

Synthesis of atomatic and heteroaromatic acetylenes with palladium catalyst

Doctoral Thesis

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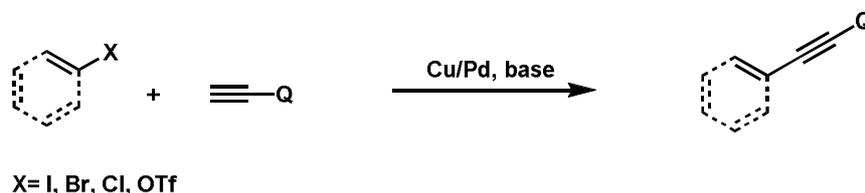
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assistant professor

Budapest, 2013.

1. Examination of Sonogashira reaction

One of the main goals of organic chemistry is the construction of carbon-carbon bonds. The field of Pd catalyzed cross-coupling reactions was honored with Nobel-prize in 2010.



The Sonogashira cross-coupling¹ is unique among these reactions. The procedure is able to create a bond between terminal acetylene and a vinyl or aryl halide, with high efficiency. The products are interesting and useful compounds in the term of biology, chemistry and material science, due to their synthetic utility and linear rigidity. In Sonogashira reaction the organometallic agent can be generated in the reaction mixture by copper and amine.

1.1. “Copper free” Sonogashira Reaction

In the Sonogashira reaction two metals are used together as a catalyst system. However the copper is useful in this reaction, it is also able to catalyze side-reactions. If a copper-free version of the reaction was developed, this issue could be eliminated. With this approach several methods exist for the conversion of substrates on a selective way.² Considering economic reasons a copper catalyzed reaction would be even more useful.

There are several procedures in the literature on the copper catalyzed Sonogashira reaction. Taillefer and co-workers utilized dioxo compounds as ligands for copper, resulting a „palladium free” reaction.³ Venkataraman created an efficient method that uses N heterocyclic bidentate ligand for the copper, and used this system for coupling acetylenes and vinyl halogenides without addition of the noble metal.⁴

¹ Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874.; Chinchilla, R.; Najera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.

² Komaromi, A.; Tolnai, G. L.; Novak, Z. *Tetrahedron Lett.* **2008**, *49*, 7294.; Komaromi, A.; Novak, Z. *Chem. Commun.* **2008**, 4968.

³ Monnier, F.; Turtaut, F. o.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203.

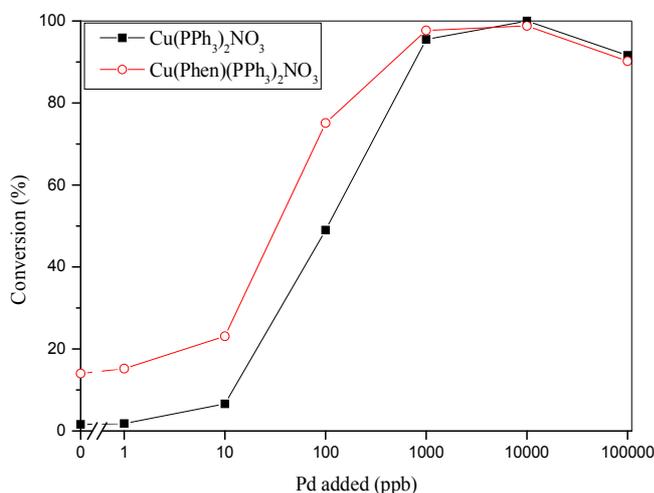
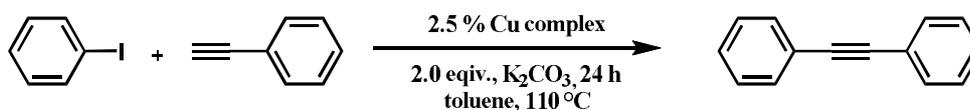
⁴ Bates, C. G.; Saejueng, P.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 1441.

1. 2. Aim of the research: Development of a Robust Method

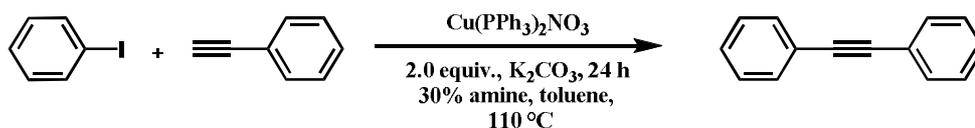
- During examining “copper-free” Sonogashira reactions, we found, that the reproducibility of these methods is often very low. The yields strongly depend on the source of the reactant and reagents, even on the antecedent of the equipment. We aimed to examine in details the reason of this phenomenon. We decided to develop a robust and reliable method for this coupling.
- Working methods: Assuming that the reason of the observations above could be the purity of compounds and equipments, we tried to establish conditions where impurities do not play any role. For this goal we utilized 99.999% pure copper for catalyst, „reagent plus” base, pure solvent, as well as we purged in *aqua regia* all the equipment we used.

