

Metal catalyzed reaction of heterocycles

Thesis of the Ph.D. dissertation

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I. INTRODUCTION

The different heterocycles on many occasions contain significant biological impacts, and they are the favourite basic substances of the medicine chemistry research. As a result of this, there is a constant demand for research on the effective preparation of heterocycle derivatives and their transformation. Our objective was the presentation of such new means of synthesis that meet this demand through metal catalyzed reactions. In my PhD thesis, I examined three fields in detail.

The first field was a new synthesis of the dibenzopyrrocoline and analogue compounds. In this process, the new aspect was the formation of palladium-catalyzed carbon-nitrogen bond.

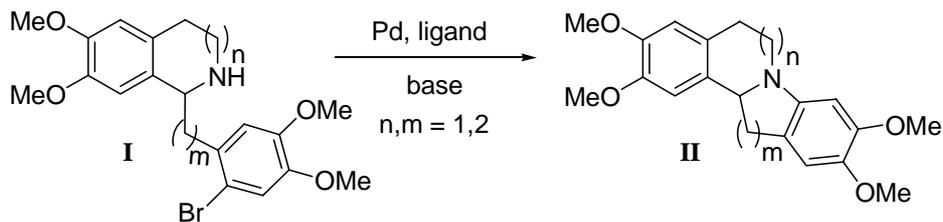
The second field of my doctoral research relates to ethynylpurine derivatives. We examined the possibility of the functionalization of the ethynyl group in 6-ethynylpurine derivatives through the addition of nucleophiles in the presence of different metal catalysers.

In addition to the above mentioned reactions, I examined the transition metal catalyzed carbon-carbon bond forming reactions. Process accompanied by the cleavage of carbon-hydrogen or carbon-carbon bond attracted particular attention from the atom-economic and sustainability point of view.

II. SCIENTIFIC RESULTS

1. The Synthesis of Palladium-catalyzed Isoquinoline-Derivatives

Throughout my PhD studies, our aim was to explore the application of palladium catalyzed intramolecular carbon-nitrogen bond formation and functionalization of dibenzopyrrocoline and analogue compounds. The first approach was to synthesize some model compounds (**I**) and investigate profoundly the effect of the reaction conditions in the mentioned transformation.

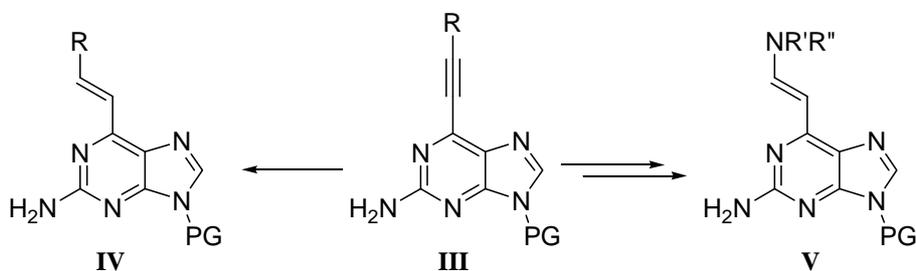


Palladium-catalyzed ring-closing reaction

The only successful ring-closing reaction was in the case of 1,2,3,4 tetrahydroisoquinoline (**I**, $n = m = 1$). The applied palladium source was $\text{Pd}_2(\text{dba})_3$. In a grate number of experiences we found that the best conversion was achieved in the case of *N,N*-bis(2',6'-diisopropyl-phenyl)dihydroimidazolium chloride.

2. The Transformation of 6-ethynylpurines Derivatives

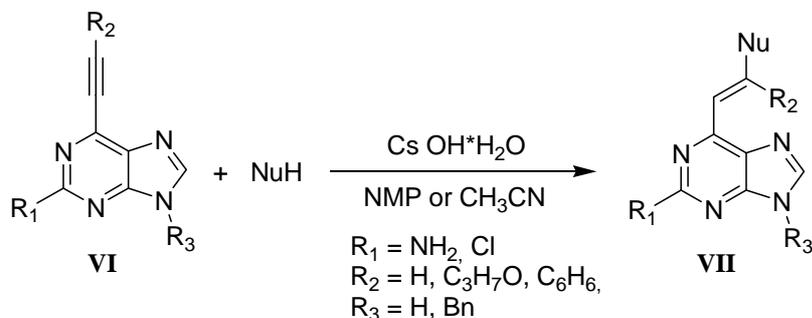
Another major part of my PhD research was to look for new synthetic transformations on 6-alkynylpurine derivatives (**III**).



