

UNIVERSITY OF PÉCS
Doctoral School of Chemistry

**Homogeneous catalytic functionalization of the steroidal
framework**

Ph.D. Thesis

by
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1. Introduction

In the second half of the twentieth century the chemistry of transition metal complexes expanded significantly. The central metal atom of these complexes is capable of, in their coordination area, binding different 'small' molecules as ligand such as dihydrogen, carbon monoxide, carbon dioxide, *etc.* In the beginning, the major aim was either transforming compounds with simple skeletons in large volume using primarily cobalt- and rhodium-containing catalytic systems, or preparing more complex starting materials with practical (*e.g.*, biological, pharmacological) importance using homogenous catalytic reactions catalyzed by rhodium, ruthenium, copper, palladium, platinum complexes. In the latter cases, several new compounds with well-defined properties have been synthesized.

One of the significant breakthroughs in synthetic organic chemistry was the application of homogenous catalytic reactions using transition metal catalysts. In these reactions the starting material and the catalyst are most often in the same solvent and therefore, every atom of the transition metal could act as active center during the catalysis.

Beyond the synthesis of compounds containing transition metal-carbon bonds, the understanding of the structure as well as binding modes is of fundamental importance. Furthermore, the better understanding of the basics of the elementary reactions occurring in the coordination sphere of the transition metal, the latter being the basic steps of the catalytic reactions, could lead to synthetic reactions of practical importance.

The industrial application of homogenous catalytic synthesis is expanding rapidly. In the process of developing new technologies for creating compounds, the aim of producing the least amount of side material along with the process being economical has become a standard requirement. All these can be met by using selective reactions for which the most modern solutions are the homogenous catalytic reactions. In this way, only small amounts of transition metal complexes with catalytic activity leading to the transformation of substrates have been applied. Good yields have been obtained using reactions with excellent chemo-, regio- and enantioselectivities.

Nowadays, researchers in synthetic organic chemistry more and more often use transition metal complexes, organometallic reagents in the synthesis of several compounds which cannot be obtained using standard methods. In some cases, the conventional synthetic approaches might be resulted in especially low yields when new functional groups were introduced into the given positions of a well-known skeleton.

The view that completely new reactions can mostly be expected from the field of organometallic catalysis is widely accepted. The increase of the practical importance of transition metal organic chemistry is proved by Nobel Prize in chemistry being awarded in 2001 to B. Sharpless, W. S. Knowles and R. Noyori for the development of enantioselective homogeneous catalytic reactions. Furthermore, development of the metathesis method in organic synthesis resulted in the Nobel Prize in chemistry in 2005 awarded to Y. Chauvin, R. H. Grubbs and R. R. Schrock. The 2010 Nobel Prize in chemistry was awarded to R. F. Heck, E. Negishi and A. Suzuki for the development of palladium-catalyzed cross-coupling reactions in organic synthesis.

The aim of my research was to explore the possibility of applying palladium-catalyzed aminocarbonylation reactions in a special field of synthetic organic chemistry. I will present some homogenous catalytic functionalization reactions of the steroidal framework. In most cases, the products of potential practical importance cannot be synthesized using standard ('conventional') synthetic methods.

2. Purposes

The aim of my doctoral dissertation was a systematic investigation of the homogeneous catalytic aminocarbonylation reactions of androstane-based compounds containing iodoalkene moiety using various monoamines and diamines as *N*-nucleophiles. The following goals were aimed at during my research:

- The synthesis of new steroidal carboxamides with possible practical and pharmacological importance (such as possible 5 α -reductase inhibitor properties) *via* palladium-catalyzed aminocarbonylation.
- The investigation of the effect of the reaction conditions such as carbon monoxide pressure, reaction time, *N*-nucleophile on the chemoselectivity of aminocarbonylation of a steroidal skeleton and to explore the structure-reactivity relationship.
- The synthesis of novel steroidal dicarboxamides (containing various linkers) showing the efficiency of the aminocarbonylation reaction.

3. Methods

Standard inert Schlenk technique and high pressure autoclave technique was used. The experiments involving high pressure (40 bar) carbon monoxide were performed in a 100 mL stainless steel (Cr/Mo/Ni = 18/8/8) autoclave.

The conversions and the product distributions were determined by using GC-MS and $^1\text{H-NMR}$. The products were identified by GC-MS or MALDI-TOF, IR, $^1\text{H-}$ and $^{13}\text{C-NMR}$ measurements and elemental (C, H, N) analyses.

