Final Report

Evaluation of novel P-based organocatalysts for the activation of small molecules and in P(III)/P(V)-redox catalysis

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Project title:	Evaluation of novel P-based organocatalysts for the activation of small molecules and in P(III)/P(V)-redox catalysis
Project duration:	1st of June 2017 till 31st of Mai 2018
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* z.B. Conference contributions, publications (with status), funding applications (with status)

1. Summary

The kickoff project “PAktiv” is separated into three parts: the activation of small molecules utilizing phosphorus based biradicaloids as organocatalysts, the enzymatic kinetic resolution of cyclic carbonates, which are prepared with phosphonium salt as catalysts, and the investigation of a catalytic Wittig reaction using phosphane oxides as pre-catalysts. The experimental work in all three projects has been finished and currently the publication of these results is ongoing in different stages.

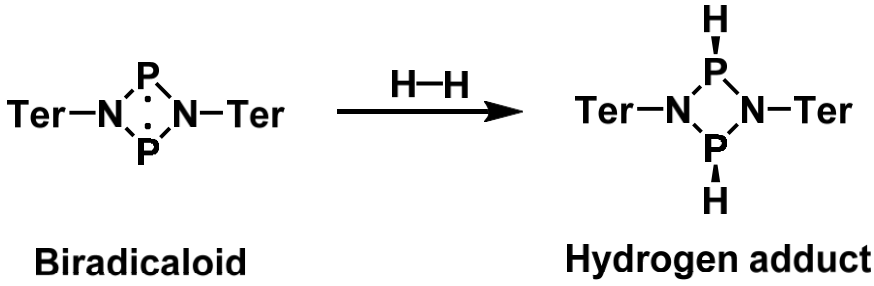
2. Introduction and aim of the project

The goal of the kickoff project P-Aktiv is the investigation of phosphorus based organocatalysts in important organic transformations. In this context, the expertise of different project partner allowed us to explore different reactivities of phosphorus compounds, e.g. biradicaloids, phosphonium salts and phosphanes. Phosphorus-based biradicaloids as organocatalysts were tested as planned as hydrogenation catalysts. Various substrates and conditions were tested and furthermore the activity in other catalytic reactions was investigated. Additionally the collaboration led to an improvement of the

synthetic pathway towards a precursor of the biradicaloid. Moreover, phosphanes and phosphane oxides were successfully investigated as catalysts in P(III)/P(V)-based redox cycling in an intramolecular variant of the catalytic Wittig reaction. This methodology allows for an easier access to 7-membered lactones, which were investigated in metabolic activity tests.

3. Results and discussion

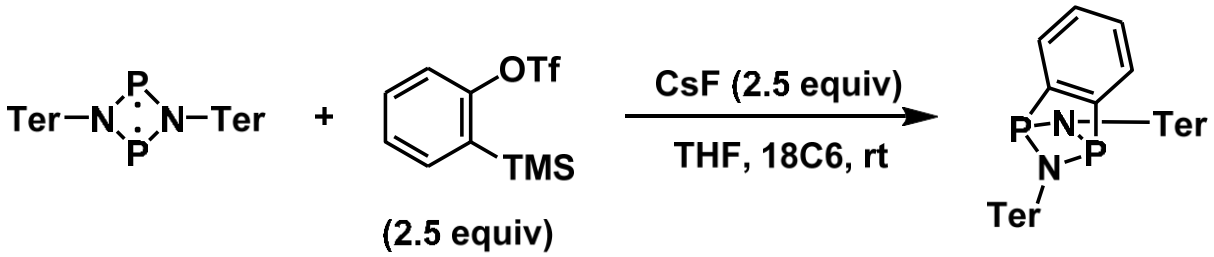
The activation of small molecules like hydrogen or CO_2 is a privileged property which is mostly limited to metal-based catalysts. The most active of these catalysts usually include either precious metals or tailored ligand systems, which are expensive and non-abundant. For this reason, great effort is put into finding catalyst based on purely organic scaffolds, also known as organocatalysts. Previous work by Schulz et al. showed the capability of a novel phosphorus based structure, a stable biradicaloid, to homolytically split hydrogen in a reversible fashion. These structures should then be evaluated as hydrogen transfer reagents and furthermore as reduction catalysts. The experimental work was conducted by MSc. Lars Longwitz using ressources both from the Schulz and the Werner laboratories. The synthesis of the biradicaloids was performed as published at a larger scale with help from the Schulz group. It was possible to obtain the desired product bearing terphenyl groups in gram scale. The synthesized biradicaloid was then converted under a hydrogen atmosphere to the hydrogen adduct (Scheme 1).



