Introduction

The goal of the proposed research, in a broader perspective, was the development of catalytic systems where chemical control can be realized over the outcome of the catalytic reactions. This goal was approached through the generation of intermediates in catalytic transformations that are having different reactivities. Exploiting these reactivities in different reactions led to diverse product structures, thus a considerable structural diversity could be accessed using a single catalyst/substrate system. On the other hand, we also became interested in controlling the stereochemical outcome of enantioselective reactions using a single chiral catalyst.

Results

Tandem reactions involving allyl alcohol isomerization chemistry

We started our investigations building on the Pd-catalyzed isomerization of allyl alcohol, where we foresaw the potential of the different types of intermediates to be involved in different further transformations (Figure 1). Thus, using the Pd/allyl alcohol system, a diverse set of possible products could be synthesized and isolated.

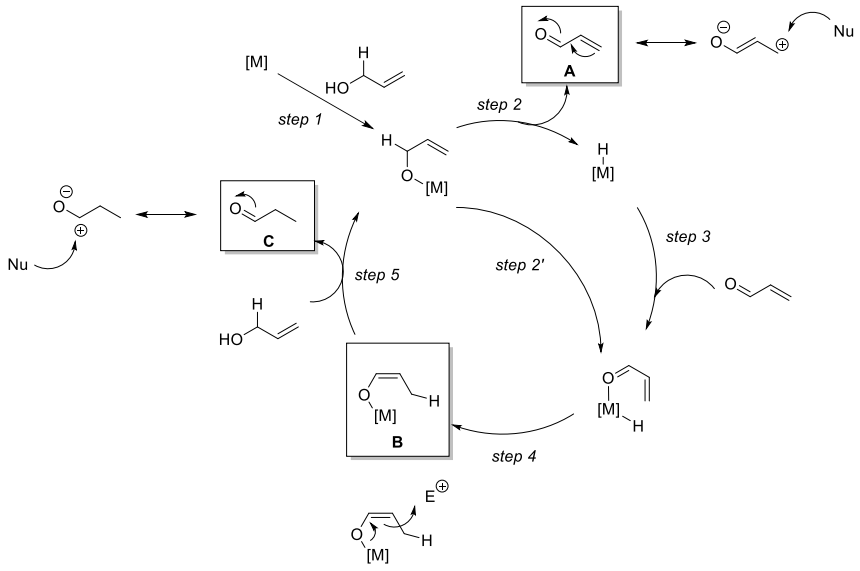

Figure 1 Schematic representation of a plausible mechanism of the transition metal [M] catalysed isomerisation of allyl alcohol. Structures **A**, **B** and **C** show possible reactivity profiles that could be individually exploited to create structurally divers products in a one-pot fashion using a single catalyst.

In the first stage of the work we investigated reactivity **B** of the enol(ate) intermediate, as depicted in Figure 1. We found that the enol(ate) forming during the isomerization of allyl alcohol can be exploited in aldol reactions with aromatic aldehydes using Pd/Al_2O_3 as an easily available, bench-stable catalyst. The highest reactivity was observed in the reaction with electron-poor aromatic aldehydes, while more electron rich species were largely non-reactive under the reaction conditions. This was a problem, as the forming α,β-unsaturated carbonyl compounds bearing aromatic rings with electron donating substituents (*t*Bu, OMe, *i*Pr) are intermediates of fragrances, such as lilial, canthoxal and cyclamal. We were able to overcome this problem by transforming the carbonyl group of the electron rich aromatic aldehyde into the

corresponding *N*-tosylimine, which compounds were giving the corresponding aldol condensation products in moderate yields.

We could involve the enol(ate) reactivity in a tandem processes with salicylaldehyde leading to 3-methylcoumarin via an aldol condensation/oxidative heterocyclization process.

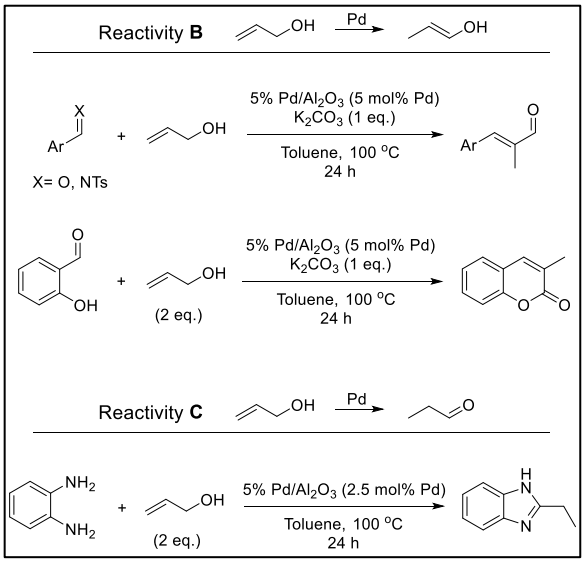

Figure 2 Examples of the use of enol-type reactivity (**B**) and carbonyl-type reactivity (**C**) for the synthesis of different products based on the Pd/allyl alcohol catalyst/reactant system.