1. 3. Dramatic Impact of Traces of Pd on the Conversion

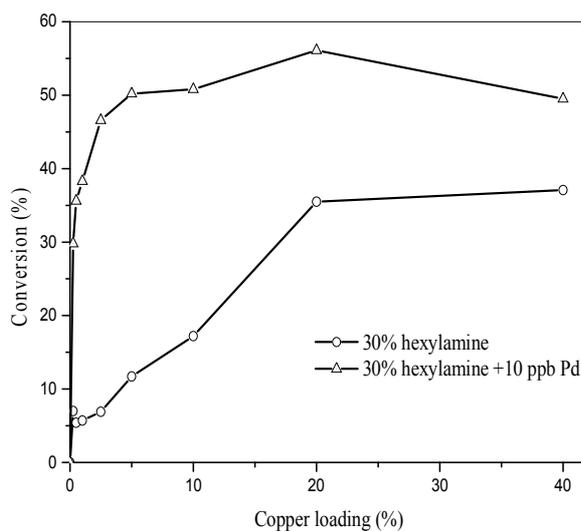
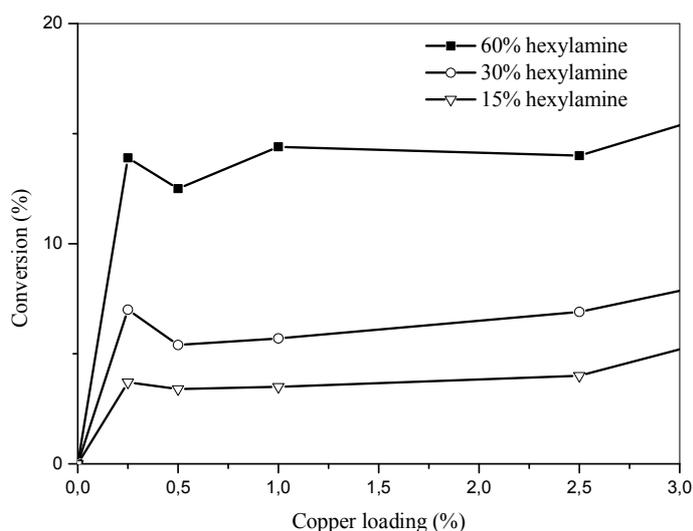
- As a result we found clean conditions (reducing the possibility of the presence of palladium impurities) that could only produce traces of the product after 24 hours. In contrast, in earlier reports copper complexes proved to be applicable catalysts for the Sonogashira reaction without the addition of any palladium.
- In systematic study we examined the effect of palladium on the reaction. As seen on the scheme below, even 1ppb (part per billion) Pd is slightly increased the conversion, but there is a huge increase in the region of 1-100 ppb added palladium. We showed that in the presence of organic bases such as amines the reaction rate significantly increased, and the transformation become even more sensitive for added palladium.



1. 4. Conclusion on the Role of the Copper: No Copper Cycle

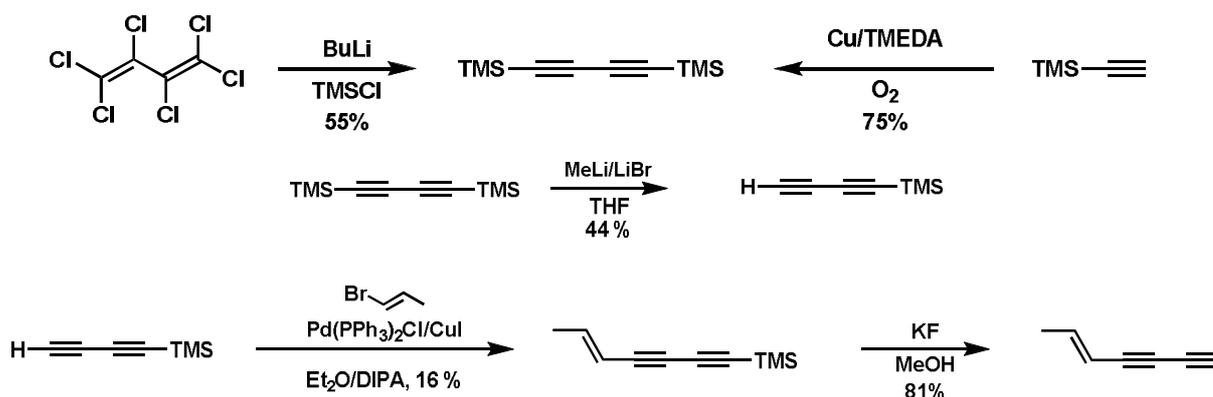
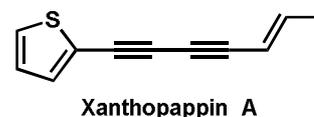


