THESES OF THE DISSERTATION

APPLICATION OF HETEROGENEOUS CATALYSTS IN PALLADIUM-CATALYZED COUPLING AND CARBONYLATION REACTIONS

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I. INTRODUCTION AND OBJECTIVES

Palladium catalysts are powerful tools in organic chemistry, catalyzing a variety of reactions and providing exceptional opportunities for the formation of carbon-carbon bonds. The unique properties and outstanding catalytic activity of the metal have driven researchers to develop more active and more efficient catalysts. The development of reusable catalysts as well as minimization of metal loss in order to recycle the expensive metal and meet the demands of the pharmaceutical industry present significant challenges. Heterogeneous catalysts can meet these expectations.

The main goal of my research was the development and testing of heterogeneous palladium catalysts. Based on the results of the research group, supported ionic liquid phase on silica greatly aids the stabilization of palladium particles on the surface. Building on these findings, six catalysts were prepared and their efficiency in aminocarbonylation reactions was compared to identify the most promising one.

In addition to ensuring reusability and minimal metal leaching, I also focused on investigating whether the supported catalyst could be applied in the functionalization of heterocyclic compounds. The pharmacological significance of imidazo[1,2-*a*]pyridines and benzo[*b*]furans stems from their diverse biological activities (such as enzyme inhibition, antibacterial, antiviral, or anticancer effects), thus new derivatives obtained by the modification of these scaffolds possess pharmacological potential. Although several related studies have been published, to the best of our knowledge, there are no examples of using heterogeneous catalysts for the conversion of iodoimidazo[1,2-*a*]pyridines and iodobenzo[*b*]furans.

In respect of the imidazo[1,2-a]pyridine derivatives, the synthesis of the iodo-substituted ring was planned, followed by a heterogeneous catalytic carbonylation reaction. In connection with benzo[*b*]furans the investigations were extended to additional palladium-catalyzed reactions and the introduction of groups that would allow further modifications.

The synthesis of hybrid molecules gained importance in the last decade, as combining different heterocycles with each other or even with organometallic compounds can lead to an enhancement or modification of biological activity. Based on this approach, the possibility of functionalizing the benzo[*b*]furan core with triazolyl and ferrocenyl groups was also studied.

II. EXPERIMENTAL METHODS

Schlenk technique was employed to ensure inert conditions during the preparation and application of heterogeneous catalysts. The aminocarbonylation reactions were carried out in a stainless steel autoclave under carbon monoxide pressure.

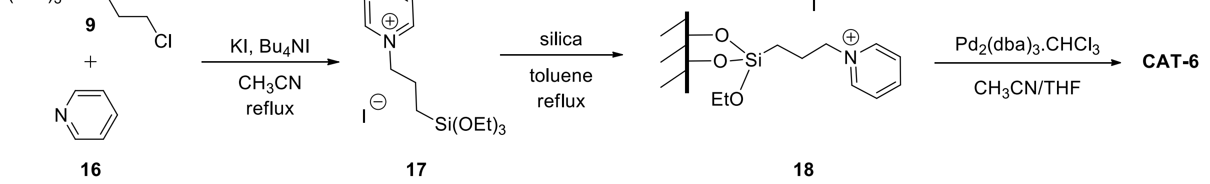
The progress of the reactions was monitored by thin-layer chromatography and gas chromatography. Extraction and column chromatography were often applied to purify the products. The structure of the synthesized compounds was confirmed by ^{1}H- and ^{13}C-NMR, IR, and MS measurements.

The palladium content of the catalysts and the reaction mixtures was determined by ICP-AES measurements. Cyclic voltammetry was performed to explore the electrochemical behavior of the ferrocene derivatives.