Reactivity **C**, the carbonyl reactivity of the allyl alcohol isomerization product propanal was exploited in a tandem imin-formation/oxidation process leading to 2-ethylbenzimidazole. These results are summarized in Figure 2.

Heterogeneous Pd-catalyzed allyl alcohol isomerization reactions described in the literature, without exception, were performed in the presence of H_2 atmosphere. This is suggested to be necessary for the formation of the Pd-H species during the catalytic cycle. Pd-H is involved in the conjugate reduction of the allyl alcohol oxidation product acrolein (Figure 1, steps 3 and 4). In our system, H_2 atmosphere could be excluded which simplified the overall process. As an explanation, we proposed support/metal synergism during the catalysis that is facilitating the oxidative dehydrogenation process of the allyl alcohol, while also positioning the acrolein in a geometry where the conjugate reduction process is efficient (Figure 3).

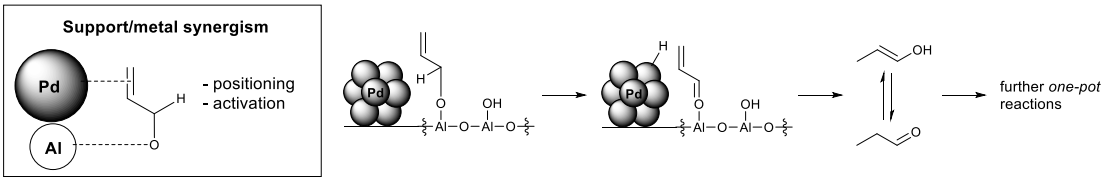

Figure 3 Proposed mechanism for the isomerisation of allyl alcohol over Pd/Al_2O_3 involving support/metal synergism.

This mode of activation was further supported by *in-situ* FTIR spectroscopic measurements in collaboration with Dr. András Sápi at the Department of Applied and Environmental Chemistry, University of Szeged.

Although using allyl alcohol as a carbonyl precursor (reactivity **C**) in tandem reactions has scarcely been described, this reactivity is not independent from the enolate form (reactivity **B**) as the two species are in equilibrium with each other. A more challenging task is to selectively exploit reactivity **A** involving the α,β-unsaturated compound acrolein. Acrolein forms in the first stage of the isomerisation process upon the oxidative dehydrogenation of ally alcohol (Figure 1, step 1) and it is not in equilibrium with any of the following species in the cycle. Thus, any reaction involving acrolein has to take place before it gets reduced to the enolate form. We investigated the reactivity of different nucleophiles towards the acrolein forming under Pd/Al_2O_3 catalysis from allyl alcohol. The results are summarized in Figure 4.

In general, the reactions of the acrolein intermediate in the allyl alcohol isomerization process led to low to moderate yields. Interestingly, by transforming the carbonyl group of 5-chlorosalicylaldehyde into the corresponding *N*-tosylimine, its reactivity could be altered from primarily electrophilic at the carbonyl carbon to primarily nucleophilic at the phenolic OH. This switch in reactivity led to different heterocyclic products.

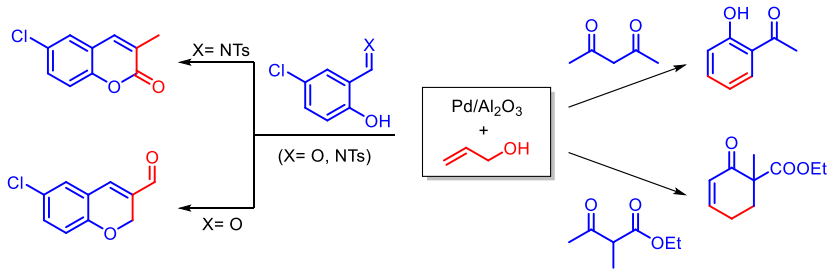

Figure 4 Pd/Al_2O_3 catalyzed reactions of allyl alcohol as an acrolein precursor.

