DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
122

DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS
122

LAURI SIKK

Computational study of the Sonogashira cross-coupling reaction

UNIVERSITY OF TARTU
PRESS
1632

Institute of Chemistry, Faculty of Science and Technology, University of Tartu, Estonia

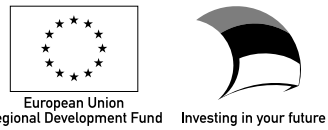
Dissertation is accepted for the commencement of the Degree of Doctor of Philosophy in Chemistry on September 19th, 2012 by the Doctoral Committee of the Institute of Chemistry, University of Tartu.

Supervisors: prof. Peeter Burk, Institute of Chemistry, University of Tartu, Tartu, Estonia
Jaana Tammiku-Taul, PhD, Institute of Chemistry, University of Tartu, Tartu, Estonia

Opponents: Zoltán Novák, Assistant Professor, Eötvös Loránd University, Institute of Chemistry, Department of Organic Chemistry, Budapest, Hungary

Commencement: 16th of November 2012 in Room 1019, 14A Ravila Street, Tartu, at 10:00

This work has been /partially/ supported by Graduate School „Functional materials and technologies" receiving funding from the European Social Fund under project 1.2.0401.09-0079 in University of Tartu, Estonia



ISSN 1406–0299
ISBN 978–9949–32–138–4 (print)
ISBN 978–9949–32–139–1 (pdf)

University of Tartu Press
www.tyk.ee
Order No. 477

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original papers, which are referred to in the text by their Roman numerals:

I Sikk, L.; Tammiku-Taul, J.; Burk, P.; Kotschy, A. Computational study of the Sonogashira cross-coupling reaction in the gas phase and in dichloromethane solution. *J. Mol. Mod.* **2012,** *18,* 3025–3033.

II Sikk, L.; Tammiku-Taul, J.; Burk, P. Computational Study of Copper-Free Sonogashira Cross-Coupling Reaction. *Organometallics,* **2011,** *30* (21), 5656–5664.

III Sikk, L.; Tammiku-Taul, J.; Burk, P. Computational Study of Copper-Free Sonogashira Cross-Coupling Reaction: Shortcuts in the Mechanism. *Proc. Est. Acad. Sci.,* accepted for publication.

Author's contribution

Paper I: Main person responsible for planning and writing the manuscript. Performed all computational work.

Paper II: Main person responsible for planning and writing the manuscript. Performed all computational work.

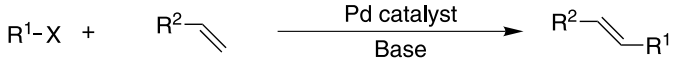
Paper III: Main person responsible for planning and writing the manuscript. Performed all computational work.

ABBREVIATIONS

OTf	Trifluoromethanesulfonate (triflate) functional group
dba	Dibenzylideneacetone
DFT	Density functional theory
B3LYP	Hybrid functional, consisting of Becke 88 exchange functional and the correlation functional by Lee, Yang and Parr
B97D	Grimme's functional including dispersion
cc-pVDZ	Correlation-consistent, valence polarized double-ζ basis set
DCM	Dichloromethane
IRC	Intrinsic reaction coordinate
NMR	Nuclear magnetic resonance
PCM	Polarizable continuum model
PES	Potential energy surface
SMD	Solvent model by Thrular and coworkers
TOF	Turnover frequency
TS	Transition state

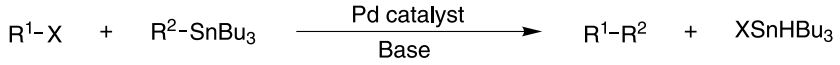
CROSS-COUPLING REACTIONS REFERENCED IN TEXT

Heck reaction



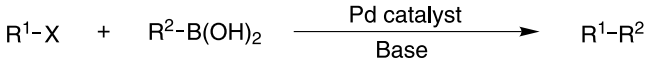
R^1 = aryl, benzyl, vinyl
X = I, Br, OTf

Stille coupling



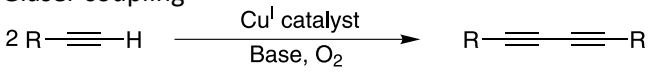
X = I, Br, Cl, OTf

Suzuki coupling

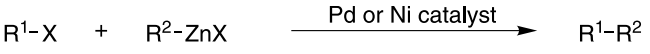


X = I, Br, Cl, OTf
R^1, R^2 = aryl, alkyl, alkenyl, alkynyl

Glaser coupling



Negishi coupling



X = I, Br, Cl, OTs
R^1 = alkenyl, aryl, allyl, benzyl, propargyl
R^2 = alkenyl, aryl, alkynyl, alkyl, benzyl, allyl

1. INTRODUCTION

The palladium catalyzed cross-coupling reactions have been very important in organic chemistry since their discovery in 1970s. This has been recently acknowledged by the Royal Swedish Academy of Sciences by awarding the Nobel prize in chemistry to Richard F. Heck, Ei-ichi Negishi, and Akira Suzuki in 2010 for palladium-catalyzed cross-couplings in organic synthesis. These C-C bond formation reactions have changed organic chemistry by allowing the parallel synthesis of precursor components, which are later linked by cross-coupling reactions (as opposed to the linear synthesis of desired molecule, used earlier).[1] Nowadays, there are a number of palladium-catalyzed cross-coupling reactions capable of C-C bond formation, which are usually distinguished on the basis of the used co-catalyst or transmetalating agent.