Scheme 1. Synthesis of the potential hydrogen transfer reagent.

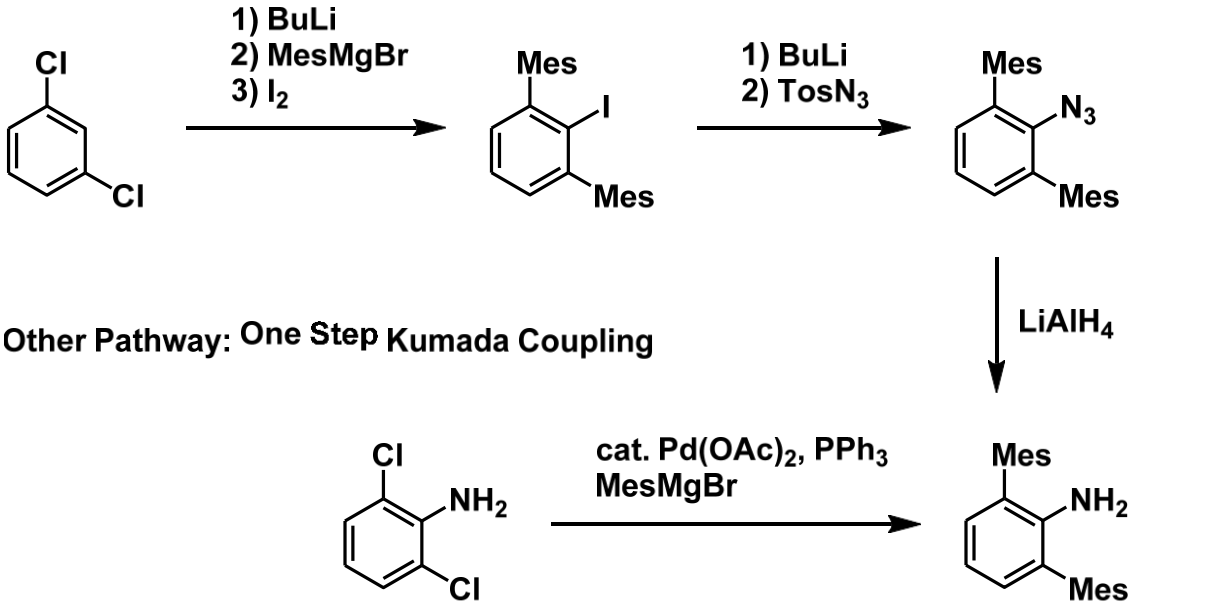
The reaction can be followed by a swift color change from orange to colorless and was also analysed by NMR spectroscopy. Subsequently, the adduct was converted with different hydrogen acceptors like styrene and benzofurane. Stirring at room temperature lead to the formation of [2+2] adducts of the

