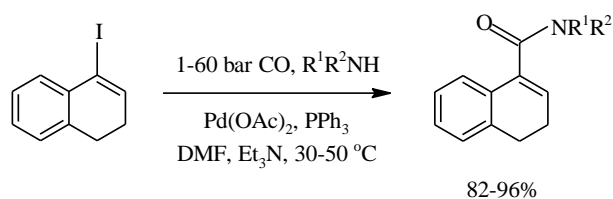


Figure 5. Synthesis of 1-carboxamido-3,4-dihydronaphthalenes

- It can be stated, that the product distribution is strongly influenced by the different reactivity of the aryl and alkenyl moieties of 1',4-diiodostyrene, as well as the carbon monoxide pressure (Figure 6). Both functionalities can be oxidatively added to palladium(0) complex in the presence of both primary and secondary amines. The dicarboxamide type products were formed as major products at atmospheric CO pressure in up to 88% yields. However, chemoselectivity can be shifted towards the carboxamide-ketocarboxamide type products with mixed functionalities.

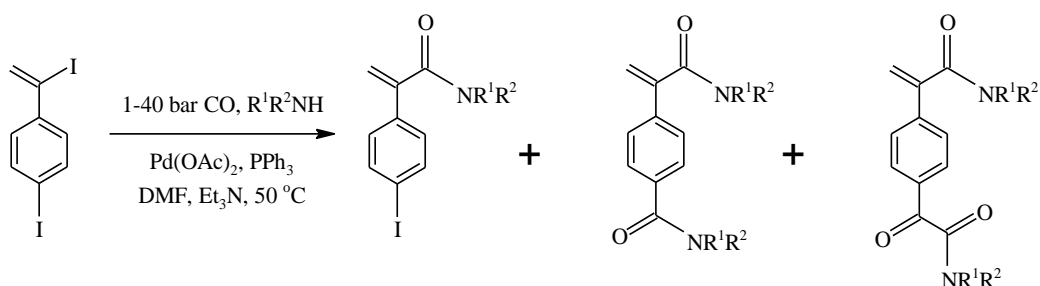


Figure 6. The aminocarbonylation reactions of 1',4-diiodostyrene

Since the reactivity of the iodoalkene moiety is higher than the iodoarene functionality, the consecutive reaction is influenced by the amine excess. Especially high chemoselectivity was observed with amino acid esters where monocarboxamides were obtained almost exclusively and were isolated in up to 90% yield. The aminocarbonylation of the iodoaryl functionality resulted in dicarboxamides with two different carboxamide functionalities..

- It was established that the product distribution depends on the CO pressure when (*E*)-1-iodo-1-dodecene was used as a substrate (Figure 7). While alkene-carboxamide was found as major product at atmospheric CO pressure, chemoselectivity was shifted

towards alkene-carboxamide. No ketocarboxamides were obtained even under more severe conditions.

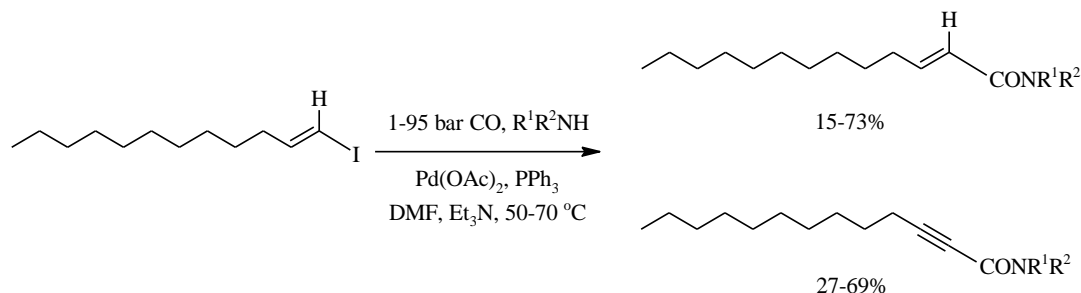


Figure 7. The aminocarbonylation reactions of (*E*)-1-iodo-1-dodecene

7. The products of the carbonylation reactions of α -iodo-6-vinyl(1,4-dioxaspiro[4,5]decane) were obtained with complete conversions. The monocarboxamide derivatives were formed with high chemoselectivity at atmospheric carbon monoxide pressure (Figure 8). The reactivity of the substrate was the highest using simple primary and secondary amines. Yields of practical interests were obtained with these *N*-nucleophiles.