We made efforts to expand the scope of this chemistry through using different allylic alcohols (longer chain primary, aliphatic secondary, cyclic secondary). However, in these cases only the isomerization product aldehydes/ketones could be isolated while only traces of aldol products were detected with different aromatic aldehydes.

Output related to *Tandem reactions involving allyl alcohol isomerization chemistry*

- D. Zsolnai, P. Mayer, K. Szőri, G. London* "Pd/Al_2O_3-catalysed redox isomerisation of allyl alcohol: application in aldol condensation and oxidative heterocyclization reactions" *Catal. Sci. Technol.*, **2016**, *6*, 3814.
- A. Dékány, E. Lázár, B. Szabó, V. Havasi, G. Halasi, A. Sápi, Á. Kukovecz, Z. Kónya, K. Szőri, G. London* "Exploring Pd/Al_2O_3 catalysed redox isomerisation of allyl alcohol as a platform to create structural diversity" *Catal. Lett.*, **2017**, *147*, 1834.
- Dániel Zsolnai "Allil-alkohol redox-izomerizáción alapuló kaszkád reakciói hordozós Pd katalizátorokon" *MSc. Thesis*, University of Szeged, 2015. (Supervisor: Gábor London)
- Attila Dékány "Allil-alkohol heterogén átmenetifém-katalizátorokkal végrehajtott gyűrűzárási reakciói" *BSc Thesis*, University of Szeged, 2016. (Supervisor: Gábor London)
- P. Mayer, D. Zsolnai K. Szőri, G. London "Allil-alkohol redox-izomerizáción alapuló kaszkád reakciói hordozós Pd katalizátorokon" *MKE Vegyészkonferencia*, Hajdúszoboszló, 2017. 07. 19-21 (Poster).

Tandem reactions over polydopamine supported Pd catalyst

In the second year of the project we started to investigate alternative catalyst (Pd) supports in allyl alcohol isomerization chemistry, which could be more suitable to tune chemically (e.g. by post-synthetic functionalization) compared to oxide supports. We begin to explore polydopamine (PDA) as a versatile material, as it is cheap, easy to prepare and bench-stable (Figure 5). The catechol moieties of the polymer were suitable to reduce Pd-salts on the surface of the polymer through their oxidation to the quinone form.

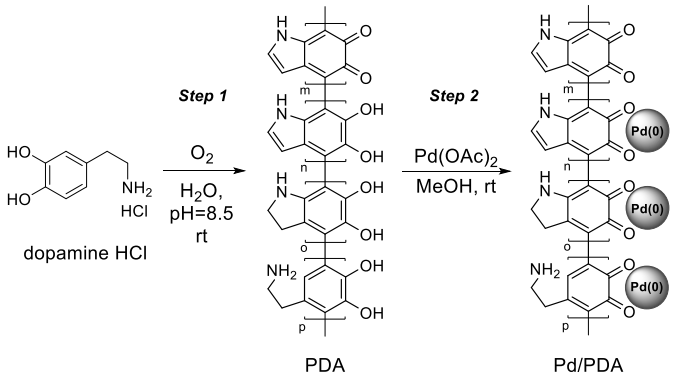

Figure 5 Polymerization of dopamine hydrochloride to PDA (Step 1) and Pd deposition onto the surface of PDA (Step 2).

Our initial experiments showed that Pd/PDA is not an ideal system for allyl alcohol based tandem chemistry as the forming aldehyde reacts with the amines of the polymer, which considerably decreases the efficiency of any further reactions. However, as we were able to prepare Pd nanoparticles as small as 1-3 nm with our optimized catalyst synthesis, we proceeded to exploit this catalyst in other chemistries, including tandem reactions. We showed that Pd/PDA is efficient in transfer hydrogenation reactions, and we also experimented to develop tandem Heck-reaction/catalytic transfer hydrogenation (CTH) sequences. For this, we used our parallel results in optimizing conditions for Heck-couplings using supported Pd catalysts.