alkene and the free biradical, no hydrogen transfer was observed. Due to the high stability of the alkene adducts, different hydrogen transfer reagents like phenyl acetylene were investigated. The reaction of phenyl acetylene with the free biradical or the hydrogen adduct both lead to the same product. To liberate the alkyne or alkene, harsh reaction conditions of 100 °C and with a hydrogen pressure of 70 bar were applied, but at those temperatures only insertion into the four membered ring and following decomposition was observed. The same ring insertion can be observed, when the adduct is heated under argon in solution. A TGA/DSC analysis showed the start of decomposition at 80 °C, which is likely correlated to the ring insertion. At higher temperatures upwards of 210 °C gradual decomposition occurs. These result indicate that while the reaction of the free biradicaloid with hydrogen is reversible, the cyclo addition with the tested alkenes and alkynes is not, thus leading to stable adducts and the release of hydrogen gas instead of hydrogenation. For this reason, the reaction of the biradicaloid and hydrogen adduct with CO2 was investigated instead. The free biradicaloid reacts gets oxidized by CO2 and carbon monoxide is released. The resulting oxide has a deep red color. While first results of the reaction of the hydrogen adduct with CO2 showed promising results and indicated a single new species in the phosphorus NMR, it was quickly apparent that the new species stems from decomposition of the ring structure. While the hydrolysis of the biradicaloid leads to a mixture of decomposition products, it is likely that the reaction of carbon dioxide with the hydrogen adduct leads to the reduction to carbon dioxide, but in the process the four membered ring gets cleaved, which is evident by the finding of higher oxidized phorsphorus species and terphenyl amine in NMR and GCMS. Aside from hydrogen, the reactivity of other possible reductants like triethyl silane was also evaluated, but no reactivity of the free biradical with the silane was observed. Furthermore, other reagents were evaluated to obtain possible [2+2] cycloaddition products with the biradicaloid. An arine precursor was employed and converted to the free arine in the presence of the biradicaloid and under optimized conditions full conversion of the starting material was observed in the 31P NMR. Due to time limitation it was not possible to isolate and characterize the main product of the reaction, but the most likely structure would be a 1,2-phenyl bridge ring system.



Scheme 2. Arine cycloaddition with the biradicaloid.

During the cooperation between the Schulz and Werner group, the synthesis of the biradicaloid was further optimized. The idea was to use a palladium catalyzed coupling reaction instead of the original three step procedure towards the desired terphenyl aniline derivate. This new route brings several advantages: 1) reduced work hours and shorter reaction times, 2) reduced amount of organic solvent, 3) the use of less hazardous/toxic reagents, 4) overall less waste and better atom economy, 5) simple procedure.

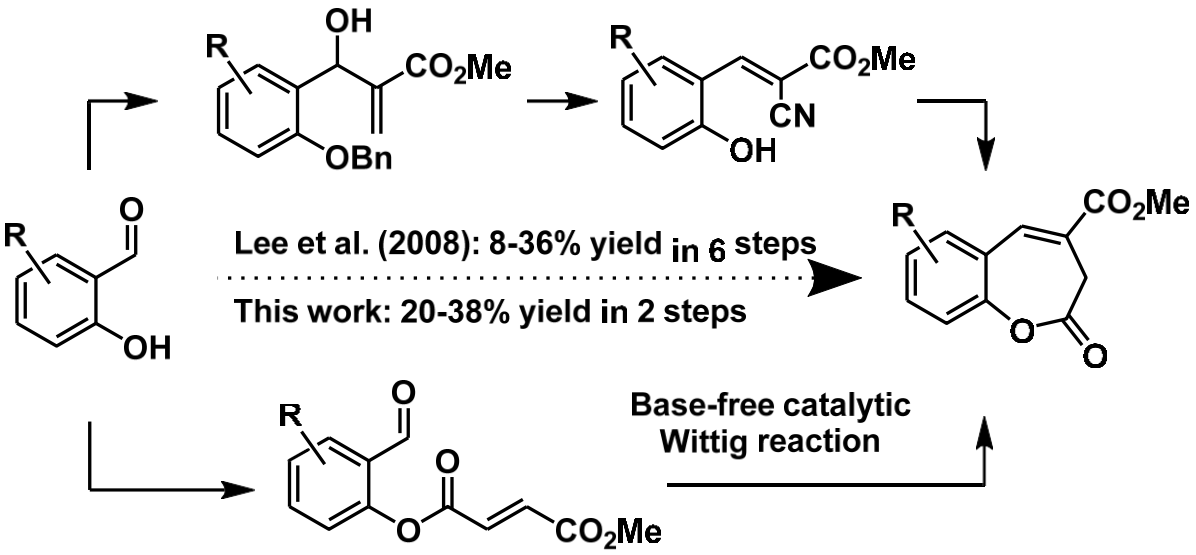


Scheme 3. Improved synthesis of the phosphorus-based biradicaloid precursor.

For this reason, the reaction was optimized and under optimized conditions the product was isolated in 51% yield in just one step. The reaction includes a cheap ligand and readily available starting materials. The possibilities to

synthesize other sterically demanding aniline derivates via this new method were also explored, but were unsuccessful.

