Investigation and utilization of the Superstable Pd(0) catalyst in C-C bond forming reactions

Thesis of PhD dissertation

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1. Introduction

The transition metal catalyzed cross-coupling reactions are reliable and effective tools for the C-C bond formation, which reaction is one of the most important synthetic transformation in the field of the organic chemistry.

Following their discovery, due to the enormous catalyst and ligand development during the past 30 years, these reactions have also gained industrial applications. The cross-coupling reactions have several benefits comparing to the traditional C-C bond forming reactions (Grignard, Wittig, Aldol), as they could be apply with better atom economy, increased functional group tolerance and less by-product.

Although the newly developed methods allowed the preparation of numerous natural products, biologically active compounds and optical devices, the scale-up process of these reactions remains a challenge. The applied catalyst and ligands are patented or expensive and they often have poor air- and thermostability. The lack of the robustness and stability makes the reactions and the storage of the catalysts difficult. The use of the inert atmosphere and the high catalyst load (1-10 mol%) is inconvenient and uneconomical. Further, in most cases a precipitate of palladium black forms during the reactions which is probably responsible for the reaction usually stops before full conversion. This uncontrolled decomposition process makes the recycling and the waste management more expensive.

However, due to the recognition of the possibilities lies in the cross coupling reactions, the development of new catalyst which could overcome the above listed difficulties is still important. Our research group have joint to this exciting development fields a few years ago.

2. Aims

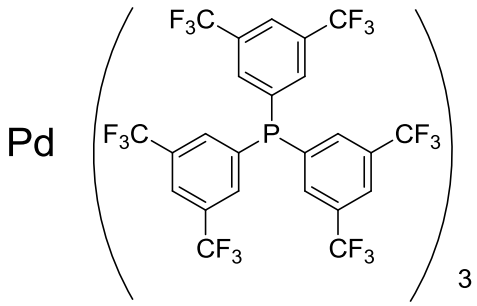
Recently, based on the literature and the previous work of our research group in the field of the immobilization of organocatalyst, we have synthesized a new, electron deficient phosphine ligands containing Pd(0) complex.

The unique stability and the presence of hydrophobic structural elements of the complex offer several practical advantages that were exploited in cross-coupling reactions.

The goal of the present work was to characterize this new complex and found explanation for the enhanced stability and the other special properties of the catalyst.

Beside the development of a scale-up process for the synthesis of the catalyst, our aim was to optimization the reaction conditions in the Superstable Pd(0) catalyzed Suzuki reactions, and expansion of the useable substrates.

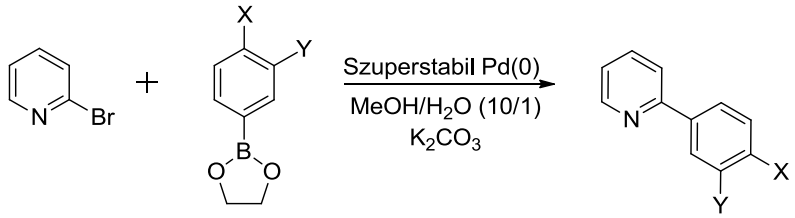
In addition to this, we wanted to expand the applicability of the catalyst towards other cross-coupling reactions (Heck and Sonogashira couplings) as well as the direct arylation reactions of (het)arenes.



3. Results

The main results and conclusions can be summarized as follows.

1. ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectroscopy, MALDI-TOF MS measurements, MP-AES and FAAS measurements and single crystal X-ray diffraction was utilized to the unequivocally characterization of the structure and the stoichiometry of the new complex. These investigations proved that the newly synthesized compound is a 3 phosphine containing 16-electron Pd(0) complex.
2. Besides the stoichiometry, the most unusual and peculiar characteristic of the complex was its high air- and thermostability. It could be stored in open vial for two years (at 40°C and 75% humidity). We also experienced a similar trend in complex stability at higher temperature as it has high melting point (225°C under N_2). Further, the presence of fluorine atoms influences the solubility profile of the complex, it is practically insoluble in most classical solvents (e.g. chloroform, hexanes, alcohols) at room temperature.
3. To probe the origin of this enhanced stability, DFT calculations were carried out. The computed geometries were in good agreement with the structural data provided by X-ray for the complex. Our results showed that the enormous complex stability is associated with the enhanced ligand-ligand dispersion interactions.
4. To reveal the catalytic behaviour of the complex, the Suzuki reaction of the 2-bromopyridine with a broad range of dioxaborolanes was chosen.

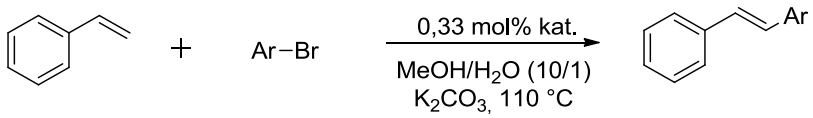


During this investigation, we found that the above mentioned reactions could be carried out in several solvent systems, including safer solvents, classified as class II and class III in industry, with low catalyst load and with good yields. The presence of the water (in low concentration 10-15 V/V%) is favourable and in the most cases, K_3PO_4 could be use as base instead of K_2CO_3.