The Sonogashira reaction (palladium-catalyzed sp-sp^2 coupling between aryl or alkenyl halide and terminal alkynes in the presence of Cu^I) was first described in 1975.[2] This was based on the earlier work of Heck *et al.*,[3] Cassar *et al.*[4] (palladium-catalyzed alkenylation of alkenes) and Stephens-Castro reaction[5] (coupling between copper acetylides and vinyl or phenyl halides). Although the use of copper co-catalyst greatly increases the reaction rate in the Sonogashira reaction, it can also induce Glaser-type homocoupling of the terminal alkyne. To supress the formation of this side-product, series of copper-free versions of the Sonogashira coupling have been developed.[6,7]

Although the Sonogashira reaction is well-known and extensively used for a long time, its proposed mechanism is mainly based on the similarity with the other cross-coupling reactions and the detailed reaction mechanism is unknown. This is mainly caused by the difficulties in isolation and characterization of the reaction intermediates, which are often unstable and present in very low concentrations.

Computational modeling of this cross-coupling reaction can provide useful information about important reaction intermediates and the role of various molecular species (base, solvent, ligand, etc.) in the reaction mixture. This thesis presents computational analysis of the Sonogashira cross-coupling reaction mechanism to get an insight into the possible reaction pathways of palladium-catalyzed cross-coupling between phenylacetylene and bromobenzene resulting in diphenylacetylene. Potential energy surfaces of possible reaction routes are analyzed and a revised reaction mechanism is proposed, based on these results. Computational data about the multiple mechanistic pathways, responsible for this cross-coupling reaction and the role of various additives in the reaction mixture, are vital for the future experimental studies on this field. The deeper understanding of the Sonogashira cross-coupling can be used to design more effective catalytic systems and, therefore, increase the rate, yield, and scope of the overall reaction.

2. LITERATURE OVERVIEW

2.1. General mechanism of the Sonogashira cross-coupling

The Sonogashira cross-coupling offers a relatively simple route for the synthesis of arylalkynes and conjugated enynes from terminal alkynes and aryl or alkenyl halides or triflates (Figure 1).[8]

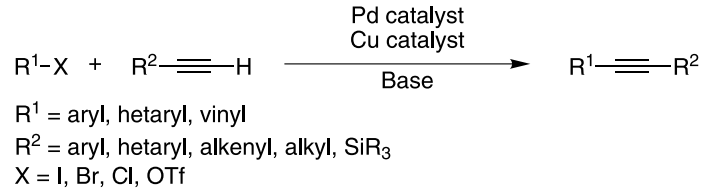
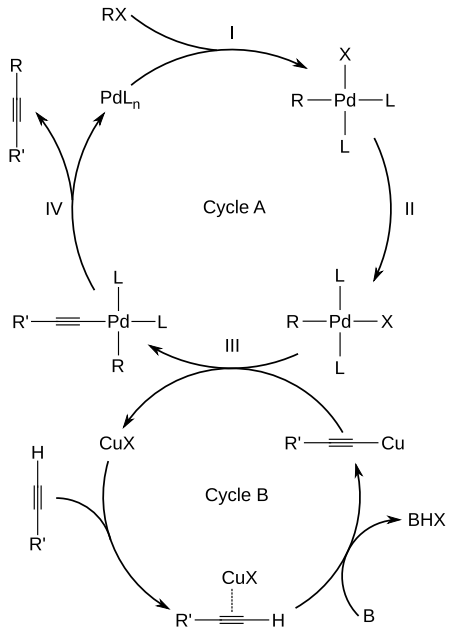


Figure 1. Net reaction of the Sonogashira cross-coupling.

The rate of the Sonogashira reaction depends heavily on the nature of aryl halide or triflate and the order of reactivity with respect to the leaving group is: I ≥ OTf ≥ Br > Cl. Vinyl halides are usually more reactive than aryl halides. Alkynes, which are substituted with electron-withdrawing groups, tend to react slower than unsubstituted alkynes.[9] The Sonogashira cross-coupling reaction is catalyzed by zerovalent palladium complex and copper(I) halide. Pd^0 can be directly introduced to the reaction mixture or generated from Pd^{II} complex. There are a number of zerovalent Pd complexes that can be used as a source for Pd^0: e.g. $Pd(PPh_3)_4$ and $Pd_2(dba)_3$. While $Pd(PPh_3)_4$ can be used as a catalyst for a number of cross-coupling reactions, $Pd_2(dba)_3$ is treated with suitable ligands to form the desired catalyst. Although these palladium complexes are extensively used in synthetic organic chemistry, they are usually not suitable for kinetic experiments, as they can contain considerable amount of Pd nanoparticles.[10] Relative instability of Pd^0 complexes is one of the reasons why Pd^{II} precatalysts are used to generate catalytically active Pd species *in situ*. $Pd(PPh_3)_2Cl_2$ and $Pd(OAc)_2$ are examples of widely used catalyst precursors, which can be reduced to Pd^0 by amines or phosphanes.[8]

The mechanism of the Sonogashira cross-coupling reaction (Scheme 1)[8] consists of cycles A and B. The catalytic cycle A starts with the oxidative addition of an aryl halide RX to a palladium catalyst PdL_n, which is followed by the isomerization of the oxidative addition product. The role of copper in the Sonogashira cross-coupling is believed to be the formation of copper acetylides from copper(I) salt and terminal acetylene in the presence of base.[8] In general, the amines, used in the reaction, are not basic enough to deprotonate acetylenes and the involvement of π-alkyne-Cu complex is presumed. Cycle B in Scheme 1 describes the formation of copper acetylide, which reacts with the palladium

complex in the transmetalation step. The product of the Sonogashira coupling (RC≡CR') is formed in the reductive elimination step and the palladium catalyst is also regenerated.