Possible transformation on 6-ethynylpurine derivatives

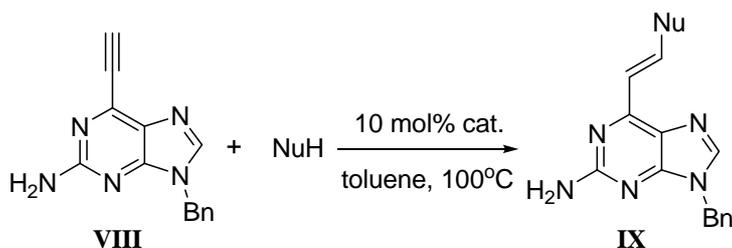
The objective was to examine the possibility of the functionalization of the ethynyl group in 6-ethynylpurine derivatives through the addition of nucleophiles. We followed the reaction in the presence of different inorganic (CsOH , KOH , K_2CO_3) and organic (EDIPA) basis, and we found only one difference in the reaction time. In the first experiments we followed the methodology published in the literature, but due to the difficulty of the removal of *N*-methyl-2-pirolidon, we switched to the acetonitrile whose

boiling point is much lower. Henceforward the next set of experiment we reacted the 6-ethynylpurine derivatives with a series of nucleophiles at 80 °C in acetonitrile in the presence of 20 mol% CsOH·H₂O.



The reaction of 6-ethynylpurine nucleophiles

The titanium-catalyzed hydroamination of alkynyl-derivatives is well known from literature. An excess of the nucleophile was reacted with 2-amino-9-benzyl-6-ethynyl-purine (**VIII**) in the presence of 10 mol% Ti(NMe₂)₂(OC₆H₂-2,6-^tBu₂-4-Me)₂ in toluene. We establish that the mentioned reactions run with same selectivity as in the CsOH·H₂O catalyzed hydroamination, thereby we found the formation of trans olefin (**IX**).



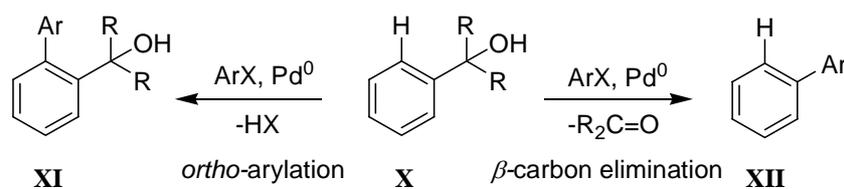
The hydroamination of 2-amino-9-benzyl-6-ethynyl-purine in the presence of bis(2,6-di-tert-butyl-4-methylphenoxy)-bisdimethyl-amide titanium

According to our initial objective, and with the help of the reactions' circumstances and conditions, throughout our study on several occasions we succeeded in increasing the

results of the reactions, decreasing the reaction time, and simplifying the breakdown of the reactions.

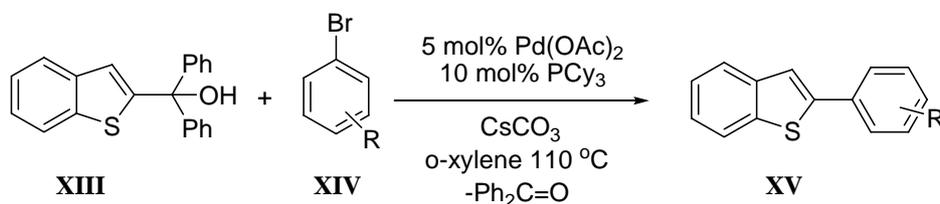
3. Palladium-Catalyzed Arylation of Arylmethanols

The third part of my work was to examine palladium-catalyzed transformation of α,α disubstituted arylmethanols with aryl halides. The mentioned α,α disubstituted arylmethanols reacted with aryl halides not only via the C-H bond cleavage, known as *ortho*-arylation, but also via cleavage of C-C bond (β -carbon elimination, *ips*-arylation). The principal aim of our research was to establish such reaction conditions where the reactions run with high selectivity.



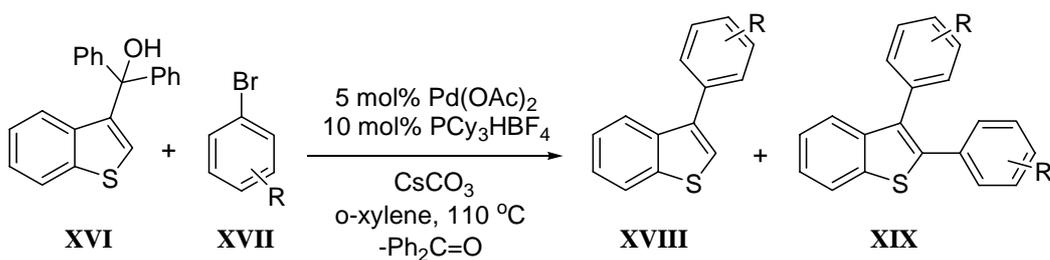
The possible structures of the products in the palladium-catalyzed arylation

We examined in detail the arylation of palladium catalyzed α,α disubstituted arylmethanols (thiophene, furan, benzofuran, benzothiophen), paying particular attention to the reaction conditions (palladium source, ligand, base) as well as the effect of the reagent to the reaction. The reactions were carried out in dry solvents, and the completion of the reaction was judged by GC-MS and TLC.