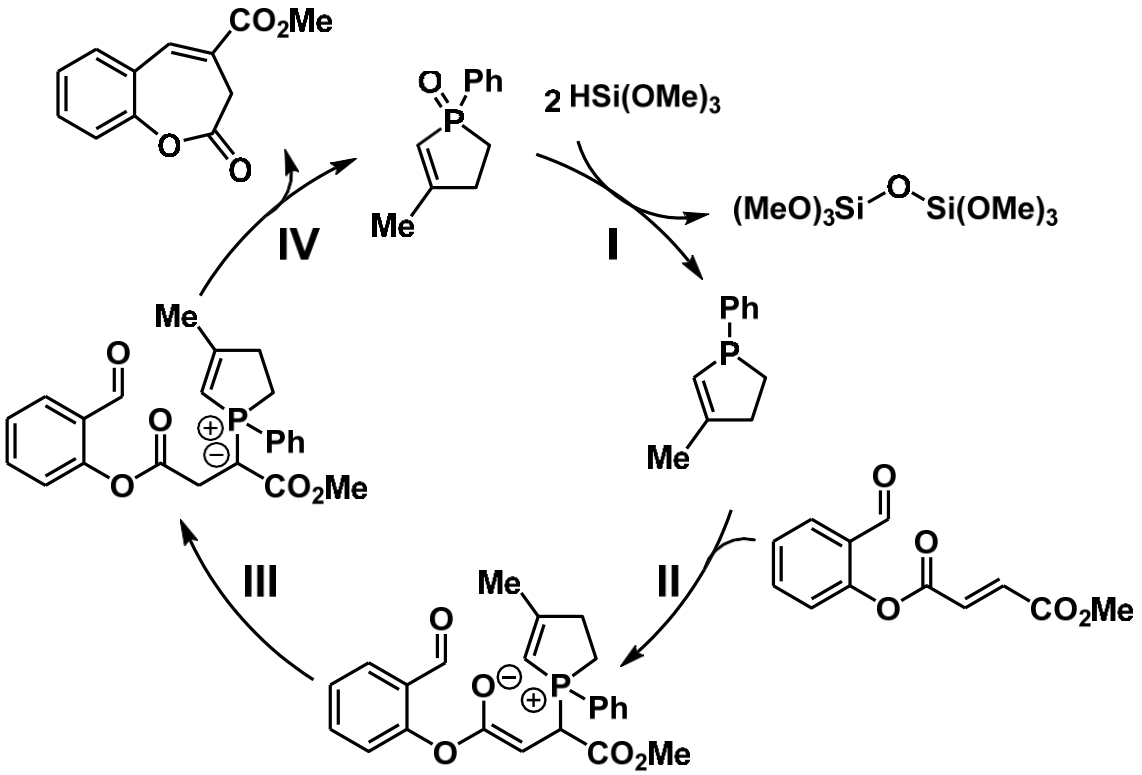
Phosphanes can be employed as catalyst in the Wittig reaction, if another terminal reductant is present. In the base-free Wittig reaction, the phosphorus ylide is formed from an electron poor alkene and the phosphane, in contrast to the classic Wittig reacting, where the deprotonation of a phosphonium salt leads to the ylide formation. The catalytic base-free Wittig reaction combines these concepts and was investigated in the Werner group previously. In this kickoff project, an intramolecular variant was developed and mechanistic studies were performed to get insight into the reaction mechanism. The target compounds of the reaction were benzoxepinones (Scheme 4), which are valuable precursors for biologically active compounds and were later evaluated in metabolic activity tests by the group of Prof. Junghanß.



Scheme 4. Synthetic pathways towards benzoxepinones.

The employed catalyst was a phospholene derivate, but other phosphanes like tributyl phosphane were also evaluated. Due to the similarity of the two carbons of the alkene functionality in the precursor, a mixture of products was obtained. The formation of a courmarin derivate was observed, which was not stable under reaction conditions. This side reaction lead to overall low to moderate yields, but the short overall pathway from salicylic aldehydes and the simplified work up still make this new route more efficient. Mechanistic studies

focused a lot on the role of the Brønsted acid as the additive, as well as the limitations of substitution on the alkene functionality. Deuteration experiments exclude a purely intramolecular reaction pathway after the Michael addition of the phosphane. A plausible catalytic cycle is displayed in Scheme 5.