4. Results

In my doctoral studies, I have examined the selective transformations of the keto functionalities of the widely used androst-4-ene-3,17-dione as the starting material.

In my experiments, palladium-catalyzed aminocarbonylation of some steroidal iodoalkene key-intermediates with various *N*-nucleophiles (simple primary and secondary monoamines (Figure 1a), amino acid methyl esters (Figure 1b) and diamines (Figure 1c)) was carried out under atmospheric and high carbon monoxide pressure (1 or 40 bar). The highly active palladium(0) catalyst was formed *in situ* from palladium acetate and triphenylphosphine in the reaction mixture.

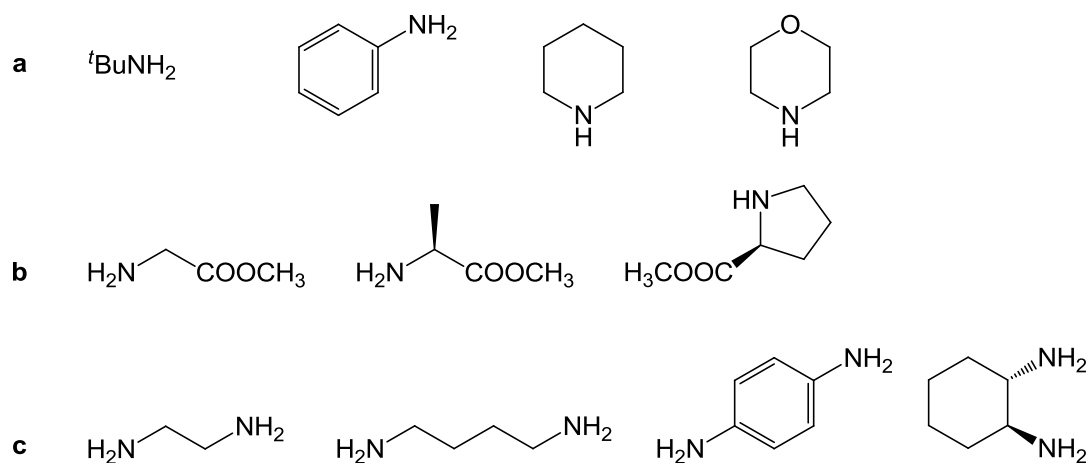
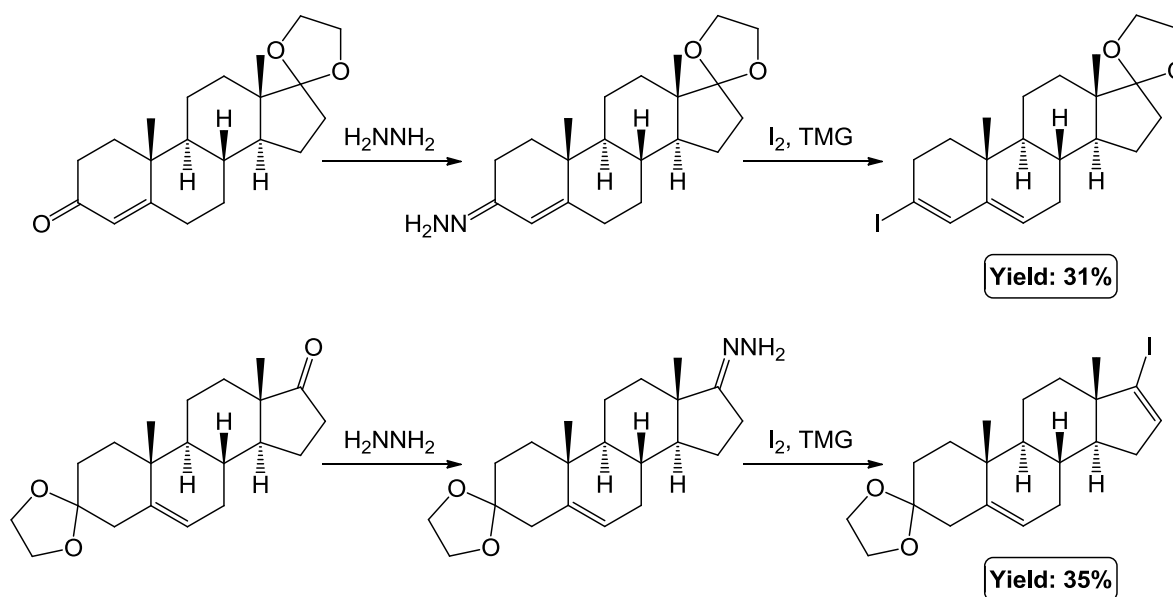


Figure 1. Structure of the various amines used in the aminocarbonylation reactions as *N*-nucleophiles.