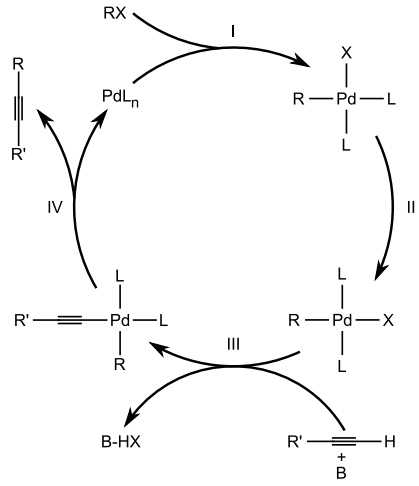


Scheme 1. Mechanism of the Sonogashira cross-coupling reaction. I: oxidative addition, II: *cis-trans* isomerization, III: transmetalation, IV: reductive elimination.

As in other cross-coupling reactions, a wide range of phosphane ligands are used for the Sonogashira coupling. Although the phosphorus(III)-based ligands have been extensively studied, the choice of ligand for a specific reaction is still complicated and "continues to rely on a combination of chemical intuition as well the testing and optimization of a range of likely candidates".[11] Phosphane ligands are usually compared on the basis of steric and electronic parameters. While it is difficult to make a good prediction about the effect of ligand on the overall reactivity of the catalyst, switching triphenylphosphane to more electron rich phosphane usually leads to the increased reaction rate.[8] Similarly, the larger steric demand of phosphane ligand can promote the formation of low-ligated palladium species and, therefore, lead to the faster reaction. An der Heiden *et al.* have investigated the effect of different bulky phosphane ligands on the rate of the Sonogashira cross-coupling reaction and their work is a very good example of the "chemical intuition and testing" mentioned earlier.[12] Due to the number of different ligands used in the Sonogashira reaction, the composition of active catalytic species (PdL_n, n = 1…4, Scheme 1) is still under discussion.

2.2. General mechanism of the copper-free Sonogashira cross-coupling

The mechanism of the copper-free Sonogashira reaction is similar to the copper co-catalyzed reaction and the "textbook" mechanism is depicted in Scheme 2.



Scheme 2. Mechanism of the copper-free Sonogashira cross-coupling reaction. I: oxidative addition, II: *cis*-*trans* isomerization, III: deprotonation, IV: reductive elimination.

As previously mentioned, amines alone are not able to deprotonate alkyne, so the coordination of metal (in this case palladium) to the triple bond is required to increase the acidity of the acetylenic proton. On the other hand, a similar coordination of alkyne to the low-ligated palladium complex can inhibit the oxidative addition by reducing the amount of available catalyst.[13] The copper-free Sonogashira reaction usually requires the use of base in large excess, often as a solvent. This causes the reaction mechanism to be more complex, as base can react with *trans*-$PdL_2(Ar^1)X$ and substitute one ligand molecule. The substitution is extensive in the case of weakly-binding ligands (e.g. $AsPh_3$) and is considered a competing process to the substitution of ligand with alkyne.[14]

2.3. Reaction steps of the Sonogashira cross-coupling

Although not many detail studies of the mechanism of the Sonogashira cross-coupling reaction (both copper-free and copper co-catalyzed) have been published, useful information can be found in the literature, as many palladium-catalyzed cross-coupling reactions (e.g. Heck, Stille, Suzuki reactions) have the

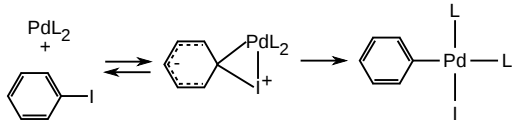
same general mechanism. All of these reactions start with the oxidative addition of an aryl or alkenyl halide to a palladium catalyst, which is usually considered to be the rate-determining step of the catalytic cycle.[15] Amatore and Pflüger have determined that the oxidative addition of PhI to $Pd(PPh_3)_4$ proceeds through a 14-electron intermediate $Pd(PPh_3)_2$ and results in *cis*-$Pd(PPh_3)_2(Ph)I$ complex. Prior to the actual oxidative addition step (Eq. 3) are two rapid preequilibrias (Eqs. 1 and 2):

$$Pd(PPh_3)_4 \rightleftarrows Pd(PPh_3)_3 + PPh_3 \qquad K_1 \qquad \text{(Eq. 1)}$$

$$Pd(PPh_3)_3 \rightleftarrows Pd(PPh_3)_2 + PPh_3 \qquad K_2 \qquad \text{(Eq. 2)}$$

$$Pd(PPh_3)_2 + PhI \rightarrow \textit{cis}\text{-}Pd(PPh_3)_2(Ph)I \qquad \text{(Eq. 3)}$$

The dissociation of $Pd(PPh_3)_4$ to $Pd(PPh_3)_3$ and triphenylphosphane is strongly shifted towards the formation of the products, but the subsequent ligand dissociation is not so extensive and $Pd(PPh_3)_2$ complex is present in trace levels.[16] The transition state of oxidative addition is described as a three-centered activated complex (see Scheme 3).[17]



Scheme 3. Three-centered transition state of oxidative addition.

This mechanism suggests that electropositive iodine stabilizes the transition state, while in the case of bromine and chlorine this type of stabilization does not have such large effect.