The coupling of α,α -diphenyl-2-(benzo[b]thienyl)-methanol and aryl bromides

Based on our research, we came to the conclusion that the desired selectivity was achieved exclusively in the case of benzothiophene derivatives. The *ipso*-coupling worked on **XIII** equally well with electron rich and electron deficient aryl halides, and the steric effects seemed to play only a minor role, if any, in influencing the yield. We observed that the yield ranged from acceptable to good and only the *ipso*-arylated (**XV**) compound was formed.



*The coupling of α,α-diphenyl-3-(benzo[*b*]thienyl)-methanol and aryl bromides*

Furthermore, we examined the palladium-catalyzed arylation of α,α-diphenyl-3-(benzo[*b*]thienyl)-methanol (**XVI**) with aryl halides. As opposed to our expectations, we experienced the creation of a product mixture. Unlike in the previous cases the reaction of **XVI** with aryl bromides usually led to the concomitant formation of 3-arylbenzo[*b*]thiophenes (**XVIII**) and 2,3-diarylbenzo[*b*]thiophenes (**XIX**). The selectivity depends on the used aryl-halide and the yields of **XVIII** were acceptable.

III. SCIENTIFIC PUBLICATIONS, PRESENTATION AND POSTERS RELATED TO THE PHD THESIS

Oral Presentations:

- "Palladium Catalyzed Synthesis of Nitrogen Heterocycles
A. Beatrix Bíró, Zoltán Vincze, András Kotschy;
Hungarian Academy of Sciences, Heterocyclic Chemistry Work-Meeting,
May 20-21, 2004, Balatonszemes, Hungary.
- "Transition-metal Catalyzed Synthesis of Heterocyclic Compounds"
A. Beatrix Bíró., J. Faragó, A. Nagy, Z. Novák, A. Kotschy
Hungarian Chemical Society (MKE) Chemistry Conference
June 28-30, 2005, Hajdúszoboszló, Hungary.
- "Palladium Catalyzed Transformation of Thiophene Derivatives"
A. Beatrix Bíró, András Kotschy
Hungarian Academy of Sciences, Heterocyclic Chemistry Work-Meeting,
June 07, 2006, Balatonszemes, Hungary.
- "Organic Moieties as Metal Surrogates in Cross-Coupling Reactions"
A. Beatrix Bíró, M.Csékei, A. Nagy, Z. Novák, A. Kotschy,
1st European Chemistry Congress (1st ECC)
August 27-31, 2006, Budapest, Hungary.

Posters:

- "Palladium Catalysed Synthesis of Nitrogen and Oxygen Heterocycles"
XXI. European Symposium on Heterocyclic Chemistry,
János Faragó, A. Beatrix Bíró, András Kotschy
September 12-15, 2004, Sopron, Hungary.
- Conference on Knowledge-based Materials and Technologies for Sustainable
Chemistry
A. Beatrix Bíró, András Nagy, Tibor Nagy, Zoltán Novák, András Kotschy
June 1-5, 2005, Tallinn, Estonia.

- "Organic Moieties as Metal Surrogates in Cross-Coupling Reactions"
13th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 13)
A. Kotschy, A. Beatrix Bíró, A. Nagy, Z. Novák
July 17-21, 2005, Geneva, Switzerland.
- "Palladium Catalyzed Formation and Functionalization of Five Membered Heterocycles"
Frontiers in Catalysis
A. Beatrix Bíró, János Faragó, András Kotschy*
September 8-10, 2005, Visegrád, Hungary.
- "Palladium Catalyzed Arylation of Five Membered Heterocycles"
Balticum Organicum Syntheticum (BOS 2006)
A. Beatrix Bíró, András Kotschy
June 25-29, 2006, Tallinn, Estonia.

Publications:

- "Preparation of 2,6-dihalogeno- 8-substituted purin compounds and process for producing the same".
András Kotschy, András Nagy, A. Beatrix Bíró
PCT Int.Appl.(2004) 36pp.WO 2004 065386
- "The Palladium- Catalyzed Preparation of Condensed Tetracyclic Heterocycles and their Application to the Synthesis of *rac*-Mangochinine"
Zoltán Vincze, A. Beatrix Bíró, Márton Csékei, Géza Timári, András Kotschy
Synthesis, **2006**, 1375-1386.
- "Selective Palladium-Catalysed *ipso* Arylation of α,α -Disubstituted Benzo[b]thien-2-ylmethanols with Aryl Bromides using PCy₃ as Ligand"
A. Beatrix Bíró, András Kotschy*
Eur. J. Org. Chem. **2007**, 6, 1905-1909.