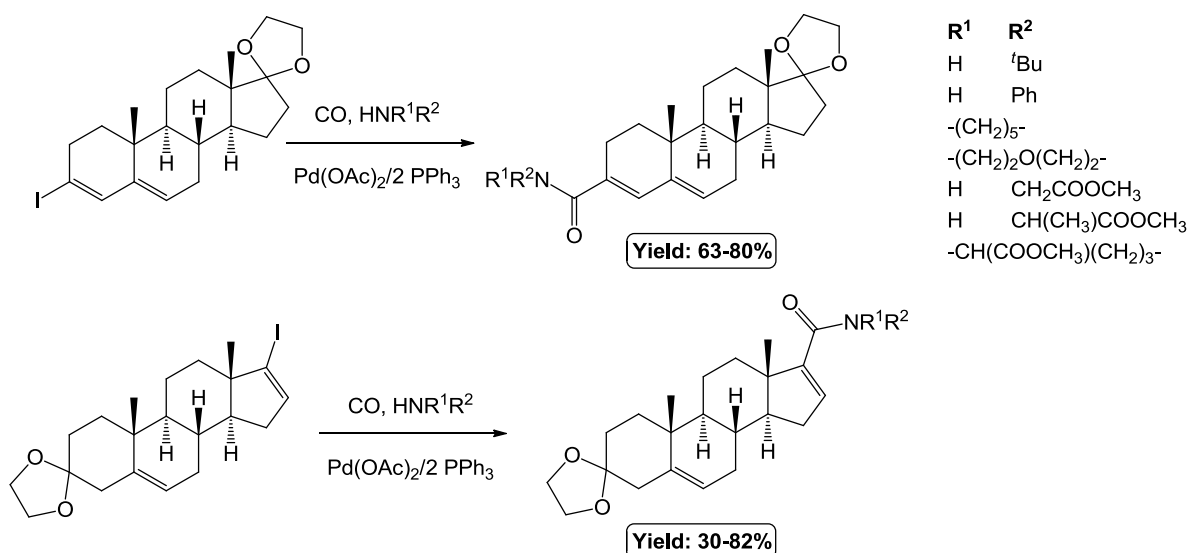
The most important results are summarized below.

- Following conventional synthetic strategies, the 3-keto or the 17-keto functionality was protected as ethylene ketal. The ketone–hydrazone–iodoalkene reaction sequence was used for the synthesis of the substrates, where the 3-iodoalkene or 17-iodoalkene functionalities served for the introduction of the first carboxamide groups (Scheme 1). In each case when the synthesis of new androstane-based compounds containing 3,5-diene moiety were carried out the appropriate derivatives containing 2,4-diene functionality were also identified.



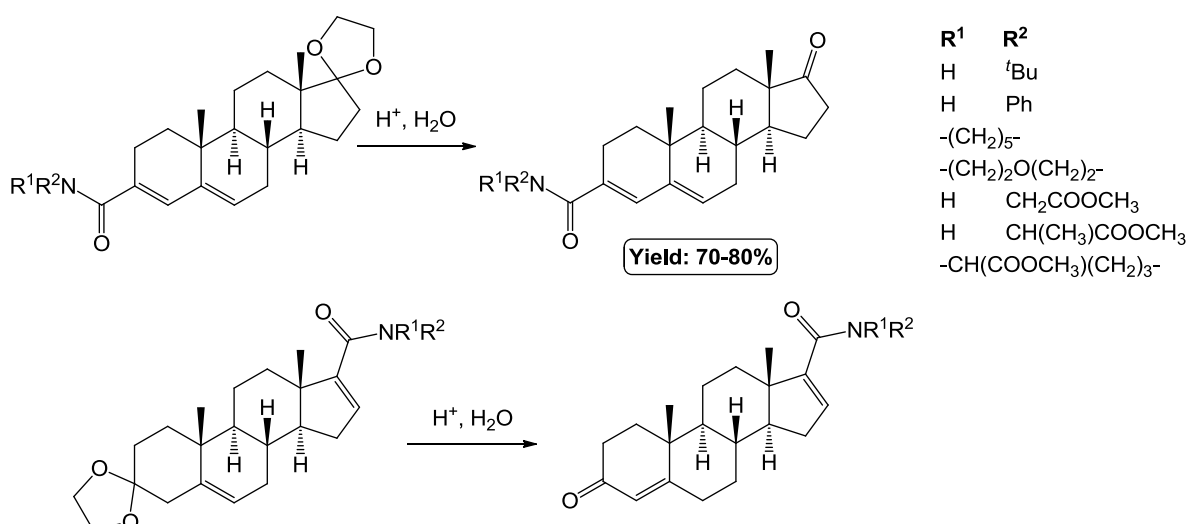
Scheme 1. Synthesis of the steroidal iodoalkene-ethylene ketal derivatives.