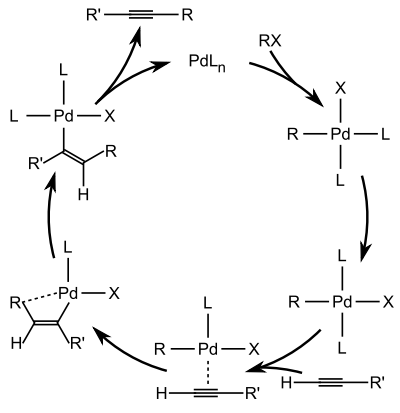
In general, the transition state of oxidative addition involves two phosphane ligands but in the case of bulky ligands, a monophosphane route is reported.[18] Barrios-Landeros *et al.* have investigated the steric effects of ligand and the role of halide identity in arylhalide on the oxidative addition mechanism.[19] Their work suggests that the mechanism of oxidative addition is more dependent on the aryl halide than on the phosphane ligand. In the case of iodoarenes, the irreversible step in the oxidative addition was the reaction of iodoarene with the palladium complex ligated by two phosphane ligands. On the other hand, in the case of chloroarenes, the irreversible step involves the reaction of chloroarene with the monoligated palladium atom. Halide anions, generated during the reaction or originating from a precatalyst (e.g. $Pd(PPh_3)_2Cl_2$) can coordinate with the low-valent palladium complex and influence the oxidative addition reaction.[20] Early kinetic studies revealed that the coordination of halide ions to the low-ligated palladium complex decreased the activity of the catalyst (greatly increased the reaction half-life). However, this deactivation could be beneficial from the synthetic point of view, as it also decreases the risk of catalyst oligo-merization or the formation of palladium-black.[21] Recently Barrios-Landeros *et*

al. suggested that aside from halide anion, the oxidative addition is also dependent on the corresponding cation and under the certain conditions can be autocatalytic.[22] Due to the fact that the oxidative addition is often believed to be the rate-limiting step in the overall reaction, many computational articles on the topic have been published.[23–25]

The product of oxidative addition, *cis*-$PdL_2(Ar^1)X$ is relatively unstable and isomerizes to the corresponding *trans*-isomer. The *cis*-products of oxidative addition have been rarely isolated,[26] which makes the investigation of the isomerization step a complicated task. The isomerization has been studied by Casado and Espinet, who concluded that a number of possible reaction mechanisms are responsible for the generation of *trans*-$PdL_2(Ar^1)I$.[27] These include solvent-assisted and autocatalytic reaction mechanisms. Authors found that the isomerization was dependent on the concentrations of halide ions and free phosphane ligand. The proposed mechanisms can be classified as associative and substitution mechanisms. The associative mechanism starts with the addition of solvent or *cis*-$PdL_2(Ar^1)I$ to *cis*-$PdL_2(Ar^1)I$ complex and after pseudorotation of the pentacoordinated palladium complex, *trans*-$PdL_2(Ar^1)I$ can be obtained. In the substitution-based mechanism, one ligand of *cis*-$PdL_2(Ar^1)I$ is exchanged with an iodine atom of another *cis*-$PdL_2(Ar^1)I$ molecule, forming a dinuclear complex, which after rearrangement and dissociation results in *trans*-$PdL_2(Ar^1)I$. Álvarez *et al.* studied the mechanisms of *cis*-*trans* isomerization computationally and found that the solvent- and ligand-assisted isomerization mechanisms have small activation energies compared to the activation energies of oxidative addition.[28] The isomerization of CH_2=CHPd$(PH_3)_2$Br through the tetrahedral four-coordinated transition state has been investigated by Braga *et al.*, but the activation energy is very high (20.3 kcal/mol).

The *cis*-*trans* isomerization is followed by the transmetalation step, where *trans*-$PdL_2(Ar^1)X$ reacts with copper acetylide and generates *cis*-$PdL_2(Ar^1)(C{\equiv}CAr^2)X$ complex. The formation of copper acetylide is believed to take place in the Cu-cycle in the presence of base. Bases, which are commonly used in the Sonogashira reactions, are not strong enough to deprotonate alkyne derivatives, therefore, the initial coordination of copper to the triple bond of acetylene is assumed. This increases the acidity of the acetylenic proton and copper acetylide can be formed. At the same time, these copper(I) acetylides can aggregate into di- and tetramers: a topic that is also important to the Cu-catalyzed alkyne-azide cycloaddition reaction.[29] Although the transmetalation step in the Sonogashira reaction has not been extensively studied, certain similarities can be expected with the other cross-coupling reactions (for example, Stille reaction).[30] The transmetalation step is expected to proceed through the substitution of one ligand with copper acetylide in *trans*-$PdL_2(Ar^1)X$ complex. This subsequent C-Cu bond cleavage and the C-Pd bond formation generate the *cis*-configured palladium complex. The acetylenes, which are often used in excess, can coordinate to the active palladium catalyst and reduce the rate of oxidative addition.[13]

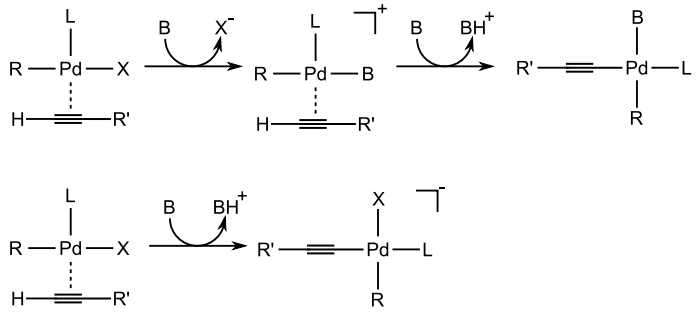
For the reaction of alkyne with *trans*-$PdL_2(Ar^1)X$, two competing mechanisms have been proposed: carbopalladation[31] (Scheme 4) and deprotonation[32] (Scheme 2) mechanisms.



Scheme 4. Carbopalladation mechanism of the copper-free Sonogashira cross-coupling reaction.

While both of these mechanisms share initial oxidative addition, *cis-trans* isomerization and alkyne coordination, the carbopalladation mechanism continues with the addition of aryl group R to the alkyne and the subsequent hydride elimination. The carbopalladation mechanism has been experimentally studied by Ljungdahl *et al.*, who concluded that this mechanism can not be active under the studied reaction conditions, as the hydride elimination does not take place.[33] The carbopalladation mechanism was later computationally studied by García-Melchor *et al.*, who showed that the hydride elimination step has an activation free energy of 40.4 kcal/mol.[34] This huge energy barrier and the low energy of some of the intermediates in the carbopalladation mechanisms show that this mechanism is inappropriate for the description of the copper-free Sonogashira reaction under the traditional reaction conditions.