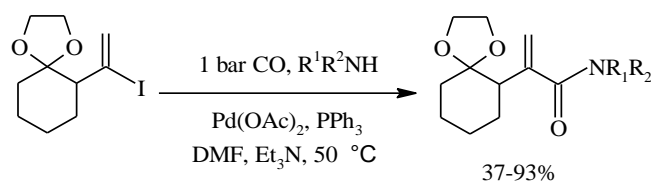


Figure 8. The aminocarbonylation reactions of the iodovinyl derivatives

The hydrolysis of the above monocarboxamide derivatives (Figure 9) resulted in the formation of the corresponding keto derivatives. Yields of practical interest can be achieved by the acid catalyst as well as by the concentration of *para*-toluenesulfonic acid. In this way, this synthesis strategy opens the way to cyclohexanone-based mixed carboxamides.

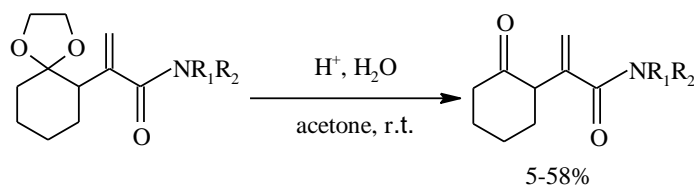


Figure 9. The hydrolysis of the monoketal derivatives

Publications

Publications forming the basis of PhD dissertation

1. A. Takács, **R. Farkas**, A. Petz and L. Kollár:
High-yielding Synthesis of 2-Arylacrylamides via Homogeneous Catalytic Aminocarbonylation of α -Iodostyrene and α, α' -Diiodo-1,4-divinylbenzene.
Tetrahedron 64 (2008) 61-66. IF: **2.897**
2. A. Takács, P. Ács, **R. Farkas**, G. Kokotos, L. Kollár:
Homogeneous Catalytic Aminocarbonylation of 1-Iodo-1-dodecene. The Facile Synthesis of Odd-number Carboxamides via Palladium-catalysed Aminocarbonylation.
Tetrahedron 64 (2008) 9874-9878. IF: **2.897**
3. A. Szilágyi, **R. Farkas**, A. Petz, L. Kollár:
High-yielding Palladium-catalysed Aminocarbonylation of 1',4-Diiodostyrene.
Tetrahedron 65 (2009) 4484-4489. IF: **3.219**
4. A. Takács, **R. Farkas**, A. Petz, L. Kollár:
Synthesis of 2-Naphthyl-acrylamides via Homogeneous Catalytic Aminocarbonylation of 1-Iodo-1-naphthyl-ethene Derivatives.
Tetrahedron 65 (2009) 4795-4800. IF: **3.219**
5. **R. Farkas**, E. A. Molnár, P. Ács, A. Takács, L. Kollár:
High-yielding synthesis of 1-carboxamido-3,4-dihydronaphthalenes via palladium-catalyzed aminocarbonylation.
Tetrahedron 69 (2013) 500-504. IF: **2.817**
6. **R. Farkas**, A. Petz, L. Kollár:
Synthesis of 2-(1,4-dioxaspiro[4,5]decan-6-yl)acrylamides from 2-Acetylcyclohexanone via Palladium-catalysed Aminocarbonylation.
Monatsh. Chem. (Accepted manuscript). IF: **1.347**

Other publications

1. M. Gergely, **R. Farkas**, A. Takács, A. Petz, L. Kollár:
Synthesis of *N*-picolylcarboxamides via palladium-catalysed aminocarbonylation of iodobenzene and iodoalkenes.
Tetrahedron 70 (2014) 218-224. IF: **2.817**