- The compounds possessing 3-iodo-3,5-diene or 17-iodo-16-ene moiety were aminocarbonylated at atmospheric carbon monoxide pressure in the presence of various primary or secondary monoamines as *N*-nucleophiles using a palladium(0) catalyst (Scheme 2).



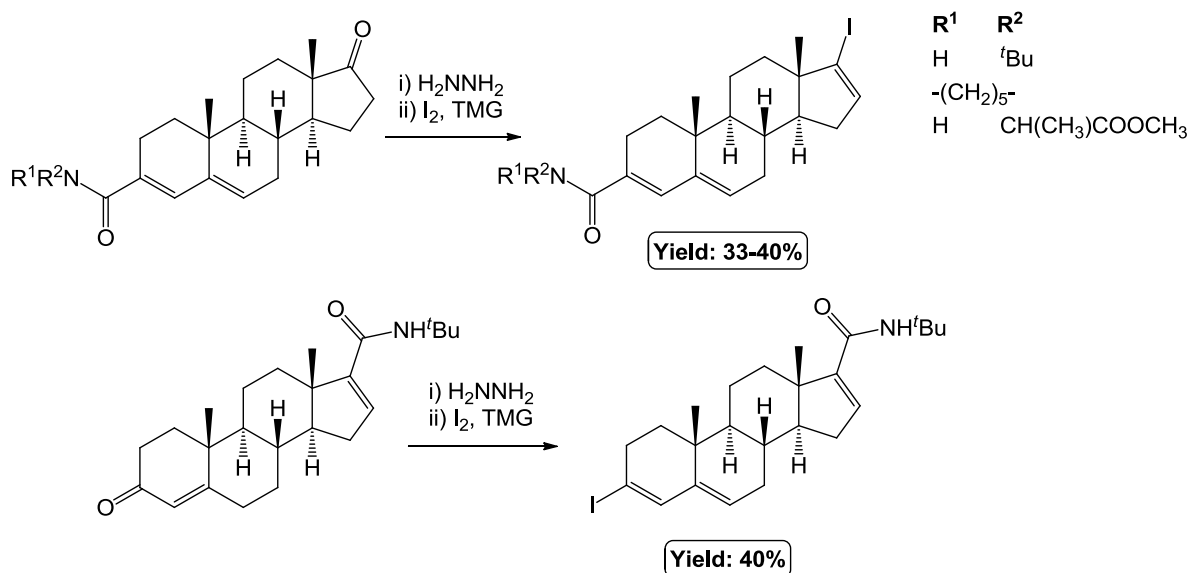
Scheme 2. Synthesis of steroidal carboxamido-ethylene ketal derivatives.

- Position-3 or -17 containing ethylene ketal moiety was deprotected to keto functionality using hydrolysis, which could serve as an ideal site for further functionalization of the framework (Scheme 3).



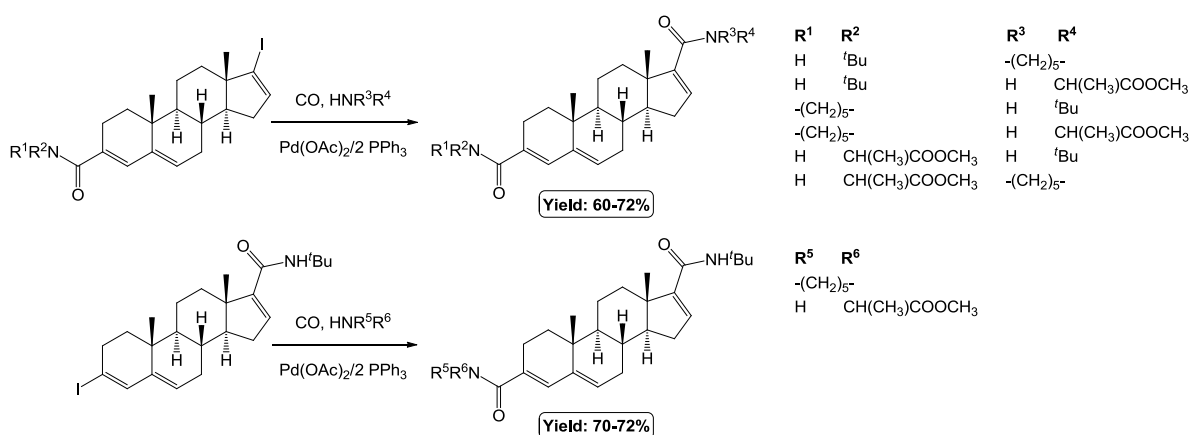
Scheme 3. Synthesis of the steroidal carboxamido-ketone derivatives.