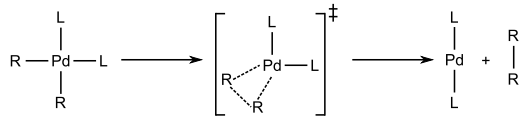
Two mechanistic pathways, proposed for the deprotonation reaction, are differentiated on the basis of the charge of the formed intermediates: anionic and cationic[33] (Scheme 5).



Scheme 5. Cationic (top) and anionic (bottom) mechanisms of deprotonation.

In both cases, the first step of deprotonation is the coordination of alkyne to *trans*-$PdL_2(Ar^1)X$. This increases the acidity of the acetylenic proton and makes the deprotonation possible. In the anionic mechanism, the next step is a base-assisted proton removal, which results in the anionic complex. Despite the activation, the proton abstraction is still believed to be rather slow and, therefore, the rate-determining process. In the cationic mechanism, the halide ion is replaced by base in the acetylene-coordinated palladium complex. This results in the cationic complex that can thereafter undergo the deprotonation by base and results in the neutral square-planar complex. The substitution of phosphane ligand by base has been investigated by Tougerti *et al.* and can be very important in the copper-free Sonogashira reaction, where base is often used in large excess.[14] As the electron-deficient intermediate is more prone to undergo the deprotonation, the substitution of halide to base becomes now the rate-limiting step of the deprotonation reaction. Ljungdahl *et al.* have demonstrated by calculations that the substituents on the alkyne derivative can have a large influence on the deprotonation mechanism[33] and this was later confirmed by García-Melchor *et al.*, who concluded that electron-withdrawing groups or moderate electron-donating groups on the phenylacetylene ring prefer the anionic mechanism, while highly electron-donating groups on the phenylacetylene ring prefer the cationic mechanism.[34]

The last step of the Sonogashira and many other cross-coupling reactions is the reductive elimination, where new carbon-carbon bond is formed and the catalyst is regenerated. The generation of new bond can only occur, when the reactive groups (in this case aryl and acetylenic groups) are in *cis*-position. The reaction is considered to follow a concerted mechanism (Scheme 6).[35]



Scheme 6. Concerted mechanism of reductive elimination.

This reaction has been investigated by Pérez-Rodríguez *et al.*[36] and Ananikov *et al.*,[37] who concluded that C-C coupling can occur both on the tetracoordinated and tricoordinated palladium complex. The size and electronic properties of the used ligands determine the mechanism of the reductive elimination, e.g. bulky phosphane ligands promote ligand dissociation and thereafter the tricoordinated transition state. In general, the tricoordinated transition states have lower activation energy than the tetracoordinated transition states.

3. CALCULATION METHODS

Calculations of the copper co-catalyzed Sonogashira cross-coupling reaction [I] were performed using Gaussian 03 program package.[38] Geometry optimizations and vibrational analysis were done using the density functional theory with hybrid B3LYP functional[39–41] and cc-pVDZ basis set.[42] In the case of copper and palladium, Stuttgart-Dresden effective core potentials with accompanying basis sets were used.[43] Solvation Gibbs energies were calculated using polarizable continuum model[44] by performing single-point calculations for all minima and transition states (using scfvac and Radii=UFF keywords).

The copper-free Sonogashira cross-coupling [II, III] was modeled by using Gaussian 09 program package[45] with hybrid B97D functional.[46,47] Same basis set (cc-pVDZ) and effective core potentials as in the case of copper co-catalyzed reaction were used. All geometry optimizations and vibrational analyses were performed in dichloromethane using continuum solvent model SMD.[48]

In all cases, harmonic frequency analysis was used to confirm that found structures correspond either to minima (number of imaginary frequencies equals 0) or transition state (number of imaginary frequencies equals 1). Unscaled frequencies from the vibrational analysis were used to obtain the Gibbs energy in the standard state (1 atm, 298.15 K). The Gibbs energy values were corrected to 1 mol/L standard state.[49] IRC analysis was used to verify that the obtained transition state connects the desired reactants and products.[50,51]

All calculations were performed in the DCM solution. This solvent was chosen as the reaction media because it is widely used in both NMR measurements of reaction kinetics and synthetic procedures. It is also a weakly coordinating solvent, justifying the use of PCM, which does not include specific solvent effects.

In the following discussion, enthalpies are used (articles II and III) to characterize the energies of stationary points found on the PES, as computational methods are less accurate for predicting entropies and free energies than enthalpies.[52] In the case of article I, only free energies are available in solvent phase and are used to characterize the PES.