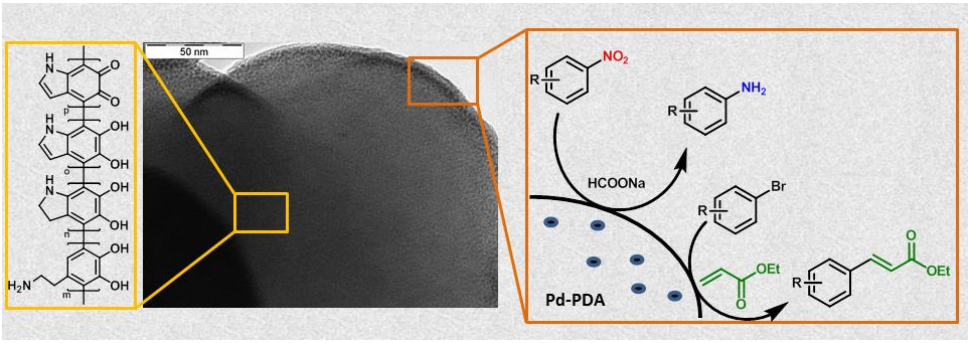

Figure 6 CTH and Heck reactions over Pd/PDA catalyst.

Although Pd/PDA was efficient in the CTH and also in Heck-type reactions, their combination was not feasible in a one-pot fashion, due to Pd leaching that is involved in the Heck-step. We also investigated the catalyst restructuring during reduction processes (CTH and catalytic hydrogenation) and its effect on the efficiency of the reactions. This work was carried out in collaboration with Dr. András Sápi at the Department of Applied and Environmental Chemistry, University of Szeged and Dr. Kornél Szőri at the MTA-SZTE Stereochemistry Research Group, University of Szeged.

Our latest investigations regarding Pd/PDA catalysis are focusing on green Suzuki-couplings and tandem Suzuki-coupling/CTH reactions of nitro groups leading to aminobiphenyls. We are able to carry out Suzuki couplings in high yields by using “homeopathic” amount (down to ppm concentration) of Pd contained in Pd/PDA. Furthermore, the tandem reaction sequence can be accomplished with the catalyst remaining active in several recycling steps.

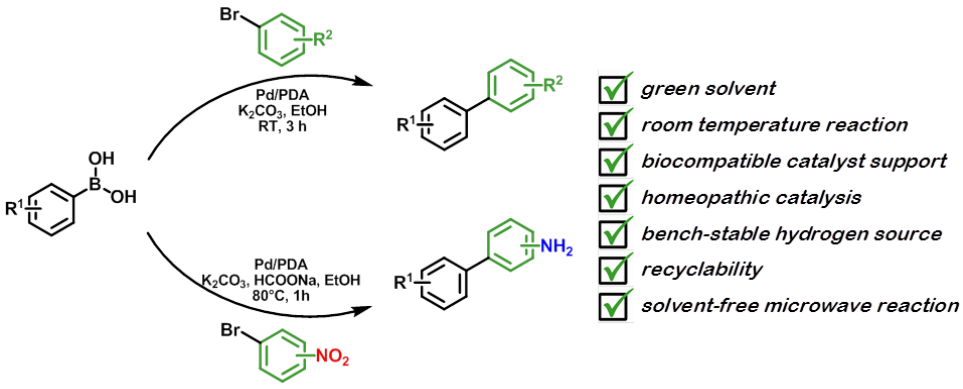

Figure 7 Pd/PDA catalyzed green Suzuki-coupling and tandem Suzuki-coupling/CTH reaction.

Output related to *Tandem reactions over polydopamine supported Pd catalyst*

- A. Kunfi*, Á. Mastalir, I. Bucsi, G. London "Heck arylation of alkenes with aryl bromides by using supported Pd catalysts: a comparative study" *Reac. Kinet. Mech. Cat.*, **2016**, *119*, 165.
- A. Kunfi, V. Szabó, Á. Mastalir, I. Bucsi, M. Mohai, P. Németh, I. Bertóti, G. London* "Palladium on Polydopamine: Its True Potential in Catalytic Transfer Hydrogenations and Heck Coupling Reactions" *ChemCatChem*, **2017**, *9*, 3236.
- T. Gazdag, Á. Baróthi, K. L. Juhász, A. Kunfi, P. Németh, A. Sápi, Á. Kukovecz, Z. Kónya, K. Szőri*, G. London* "Effect of particle restructuring during reduction processes over polydopamine-supported Pd nanoparticles" *J. Nanosci. Nanotechnol.* (Invited article for Special Issue: "Shape tailored nanocrystals in catalysis") *Submitted.*
- A. Kunfi, G. London* "On the green aspects of polydopamine supported palladium catalyst in Suzuki-coupling and one-pot Suzuki-coupling/nitroarene reduction reactions" *Manuscript in preparation.*
- A. Kunfi, G. London "Polidopamin hordozós Pd nanorészecskék alkalmazása katalitikus átalakításokban" *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*, Balatonszemes, 2017. május 15-17
- This topic served as the basis of the *BSc. Thesis* of Vivien Szabó (2017, University of Szeged). Her work was supervised by Dr. Ágnes Mastalir (SZTE) and Attila Kunfi (MTA TTK/SZTE).