- The ketone–hydrazone–iodoalkene reaction sequence was used for the synthesis of the substrates, where the 17-iodoalkene or 3-iodoalkene functionalities served for the introduction of the second carboxamide groups (Scheme 4).



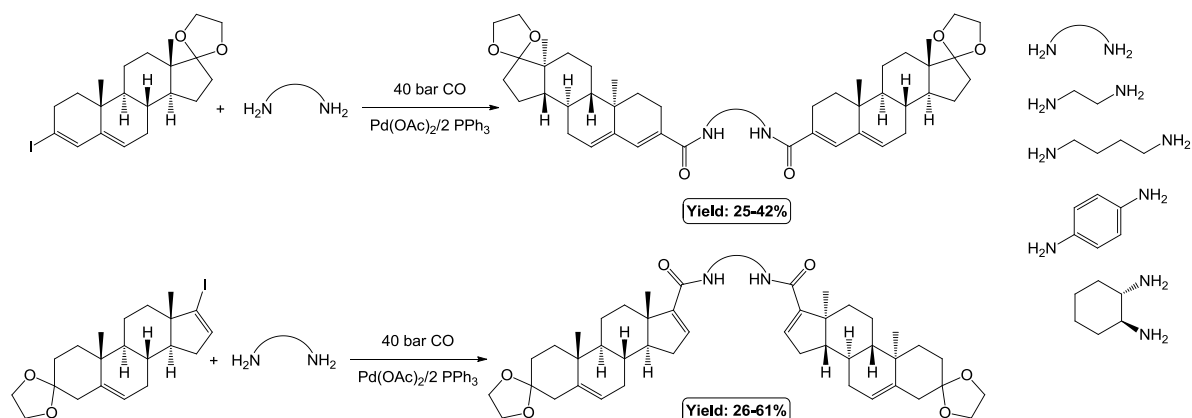
Scheme 4. Synthesis of the steroidal monocarboxamido-iodoalkene derivatives.

- The compounds possessing 17-iodo-16-ene or 3-iodo-3,5-diene moiety were aminocarbonylated at atmospheric carbon monoxide pressure in the presence of various primary or secondary monoamines as *N*-nucleophiles using a palladium(0) catalyst resulting in the hetero-3,17-dicarboxamides (‘mixed dicarboxamides’) (Scheme 5).



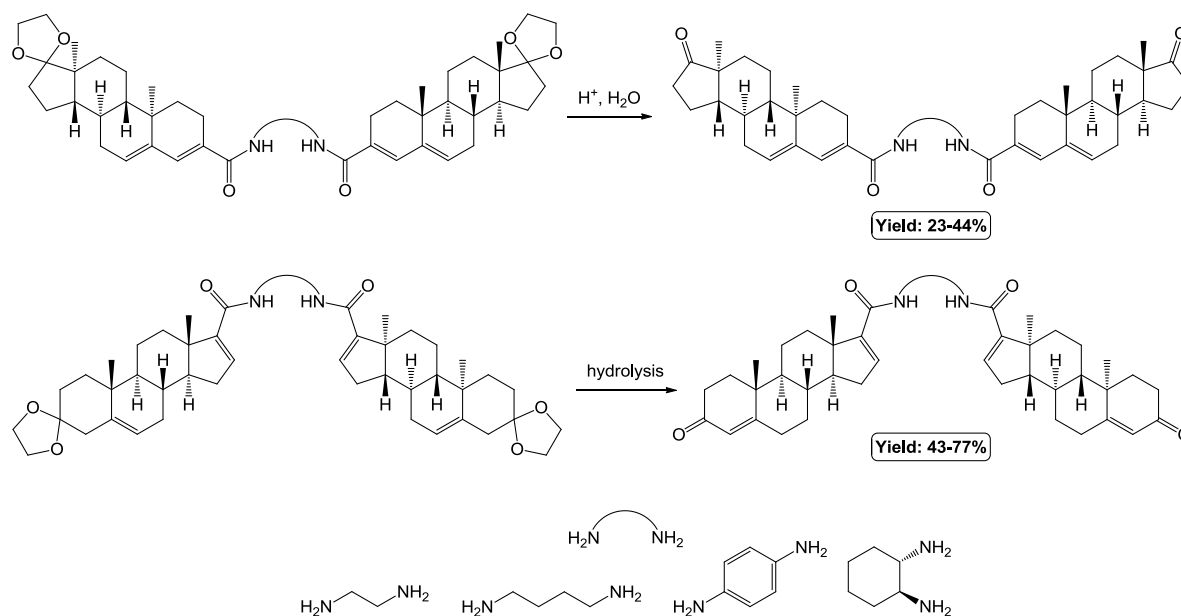
Scheme 5. Synthesis of the steroidal hetero-3,17-dicarboxamides (‘mixed dicarboxamides’).