- Our results indicate the important role of palladium in the Sonogashira reaction. To prove the exclusive role of copper as catalyst in the C-C bond formation, we examined the effect of copper ratio on the reaction. In a wide scale the yield is increasing with the copper loading, which can indicate the role of copper as a catalyst or the impurities of the complex used.
- In the 1-3 % interval the conversion is independent from the copper loading. We hypothesized that in this range, due to the very low Pd concentrations (that is there according to the ICP-MS measurements) the presence of more copper-acetylide does not speed up the reaction, as the rate limiting factor is the amount of Pd present in the reaction mixture.
- The fact, that with the use of 10 ppb palladium we reach the plateau at higher copper loading (at 5 % instead of 0.25 %) indicates that in the presence of more palladium, it becomes rate limiting in the higher copper content region.
- We concluded, that the copper catalyst is not the responsible metal for the achievement of the carbon bond formation.

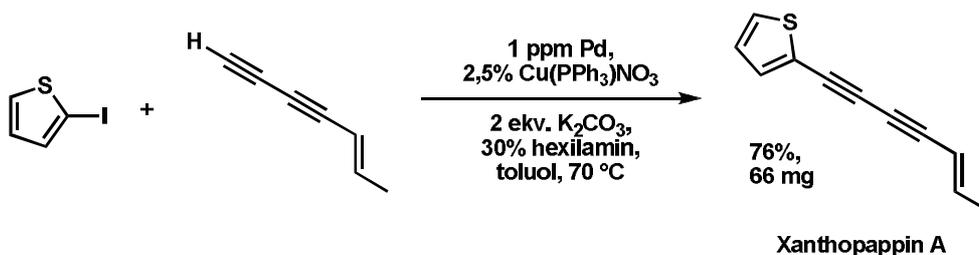


1. 5. The Use of the Results: Total Synthesis with Extra Low catalyst loading

- Aim: Total synthesis of Xanthopappin A⁵ in a pure form for the first time, with the use of extreme low palladium loading. This methodology combines the economic benefits of copper catalyst, with the robustness of classical Sonogashira methods.
- For the key coupling reaction we synthesized the acetylene part following literature procedures.



- In accordance to our consequences on Sonogashira reaction, despite the use of lower temperature we were able to obtain Xanthopappin A in a pure form for the first time, with the addition of only 1 ppm of palladium.



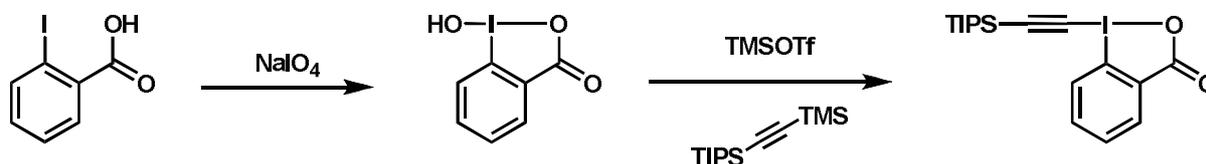
⁵ Tian, Y.; Wei, X.; Xu, H. *J. Nat. Prod.* **2006**, *69*, 1241.

2. The Direct C2 Alkynylation of Indoles with Hypervalent Iodine Reagents

2. 1. Hipervalent Iodines

The λ^3 hypervalent bond consist of 4 electrons and 3 centers. The presence of two non bonding electron pairs around the iodine center provides T shape for the molecule. Due to high energy content the molecule is prone to undergo nucleophilic attack, while the aryl iodide acts as an exceptional leaving group. This allows us to introduce alkynes in an electrophilic manner, such as substitution of a slightly acidic C-H proton. This approach is called direct functionalization because C-H bond can transformed in a catalytic process to obtain C-C bond.⁶

In electrophilic ethynylation the most efficient compounds are cyclic benziodoxolone reagents. TriIsoPropylSilylEthynylBenziidoXolone (TIPS-EBX)⁷ is an applicable reagent for the production of acetylene compounds on a wide range. However, TIPS-EBX is commercially available, it is easy to make on a decagram scale from 2-iodobenzoic acid and protected acetylene.⁸