Dual stereocontrol in organocatalytic asymmetric transformations

As the PI in the first year of the project was working closely with the MTA-SZTE Stereochemistry Research Group at the University of Szeged, he got involved in the topic of "dual stereocontrol" that he judged promising to partially finance from the budget of PD 115436.
Although this chemistry does not involve Pd catalysis, it is much related to the basic aims of the proposal. Here the goal was to use a single chiral catalyst to obtain both enantiomers of a chiral product selectively. Thus, there is no need for the synthesis of different enantiomers of a chiral catalyst, which makes the production of valuable chiral building blocks easier and cheaper. Furthermore, we showed that this dual control of stereochemistry can be accomplished in water, an environmentally benign reaction media.

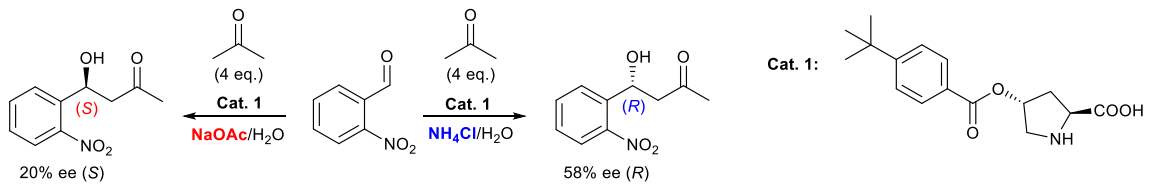

Figure 8 Dual stereocontrol in asymmetric aldol reactions.

Output related to *Dual stereocontrol in organocatalytic asymmetric transformations*

- A. A. Gurka, K. Szőri, G. Szőllősi, M. Bartók, G. London* "Tuning the sense of product stereochemistry in aldol reactions of acetone and aromatic aldehydes in the presence of water with a single chiral catalyst" *Tetrahedron Lett.*, **2015**, *56*, 7201.
- A. A. Gurka, K. Szőri, M. Bartók, G. London* "Dual stereocontrol in aldol reactions catalysed by hydroxyproline derivatives in the presence of a large amount of water" *Tetrahedron Asymm.*, **2016**, *27*, 936.
- A. A. Gurka, K. Szőri, M. Szőri, M. Bartók*, G. London* "Application of hydroxyproline derivatives in enantioselective α-amination reactions in organic and aqueous environments: a structure-activity relationship study" *Struct. Chem.*, **2017**, *28*, 415. (Special Issue: Honoring George A. Olah at 90)
- A. A. Gurka, G. London* "Dual stereocontrol in enantioslective aldol reactions" *Org. Prep. Proc. Int.*, **2017** (Invited Review article). *Accepted.* (DOI: 10.1080/00304948.2017.1374086)

These articles are forming the basis of the *PhD Thesis* of Attila A. Gurka (University of Szeged, expected defense: 2017 October). The PI is the supervisor of this Thesis in 50% (with Dr. György Szőllősi, MTA-SZTE Stereochemistry Research Group).

Further work not closely related to, but partially funded by PD 115436

Synthesis of new monomers for the preparation of novel conductive polymeric materials

In collaboration with Dr. Csaba Janáky (University of Szeged).

Output related to *Synthesis of new monomers to prepare novel conductive polymeric materials*

- D. Hursán, G. London, B. Olasz, C. Janáky* "Synthesis, characterization, and electrocatalytic properties of a custom-designed conjugated polymer with pyridine side chain" *Electrochimica Acta*, **2016**, *217*, 92.

Other notes

The PI of this project changed his Host Institute and moved from Szeged (MTA-SZTE Stereochemistry Research Group) to Budapest (Institute of Organic Chemistry, Research Centre for Natural Sciences) at the end of the first year of the project. This did not have major influence on the work related to PD115436. Due to minor changes in the time schedule upon changing working place, the budget for conference attendance was rearranged and was spent on consumables.

Attila Kunfi joined the project as a PhD student (supervised by the PI) at the second year, after being accepted to the Graduate School of Chemistry at the University of Szeged. His work focuses on polydopamine-related surface chemistries.