4. RESULTS AND DISCUSSION

4.1. Reaction mechanism of the copper co-catalyzed Sonogashira reaction

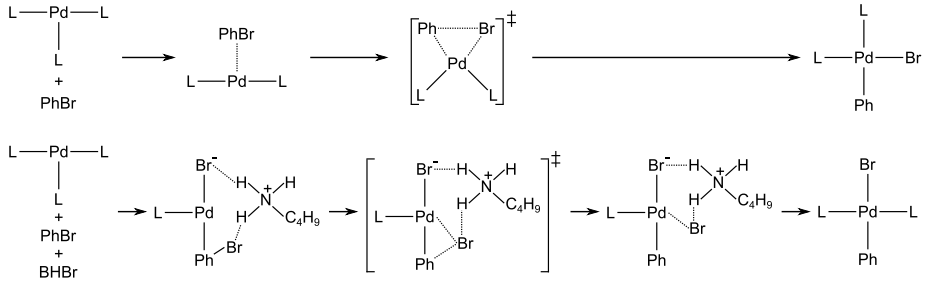
In article I, the copper co-catalyzed Sonogashira reaction between bromobenzene, PhBr, and phenylacetylene, PhC≡CH, was investigated computationally. Palladium diphosphane, $Pd(PH_3)_2$, was used as an active catalyst, CuBr as a co-catalyst and trimethylamine, Me3N, as a base. Two mechanisms of the oxidative addition were modeled: biligated and anionic mechanisms. In the case of biligated mechanism, bromobenzene reacts with $Pd(PH_3)_2$ and forms *cis*-$Pd(PH_3)_2(Ph)Br$, according to the mechanism in Scheme 3. The Gibbs energy (in DCM) of the transition state is 27.9 kcal/mol higher than the starting compounds. The alternative anionic pathway starts with the coordination of bromide ion to $Pd(PH_3)_2$ and the subsequent bromobenzene addition. Bromide ion in the transition state of the anionic oxidative addition pathway is coordinated to phosphane ligands and the Gibbs energy (in DCM) of this TS is 35.7 kcal/mol higher than the starting compounds. Comparing these results with the gas-phase Gibbs energies (25.7 kcal/mol and 10.2 kcal/mol, respectively), the anionic pathway has much lower activation energy. This difference is probably caused by the overestimation of the solvation free energy of bromide ion as demonstrated by Senn *et al.*[23] For the *cis*-*trans* isomerization, trigonal bipyramidal transition state was not found and the rearrangement of T-shaped complex was considered. Two possible reaction pathways, which consisted of ligand dissociation, rearrangement of T-shaped complex, and ligand association steps were modeled. The energetically favored pathway starts with the dissociation of phosphane ligand from *trans*-position, relative to phenyl group in *cis*-$Pd(PH_3)_2(Ph)Br$. The subsequent bromine atom migration has an activation free energy of 9.0 kcal/mol in DCM (7.7 kcal/mol relative to starting compounds: $Pd(PH_3)_2$ and PhBr). The isomerization step results in the formation of *trans*-$Pd(PH_3)_2(Ph)Br$ complex.

The transmetalation step starts with the coordination of copper acetylide, which is formed from phenylacetylene and copper(I) bromide, to *trans*-$Pd(PH_3)(Ph)Br$ complex. While the biligated *trans*-product of the oxidative addition is more stable than the monoligated complex, no transmetalation reaction could be found starting from it. The activation free energy for the transfer of phenylacetylide group from copper to palladium is very small (0.1 kcal/mol in the gas phase, –0.7 kcal/mol in DCM). The negative activation energy in DCM can arise from the shortcomings of the used solvent model. The product of transmetalation step is *cis*-$Pd(PH_3)_2(Ph)(C{\equiv}CPh)$ complex, which after overcoming a moderate free energy barrier (8.5 kcal/mol in the gas phase, 11.9 kcal/mol in DCM) forms the complex of diphenylacetylene with $Pd(PH_3)_2$. The dissociation of this complex regenerates the palladium complex and concludes the catalytic cycle. The total energy of the Sonogashira cross-coupling reaction is -18.3 kcal/mol in the gas phase and -28.0 kcal/mol in DCM,

while the oxidative addition is the rate-limiting step in both cases, as its transition state is the highest point in PES.

4.2. Reaction mechanism of the copper-free Sonogashira reaction

In articles II and III, the copper-free Sonogashira cross-coupling reaction has been modeled. While the reaction substrates are the same as in article I (bromobenzene and phenylacetylene), new catalyst and base (tetrakis(triphenylphosphano)palladium and *sec*-butylamine, respectively) have been chosen to match the experimental conditions. The oxidative addition step can be influenced by a number of factors (coordination number of palladium, base, halide ions), therefore, five possible pathways were calculated: monoligated, biligated, anionic, base-assisted, and salt-assisted. These reaction routes are differentiated on the basis of the ligating species of palladium in TS. Monoligated: one triphenylphosphane, biligated: two triphenylphosphanes, anionic: one triphenylphosphane and one bromide ion, base-assisted: one triphenylphosphane and one *sec*-butylamine, salt-assisted: one triphenylphosphane and one *sec*-butylammonium bromide. In all cases, the first step is the dissociation of one phosphane ligand from $Pd(PPh_3)_4$ and the formation of $Pd(PPh_3)_3$. This equilibrium is shifted towards the formation of tricoordinated palladium complex (ΔG = –0.7 kcal/mol, ΔH = 19.7 kcal/mol), which can thereafter interact with a multitude of compounds in the reaction mixture. Comparing the transition state energies of different pathways, two of the most favorable mechanistic routes are the biligated and salt-assisted oxidative addition pathways (Scheme 7) with transition state enthalpies of 29.1 kcal/mol and 31.2 kcal/mol in DCM, relative to starting compounds.



Scheme 7. Biligated (top) and salt-assisted (bottom) mechanisms of oxidative addition.

It is important to note that these two reaction pathways result in different products. While the biligated mechanism results in *cis*-$Pd(PPh_3)_2(Ph)Br$ complex, the salt-assisted route yields *trans*-$Pd(PPh_3)_2(Ph)Br$. As *sec*-butylammonium