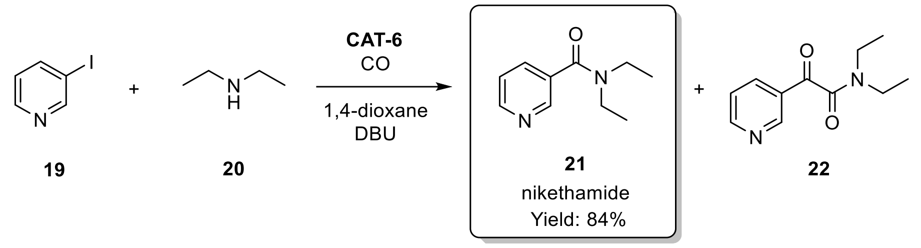
III. NEW SCIENTIFIC RESULTS

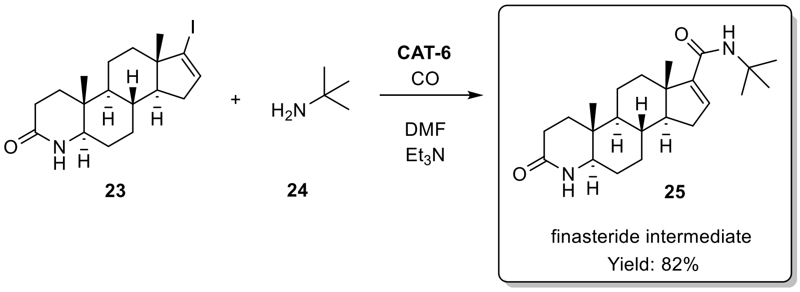
1. Three heterogeneous palladium catalysts containing adsorbed ionic liquid phase were prepared and their activity and stability were studied in aminocarbonylation reactions. In the presence of the catalyst obtained from the support modified with pyridinium cations excellent activity and selectivity were observed during catalyst recirculation. The dissolution of the ionic liquid was confirmed, which had caused significant palladium leaching.

2. In order to improve the stability of the catalysts, three heterogeneous catalysts were prepared by using supports with grafted cations. Compared to imidazolium and phosphonium type SILPs, outstanding activity and selectivity as well as good recyclability could be achieved using SILP phases modified by pyridinium cations. Under optimised conditions **CAT-6** provided minimal palladium leaching (0.2% in the first run and under 0.13% in further runs).

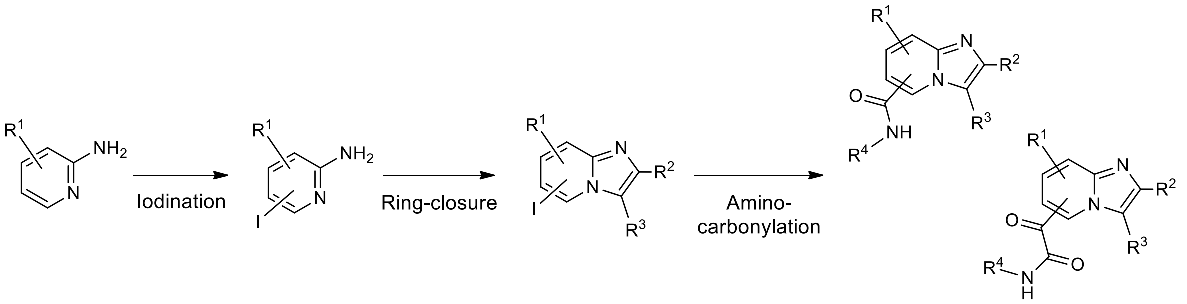


3. **CAT-6** catalyst was succesfully applied in the synthesis of two pharmacologically active derivatives. Excellent selectivity (over 95%) and yield (84%) were achieved in the sythesis of nikethamide. The finasteride intermediate was isolated in 82% yield. The **CAT-6** catalyst proved to be reusable in five successive runs in both cases.

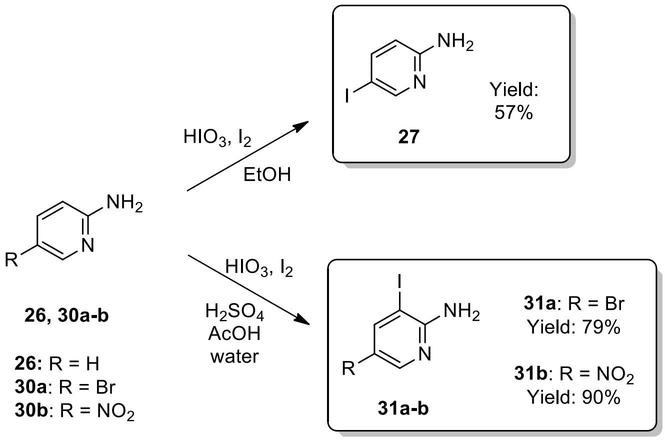




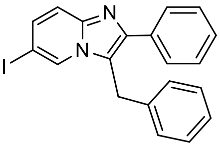
4. A three-step reaction route was developed to synthesize and functionalize different imidazo[1,2-*a*]pyridine derivatives.



a) The iodination of 2-aminopyridine derivatives resulted in 2-amino-5-iodopyridine (**27**), 2-amino-5-bromo-3-iodopyridine (**31a**) and 2-amino-3-iodo-5-nitropyridine (**31b**).