2. 2. Direct Alkynylation of Indoles

The core of indole is one of the privileged structures in organic chemistry, as many pharmaceutically active compounds and natural products contain this moiety. Functionalization of indole is therefore an important task in this field. Direct ethynylation of indole is a current challenging synthetic problem of organic chemistry. Although, some methodologies have been developed, but they are mainly take advantage of the original reactivity of indole and ensures functionalization at the C3 position of the indole frame. The

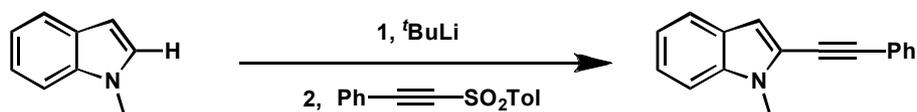
⁶ Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.; Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523.; Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.

⁷ Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165.

⁸ Brand, J. P.; Waser, J. *Synthesis* **2012**, *44*, 1155.

few examples for direct alkylation of the C2 position is limited to indoles where position C3 is occupied.

The only selective method applies strong lithium base and arylsulfonylacetylenes. Due to the use of such a strong base, the scope of the method is limited.⁹

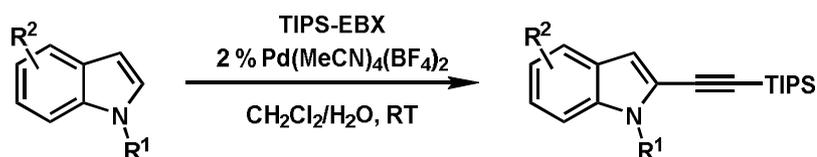


2. 3. Aim: Method for C2 Selective Alkylation of Indole

- Before our studies, methodology has not been described for the direct selective C2 alkylation with wide scope of indoles, therefore we aimed to develop a novel methodology for the direct ethynylation of indoles via C-H activation.

2. 4. Optimization of the reaction conditions

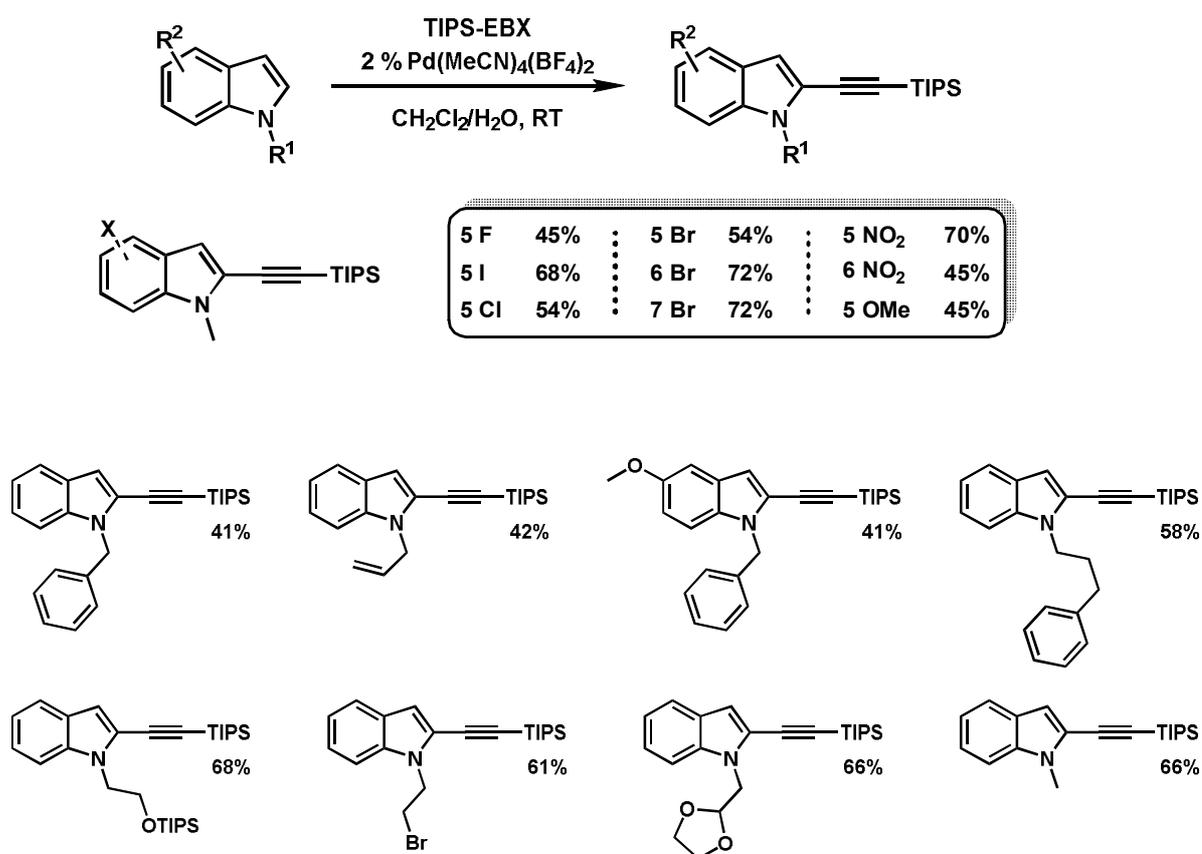
- We have found that, in the presence of palladium catalyst and TIPS-EBX indole can be selectively alkynylated in C2 position, however the conversion is low.
- Further screening showed that the reaction is limited to N-substituted indoles. Study of the activity of a wide range of Pd sources we found that the most effective catalysts was Pd(MeCN)₄(BF₄)₂, an easily accessible and stable Pd complex, that provides weakly coordinated catalyst metal.
- The positive response of solvent and additive screening was the improvement of yield by using dichloromethane/water mixtures. We demonstrated the important role of water in the catalytic transformation.
- We have found the above conditions optimal:



⁹ García Ruano, J. L.; Alemán, J.; Marzo, L.; Alvarado, C.; Tortosa, M.; Díaz-Tendero, S.; Fraile, A. *Chem. Eur. J.* **2012**, *18*, 8414.; García Ruano, J. L.; Alemán, J.; Marzo, L.; Alvarado, C.; Tortosa, M.; Díaz-Tendero, S.; Fraile, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 2712.

2. 5. Substrate Scope

- To establish the generality of the method, we examined the reactivity of differently substituted indoles. As a result of our study we have found that a great variety of functionalities are well tolerated both on the indole core and the N substituent. The method is also compatible with halogens on the indole benzene ring, which makes further fictionalizations possible through classical cross-coupling reactions.



- In summary, we found conditions for direct selective C2 alkylation with wide substrate scope and user friendly reaction condition, that do not require dry solvents or inert atmosphere.

Papers

1. „Dramatic Impact of ppb Levels of Palladium on the “Copper-Catalyzed” Sonogashira Coupling”
Tolnai, G. L.; Gonda, Z.; Novák, Z.
Chem. Eur. J. **2010**, *16*, 11822.
2. „C2 Selective Direct Alkynylation of Indoles”
Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J.
Org. Lett. **2013**, *15*, 112.;
(Highlighted in: *Synfacts* **2013**, *9*, 0276.)
3. "Copper-free Sonogashira coupling in amine-water solvent mixtures",
Anna Komáromi, Gergely L. Tolnai, Zoltán Novák
Tetrahedron Letters, **2008**, *49(51)*, 7294-7298.
4. “Palladium Catalyzed Methoxylation of Aromatic Chlorides with Borate Salts”
Gergely L. Tolnai, Bálint Pethő, Péter Králl, Zoltán Novák
Adv. Synth. Catal.– Accepted for publication

Lectures

1. „A "rézkatalizált" Sonogashira reakció palládiumérzékenysége”
Tolnai, G. L.; Gonda, Z.; Novák, Z. *MTA Heterociklusos Kémiai Munkabizottsági ülés, Balatonszemes, 2011 szeptember*
2. „Indolvázias vegyületek közvetlen szelektív C2 alkinilezése”
Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J.
MTA Heterociklusos Kémiai Munkabizottsági ülés, Balatonszemes, 2013 június
3. „Aryl-metil éterek előállítása palládiumkatalizált keresztkapcsolási reakcióban”
Pethő Bálint, Tolnai Gergely, Novák Zoltán,
MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2013. június

Posters

1. „Alkoxylation of Aromatic Chlorides”
Gergely László Tolnai, Bálint Pethő, Péter Králl, Zoltán Novák
18th European Symposium on Organic Chemistry, Marseille, 2013, June
2. „Szén-oxigén kötés kialakítása palládium-katalizált keresztkapcsolási reakciókban”
Pethő Bálint, Tolnai Gergely László, Králl Péter, Novák Zoltán,
Vegyészkonferencia, Hajdúszoboszló, 2013 July
3. „Cross-coupling reactions of aryl trialkylammonium salts with Grignard reagents”
17th European Symposium on Organic Chemistry, Crete, 2011, July