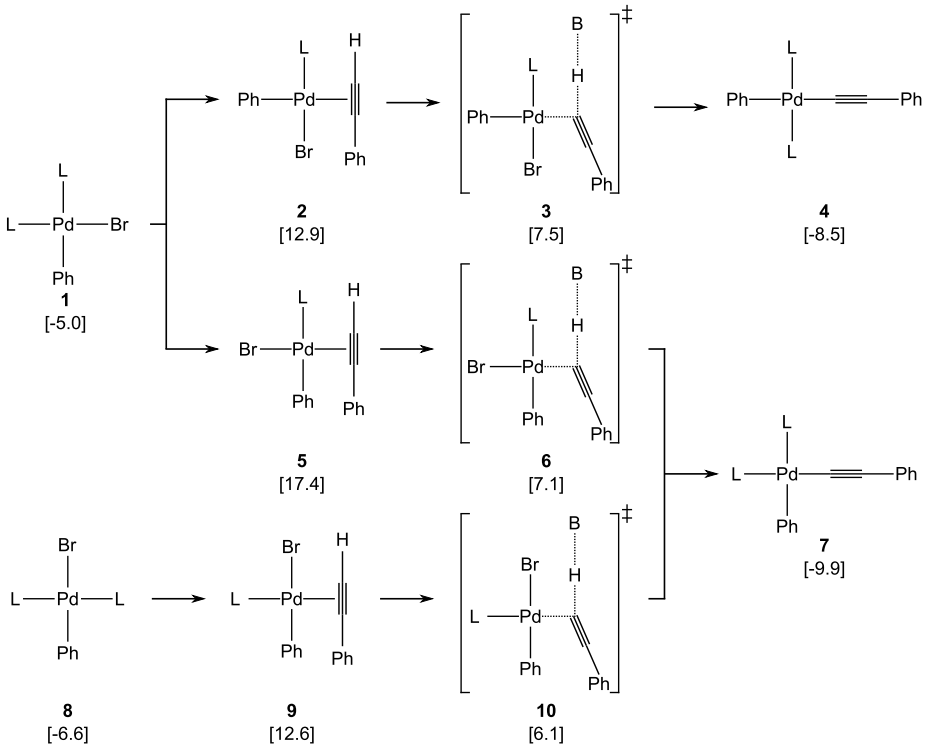
bromide is one of the products of the Sonogashira reaction (see Scheme 2), the change of oxidative addition mechanism can be expected as reaction proceeds and more salt is formed. Base can also influence the oxidative addition by coordinating to the tris(triphenylphosphano)palladium and the formation of $Pd(Pd(PPh_3)_3$(base) complex. In the case of *sec*-butylamine, this complex is very stable (ΔH = –12.7 kcal/mol, relative to starting compounds) and can inhibit the reaction by reducing the concentration of catalytically active palladium complex. In the transition state of salt-assisted mechanism, protons of the ammonium group interact with bromine atoms in the complex, forming a stable bridge-like structure. This is only possible for primary and secondary amines and can be one of the reasons why in some cases these amines show better yields than stronger tertiary amines.[53]

The *cis*-*trans* isomerization transition states described in article I could not be found with the computational methods used in article II and III. This is probably caused by different steric and electronic effects of the used ligands and is a good example of the possible errors that this type of minimalistic model systems can cause. The autocatalytic *cis*-*trans* isomerization mechanism, proposed by Casado and Espinet,[27] was also modeled. This reaction is based on the formation of dinuclear $[PhPd(\mu\text{-}Br)(PPh_3)_2]_2$ complex and its subsequent dissociation to thermodynamically more stable *trans*-$Pd(PPh_3)_2(Ph)Br$. The enthalpy of the dinuclear complex $[PhPd(\mu\text{-}Br)(PPh_3)_2]_2$ is 9.6 kcal/mol, relative to starting compounds, and the overall reaction enthalpy of *cis*-*trans* isomerization is –1.6 kcal/mol. This indicates that the isomerization step occurs faster than the oxidative addition and is directed towards the formation of *trans*-$Pd(PPh_3)_2(Ph)Br$.

Phenylacetylene can react with both, *cis*-$Pd(PPh_3)_2(Ph)Br$ and *trans*-$Pd(PPh_3)_2(Ph)Br$ complex in the deprotonation step. While the reaction of *trans* oxidative addition product has been widely accepted as the major route of the reaction,[33,34] similar pathway with respective the *cis* complex has to be considered as an alternative or a side reaction. The latter is especially important in the case of bidentate ligands, which can not form *trans* oxidative addition product.[54] The deprotonation step starts with the substitution of triphenylphosphane ligand with phenylacetylene, which is followed by the coordination of base, proton abstraction, and substitution of the corresponding salt to phosphane ligand. Three calculated reaction pathways are depicted in Scheme 8.

Reaction of *trans*-$Pd(PPh_3)_2(Ph)Br$ with alkyne results in the formation of *cis*-$Pd(PPh_3)_2(PhCC)Ph$, but *cis*-$Pd(PPh_3)_2(Ph)Br$ can result in either *cis*- or *trans*- $Pd(PPh_3)_2(PhCC)Ph$. The enthalpies of these two transition states (Scheme 8: **3** and **6**) are very similar, but the course of the reaction is determined by the ligand substitution step preceding the transition state of deprotonation. Dissociation of the phosphane ligand in *trans*-position to the phenyl group from *cis*-$Pd(PPh_3)_2(Ph)Br$ is very endothermic (ΔH = 47.5 kcal/mol) and the stability of alkyne-substituted complex **2** over alternative complex **5** (Scheme 8) directs the reaction towards the formation of *trans*-$Pd(PPh_3)_2(PhCC)Ph$. In the case of transition state **10** (see Scheme 8), deprotonation occurs through a concerted

mechanism, where one of the protons of amine group interacts with bromine atom.

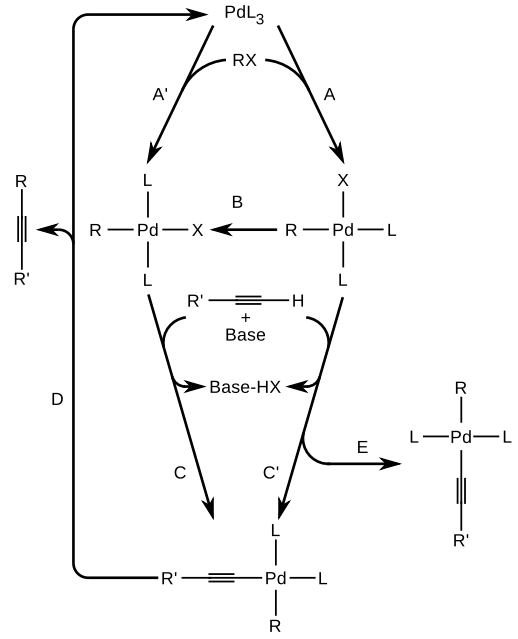


Scheme 8. Deprotonation step of the copper-free Sonogashira cross-coupling reaction. Enthalpies (in square brackets) are in kcal/mol, relative to starting compounds of the catalytic cycle.