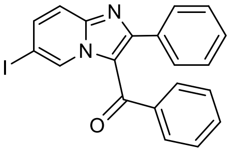


b) Seven methods were tested to form the imidazo[1,2-*a*]pyridine core. While the ring closure was easily accomplished under various conditions in the presence of 2-aminopyridines without the iodo substituent, the transformation of iodinated analogs proved to be more challenging. Utilizing the previously gained experience two iodoimidazo[1,2-*a*]pyridine derivatives (**43, 46**) were obtained in poor and three (**48, 49, 50**) in good yields.



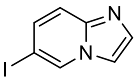
43

Yield: 30%



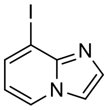
46

Yield: 41%



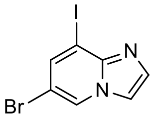
48

Yield: 91%



49

Yield: 84%



50

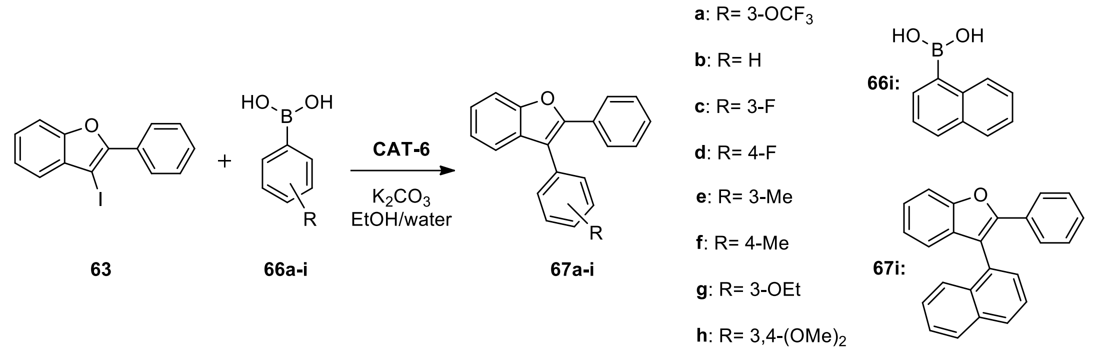
Yield: 86%

c) The aminocarbonylation reactions of the iodoimidazo[1,2-*a*]pyridine derivatives were studied in the presence of the heterogeneous catalyst (**CAT-6**): the effect of the solvent, base, pressure and temperature was investigated. Excellent recyclability of **CAT-6** could be achieved using lower temperature and higher pressure (100 °C, 30 bar) together with DMF as solvent and triethylamine as base. Under these conditions dicarbonylation proved to be the favorable reaction. In the presence of toluene/DBU solvent/base system decreased temperature and increased pressure resulted in a selectivity change towards the amide. As it was expected, when aromatic amines were applied as reagents the formation of only monocarbonylated products was observed. Furthermore, aminocarbonylation of 8-iodoimidazo[1,2-*a*]pyridines showed definite selectivity towards amide products under various conditions even in the case of aliphatic amines. Altogether 17 aminocarbonylated derivatives – 12 amides and 5 ketoamides – were produced in good yields (64-91%).

5. The heterogeneous catalyst (**CAT-6**) was suitable for the functionalization of 3-iodo-2-phenylbenzo[*b*]furan (**63**) in the presence of simple amines, acetylenes and boronic acids, in other words, in addition to aminocarbonylation the applicability of **CAT-6** was proven in Suzuki- and Sonogashira coupling as well.

a) High conversion and yield were achieved in the reaction of 3-iodo-2-phenylbenzo[*b*]furan (**63**) and propargylamine in ten consecutive runs.

b) The use of ethanol/water solvent mixture together with potassium carbonate base was identified as the optimal condition for Suzuki reaction. Under these conditions the catalyst was efficient in at least seven runs without any loss of its activity, moreover the palladium loss was also minimal (0.1-0.9%). This methodology was applied successfully in the synthesis of nine different 3-arylbenzo[*b*]furan derivatives in 80-95% yields.