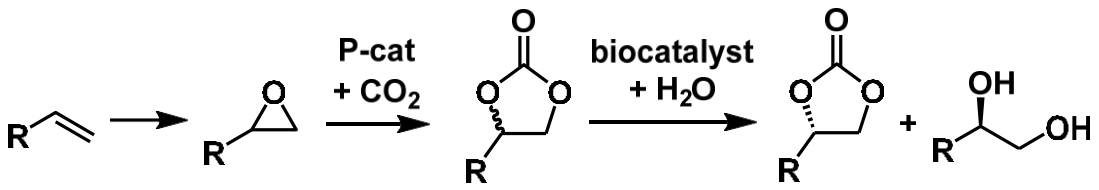


Scheme 5. Proposed catalytic for the intramolecular base-free catalytic Wittig reaction.

In the first step (I.) the phosphane oxide precatalyst is reduced by the silane to the phosphane. Subsequently, a Michael addition (II.) can take place, which is reversible. After a 1,2 proton shift (III.), which is very likely influenced by the acid, the carbon nucleophile forms and reacts with the present electrophile (IV.). This releases the catalyst as the oxide and re-enters the catalytic cycle. The synthesized compounds were tested in metabolic activity test by Catrin Roolf (Group C. Junghanß). The benzoxepinones did not show significant activity compared to the control.

Further investigations included the chemoenzymatic synthesis of valuable chiral cyclic carbonates and diols using P-based catalysts in combination with enantioselective enzymes. Herein phosphonium salts were utilized as potent

organocatalysts for the synthesis of chiral cyclic carbonates, which were subsequently selectively hydrolyzed using hydrolytic enzymes (scheme 6).



Scheme 6. Chemoenzymatic pathway towards enantiopure cyclic carbonates and diols.

A selection of aromatic and aliphatic compounds was converted using pig liver esterase, either as classical preparation from animal tissue or in recombinant form, whereas only 4 out of 6 isoenzymes showed sufficient activity and selectivity. The best process parameters were obtained using the classical enzyme preparation or isoenzyme 6, which exhibited their highest activity at pH 7.5 with a small percentage of acetonitrile (<10% (v/v)) to achieve sufficient substrate solubility in the aqueous phase. After optimization enantiomeric excesses of up to 97% were obtained.

4. Further achievements/ benefit from the project

Three presentations were held on the basis of this project:

1. „P-based processes – from reagents to catalysts", T. Werner, *Summer School "Advanced Organocatalysis" ADVOCAT*, 26.–30. August **2018**, Cologne University - Kardinal Schulte Haus, Bergisch Gladbach, Deutschland (INVITED).
2. „Recent advances in catalytic Wittig-type reactions based on P(III)/P(V) redox cycling", T. Werner, 22nd International Conference on Phosphorus Chemistry (ICPC), 08.–13. Juli **2018**, Budapest, Ungarn. (KEYNOTE)
3. "Evaluation of novel P-based organocatalysts in the activation of small molecules and P(III)/P(V)-redox catalysis", L. Longwitz, A. Grandane, U. Kragl, J. von Langermann, A. Schulz, C. Junghanß, H. M. Escobar, C. Roolf, T. Werner*, 3. Internes P-Campus Symposium, 8.-9. November **2017**, Rostock, Deutschland.

Two manuscritps have been accapted for publication:

1. Lars Longwitz, Thomas Werner, Recent advances in catalytic Wittig-type reactions based on P(III)/P(V) redox cycling. *Pure Appl. Chem.* **2018,** DOI: 10.1515/pac-2018-0920.

2. Aiga Grandane, Lars Longwitz, Catrin Roolf, Anke Spannenberg, Hugo Murua Escobar, Christian Junghanss, Edgars Suna, Thomas Werner, Intramolecular Base-Free Catalytic Wittig Reaction: Synthesis of Benzoxepinones. *J. Org. Chem.* accepted.