5. Our experiments, which were carried out in microwave reactor showed that the catalytic activity and stability of the complex could be improved via using it in a combination with

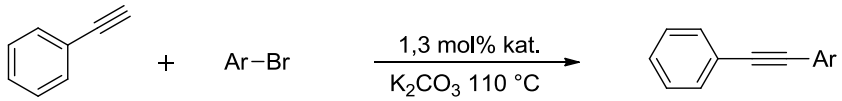
other phosphine ligands, especially 1,4-bis(diphenylphosphino)butane. After the optimization of the reaction conditions, the coupling of several dioxaborolanes with the more challenging 2-chloropyridine was realized with excellent yields within only 5 minutes. Further, the key intermediate of the fungicide Boscalid could be obtained with good yield.

6. The new catalyst was successfully applied in the Heck reaction of styrene with various bromobenzene derivatives.



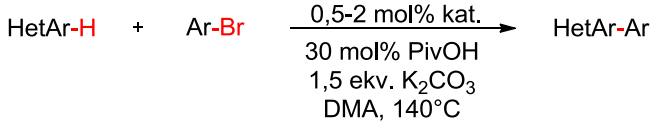
In these transformations, the amide type solvents (NMP, DMF) and the low toxicity glycerol-formal provided good yields. However, we also found that there are less useful solvents comparing with our results gained in the Suzuki reactions. The substituents of the aromatic halides significantly influenced the yields, and the best results were obtained in the presence of the electron withdrawing substituents. The sterically crowded bromobenzene derivatives gave the poorest results. The Heck reaction of the bromobenzene and the styrene were also carried out in microwave reactor, however the coupling of the less reactive chlorobenzene failed.

7. The activity of the catalyst was also investigated in the Sonogashira reaction of phenylacetylene with unsaturated bromo derivatives.



The best results were obtained via using the catalyst in the presence of K_2CO_3 as base, but in the absence of copper additives. Next, the effect of the applied solvent systems on the yields of the diphenylacetylenes was investigated. The coupling of 4-bromotoluene in n-BuOH at 110°C gave full conversion after a day and also good results were obtained using MeOH/H_2O (5/1), DMSO and glycerol formal solvents. However, experiments, carried out in NMP or MIBK solvents were unsuccessful. The isolated yields obtained in the Sonogashira reactions were less favourable compering the yields of the Suzuki and the Heck reactions.

8. The palladium contamination of the products of the above mentioned cross-coupling reactions were determined by ICP-AES measurements. The purification of the crude reaction mixtures was effected to the palladium contamination of the products. The palladium contents of the compounds, which were isolated by flash column chromatography, were below the detection limit. Surprisingly, data obtained in the same reaction type and purification methodology could be significantly different. However, several substrates could be isolated with low palladium contamination using simple purification methods.
9. Next, we extended the applicability of the complex towards the direct arylation reaction of several (het)arenes (benzene, furan, thiazol, benzothiophene, imidazole, oxazole).



After optimization of the reaction conditions, 16 biaryl molecules were prepared using various aryl bromides. The (het)arene starting materials could be reacted with full conversion in reasonable reaction times applying the Superstable Pd(0) catalyst and the products could be isolated with moderate too god yields. These reactions performed well in the presence of low catalyst load (0.5-2mol%) and there was no need to run the reaction at strictly inert atmosphere. The 1-Me-imidazole, previously recognised as poor substrate reacted smoothly in the presence of the new catalyst, however the reaction failed when sterically congested substrates or the less reactive chloroacetophenon were used as coupling partner.

10. Finally, exploiting the opportunities arising from the complex stability and poor solubility, we expanded the synthetic application of the catalyst with two practically important idea using in flow reactor and preparing an advantageous formula via mixing the catalyst with potassium-carbonate.

4. Papers forming the basis of the dissertation

[1] A. Jakab, Z. Dalicsek, T. Holczbauer, A. Hamza, I. Pápai, Z. Finta, G. Timári, T. Soós: „Superstable Palladium(0) Complex as an Air- and Thermostable Catalyst for Suzuki Coupling Reactions", Eur. J. Org. Chem. (Article first published online: 21 NOV 2014) DOI: 10.1002/ejoc.201403214

[2] A. Jakab, Z. Dalicsek, T. Soós: „Robust and Efficient Catalyst Possessing Electron-deficient Ligand for the Palladium-Catalyzed Direct Arylation of Heteroarenes", Eur. J. Org. Chem. (Article first published online: 31 OCT 2014) DOI: 10.1002/ejoc.201402586