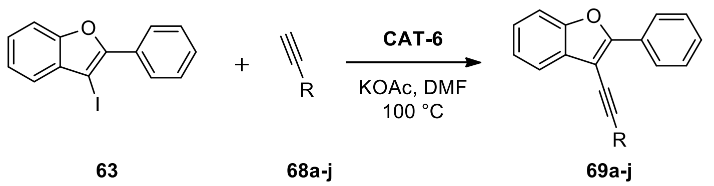
63 + **66a-i** → **67a-i**

a: R= 3-OCF_3
b: R= H
c: R= 3-F
d: R= 4-F
e: R= 3-Me
f: R= 4-Me
g: R= 3-OEt
h: R= 3,4-$(OMe)_2$

66i:

67i:

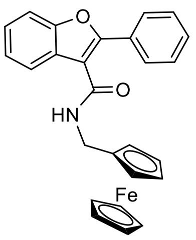
c) In the case of Sonogashira reaction the application of potassium acetate base and a temperature of 100 °C was found to lead to promising results. **CAT-6** catalyst was tested both in the presence and in the absence of CuI cocatalyst. Although longer reaction time was required to achieve complete conversion under copper-free conditions, it was still more beneficial with respect to the stability, recyclability of the catalyst and palladium leaching (1-2%) indeed. Ten different 3-alkynylbenzo[*b*]furan derivatives were synthesized in Sonogashira reaction in 50-92% yields.



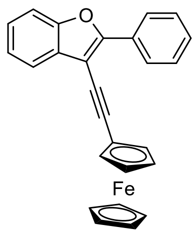
63 + **68a-j** → **69a-j**

a: R= Ph
b: R= 4-MeO-C_6H_4
c: R= 4-NH_2-C_6H_4
d: R= 4-Me-C_6H_4
e: R= 4-F-C_6H_4
f: R= 4-NO_2-C_6H_4
g: R= $CH_3(CH_2)_5$-
h: R= CH_3COOCH_2-
i: R= $HOCH_2$-
j: R= $(CH_3)_3Si$-

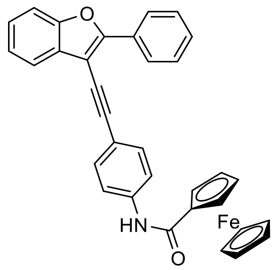
6. **CAT-6** catalyst was found to be efficient in the synthesis of hybrid molecules as well. Three hybrids (**75, 77, 81**) were successfully prepared by the combination of benzo[*b*]furan core and ferrocenyl group. Palladium catalyzed reactions followed by azide-alkyne cycloaddition provided one triazole-benzo[*b*]furan (**83b**) and two ferrocene-triazole-benzo[*b*]furan hybrids (**83a, 84**). The toxicity of ferrocene-benzofuran derivatives on human breast cancer cell lines (MCF7, MDA-MB-231) were also studied. The results led to the conclusion that, in addition to the ferrocenyl group amide and triazolyl groups also play a significant role in the biological effect.