- The 3-iodo-3,5-diene-17-ethylene ketal derivative or the 17-iodo-16-ene-3-ethylene ketal derivatives were aminocarbonylated at high carbon monoxide pressure (40 bar) in the presence of various diamines to give dimeric steroids containing dicarboxamide spacers (Scheme 6). The dicarboxamides containing 2,4-diene moieties formed as minor products were also identified in all cases.



Scheme 6. Synthesis of dimeric steroids possessing ethylene ketal moieties.

- Various dimeric steroids containing dicarboxamide spacers possessing ethylene ketal moiety in position-17 or -3 were deprotected to keto functionality using hydrolysis, which could serve as an ideal site for further functionalization of the framework (Scheme 7).



Scheme 7. Synthesis of various dicarboxamido-diketone steroid dimers.

5. Publications

Related to the PhD thesis:

1. P. Ács, A. Takács, **M. Kiss**, N. Pálincás, S. Mahó, L. Kollár:
Systematic investigation on the synthesis of androstane-based 3-, 11- and 17-carboxamides *via* palladium-catalyzed aminocarbonylation.
Steroids **2011**, 76, 280–290. **IF: 2.829**
2. **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 **2013**, 78, 693–699. **IF: 2.716**
3. Takács A., Farkas R., **Kiss M.**, Petz A., Csók Zs., Kollár L.:
Palládium-katalizált aminokarbonilezési reakciók.
Magyar Kémiai Folyóirat – Kémiai Közlemények **2013**, 119, 120-128.
4. **M. Kiss**, S. Mahó, K. Böddi, B. Boros, L. Kollár:
Palladium-catalyzed diaminecarbonylation. Synthesis of androstene dimers containing 3,3'- or 17,17'-dicarboxamide spacers.
Monatsh. Chem. **2015**, 146, 357-364. **IF: 1.347**
5. R. M. B. Carrilho, A. R. Almeida, **M. Kiss**, L. Kollár, R. Skoda-Földes, J. M. Dąbrowski, M. J. S. M. Moreno, M. M. Pereira:
One-step synthesis of dicarboxamides *via* Pd-catalysed aminocarbonylation using diamines as *N*-nucleophiles. **IF: 3.154**
Eur. J. Org. Chem. (Accepted for publication)
6. A. Takács, **M. Kiss**, L. Kollár:
Highly selective synthesis of carboxamides *via* transition metal catalysed aminocarbonylation.
Curr. Green Chem. (Accepted for publication)

Conferences

Poster:

N. Pálincás, P. Ács, A. Takács, **M. Kiss**, S. Mahó, L. Kollár:

Systematic investigation on the synthesis of androstane-based 3-, 11- and 17-carboxamides *via* palladium-catalyzed aminocarbonylation.

19th EuCheMS International Conference on Organometallic Chemistry. July 3-7, 2011. Toulouse, France. Abstract Book P148.

Oral presentation:

M. Kiss, N. Pálincás, A. Takács, S. Mahó, L. Kollár:

A systematic approach to the synthesis of androstane-based 3,17-dicarboxamides and steroid dimers containing 17,17'-dicarboxamide spacers *via* palladium-catalyzed aminocarbonylation

10th János Szentágothai Transdisciplinary Conference and Student Competition. November 4-5, 2013. Pécs, Hungary. Abstract Book page 29.