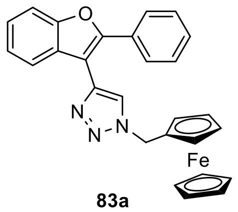
75
Yield: 61%



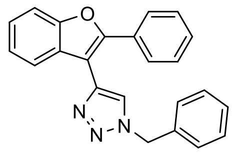
77
Yield: 83%



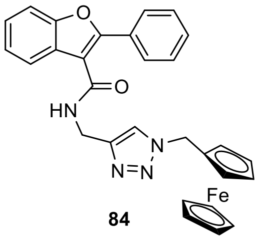
81
Yield: 98%



83a
Yield: 74%



83b
Yield: 78%



84
Yield: 80-83%

IV. THE SIGNIFICANCE OF THE RESEARCH

The results of my research advance the knowledge of the properties and applicability of heterogeneous palladium catalysts. The stability of the prepared catalyst was increased by the covalent attachment of the ionic liquid to the surface. The comparison of different phases made it clear that outstanding activity and selectivity together with good recyclability and low metal leaching could be achieved in the presence of the catalyst obtained from the support modified with pyridinium cations. To the best of my knowledge, this was the first time a heterogeneous palladium catalyst was applied in the functionalization of imidazo[1,2-*a*]pyridine and benzo[*b*]furan cores. Excellent results were achieved in aminocarbonylation, Suzuki, and Sonogashira coupling reactions and the catalyst proved to be efficient in the synthesis of hybrid molecules as well. 17 amides, 7 ketoamides, 9 aryl-, and 10 alkynylbenzo[*b*]furan derivatives, and 6 hybrid molecules were synthesized in total.

V. SCIENTIFIC PUBLICATIONS AND POSTERS RELATED TO THE DISSERTATION

Publications

Béla Urbán, **Enikő Nagy**, Petra Nagy, Máté Papp, Rita Skoda-Földes: Double carbonylation of iodoarenes in the presence of a pyridinium SILP-Pd catalyst, *J. Organomet. Chem.* **2020,** *918*, 121287.

IF: 2.37 (2020)

Bernadett Adamcsik, **Enikő Nagy,** Béla Urbán, Péter Szabó, Péter Pekker, Rita Skoda-Földes: Palladium nanoparticles on a pyridinium supported ionic liquid phase: a recyclable and low-leaching palladium catalyst for aminocarbonylation reactions, *RSC Adv.* **2020**, *10*(40), 23988-23998.
IF: 3.36 (2020)

Enikő Nagy, Zoltán Nagymihály, László Kollár, Máté Fonyó, Rita Skoda-Földes: Synthesis of 3-Aryl- and 3-Alkynylbenzofurans in the Presence of a Supported Palladium Catalyst, *Synthesis*, **2023**, *55*(01), 131-140.
IF: 2.6 (2022)

Enikő Nagy, Márk Váradi, Zoltán Nagymihály, László Kollár, Krisztina Kovács, Kitti Andreidesz, Ágnes Gömöry, Nikolay Tumanov, Johan Wouters, Rita Skoda-Földes: Synthesis of Novel Ferrocene-Benzofuran Hybrids via Palladium- and Copper-Catalyzed Reactions, *Inorganics*, **2022**, *10*(11), 205.
IF: 2.9 (2022)

Enikő Nagy, Attila Máriás, Margit Kovács, Rita Skoda-Földes: Aminocarbonylation of iodo-imidazo[1,2-*a*]pyridine derivatives in the presence of a heterogeneous palladium catalyst (*manuscript under preparation*)

Posters

Enikő Nagy, Bernadett Adamcsik, Máté Papp, Béla Urbán, Rita Skoda-Földes: Aminocarbonylation in the presence of supported palladium catalyst, 6th International Conference on New Trends in Chemistry, Kyrenia (Cyprus), online, April 16-18, 2020.

Enikő Nagy, Zoltán Nagymihály, László Kollár, Rita Skoda-Földes: Synthesis of different benzofuran derivatives in the presence of a supported palladium catalyst, ECHC - XXIX European Colloquium on HETEROCYCLIC CHEMISTRY, online, April 26-28, 2021.

Enikő Nagy, Zoltán Nagymihály, László Kollár, Rita Skoda-Földes: Synthesis of different benzofuran derivatives in the presence of a supported palladium catalyst, International Symposium on Synthesis and Catalysis, Évora (Portugal), August 31 – September 03, 2021.

Enikő Nagy, Zoltán Nagymihály, László Kollár, Rita Skoda-Földes: Synthesis of different benzofuran derivatives in the presence of a supported palladium catalyst, XXXVIII Biennial Meeting - Spanish Royal Society of Chemistry (RSEQ), Granada (Spain), June 27-30, 2022.

Scientific publications not related to the dissertation

Nagy Enikő, Maksó Lilla, Ispán Dávid, Hancsók Jenő, Skodáné Földes Rita: Több mint egyszerű oldószer – ionfolyadékok alkalmazása katalitikus reakciókban, *Magyar Kémiai Folyóirat,* **2021**, 127, 103-109.