The reductive elimination is only possible, when the aryl and acetylide groups are in *cis*-position. Three reaction pathways were modeled: biligated, monoligated, and anionic. The activation enthalpy of biligated mechanism is 9.1 kcal/mol and the reaction of C-C bond formation is very exothermic (ΔH = –21.7 kcal/mol). The monoligated reductive elimination starts with the formation of *trans*-Pd(PPh_3)(PhCC)Ph. This can take place as the last step of deprotonation, while ligand concentration in the reaction mixture is very low. This monoligated complex is very unstable, compared to the biligated *trans*-Pd(PPh_3)$_2$(PhCC)Ph (ΔH = 32.1 kcal/mol), but the activation enthalpy of C-C bond formation (9.2 kcal/mol) is very close to the biligated activation energy. Similarly to the monoligated pathway, the anionic reductive elimination can arise from the end of deprotonation step, when the cation of generated ammonium salt dissociates and *cis*-Pd(PPh_3)(PhCC)PhBr^- is generated, where the bromide ion and phenyl group are in *trans*-position. This anionic species is

also unstable, compared to the neutral biligated complex (ΔH = 32.2 kcal/mol), which is caused by the separation of charges in a nonpolar solvent (DCM). The activation enthalpy of respective C-C bond formation is 12.2 kcal/mol, which is higher than for both of the other pathways. The energetically most favorable mechanism of reductive elimination is the biligated mechanism, which results in the formation of diphenylacetylene complex with $Pd(PPh_3)_2$, which subsequently dissociates and through the addition of ligand forms the active palladium catalyst $Pd(PPh_3)_3$ and diphenylacetylene.

The calculated reaction pathways allow the construction of modified reaction scheme for the copper-free Sonogashira cross-coupling reaction, which is presented in Scheme 9.



Scheme 9. Mechanism of the copper-free Sonogashira cross-coupling reaction.

The reaction starts with the coordination of aryl halide RX to the catalytically active palladium complex PdL_3 and can result in either *cis*- or *trans*-PdL_2RX (reactions A and A', respectively). The *cis*-complex can isomerize to the corresponding *trans*-complex (reaction B), which is energetically favored. Both of the products of oxidative addition can react with aryl halide in the presence of base and give the *cis*-product of deprotonation (reactions C and C'). At the same time, *cis*-PdL_2RX can produce an unreactive *trans*-product of deproto-

nation through the alternative route E. During the reductive elimination, diarylacetylene is formed and the palladium catalyst is regenerated. The presented reaction mechanism is composed of three interconnected catalytic cycles (A, B, C, D; A', C, D; A, C' ,D) and one reaction step (E), which results in a stable unreactive intermediate that can drastically lower the catalyst concentration and potentially stop the catalytic cycle.

5. CONCLUSIONS

The mechanism of the Sonogashira cross-coupling between phenylacetylene and bromobenzene resulting in diphenylacetylene was computationally investigated using the DFT methodology in dichloromethane. Both the copper co-catalyzed and copper-free reactions were modeled.

The copper co-catalyzed Sonogashira cross-coupling is exothermic and strongly directed towards the formation of reaction products (diphenylacetylene and the regenerated palladium catalyst). The highest point in the potential energy surface is the transition state of oxidative addition, suggesting that this step is the slowest in the overall reaction and, therefore, limiting the reaction rate. On the other hand, the formation of copper(I) acetylide from CuBr and phenylacetylene in the presence of triethylamine is endothermic and directed towards the formation of reactants. This suggests that the concentration of copper(I) acetylide in the reaction mixture is expected to be low, which can significantly lower the overall rate of the Sonogashira cross-coupling reaction.

Our calculations show that there are a number of mechanistic pathways for the copper-free Sonogashira reaction, which can all operate simultaneously in a competitive manner. The base can have a very strong effect on the overall reaction, as it can coordinate to palladium catalyst and inhibit the reaction. At the same time, the structure of base can be of importance in the case of oxidative addition and deprotonation, as these are parts of the reaction pathways that utilize specific coordination. The oxidative addition has two competing pathways (biligated and salt-catalyzed) that result in different products, *cis*-PdL_2RX and *trans*-PdL_2RX, respectively. While both of these react with phenylacetylene in the deprotonation step, the *cis*-isomer can form the unreactive *trans*-product of deprotonation. These results suggest that the addition of halide salt in the reaction mixture could avoid the concentration decrease of active palladium complexes, by catalyzing the oxidative addition and the formation of *trans*-PdL_2RX. The deprotonation step, starting from *trans*-PdL_2RX, proceeds through a concerted transition state, where the proton of *sec*-butylamine is directed towards the bromine atom of palladium complex. This suggests that in the case of primary and secondary amines, where this type of interaction is possible, the respective transition state is stabilized and the deprotonation step can be faster than in the case of tertiary amines. The reductive elimination step proceeds through the biligated pathway and is not influenced by halide ions. On the other hand, very low ligand concentrations can cause the reaction to follow the monoligated reaction route.

The reaction rate or turnover frequency of copper-free catalytic cycle is determined by the energies of transition state of oxidative addition and catalytically active palladium complex $Pd(PPh_3)_3$, relative to the energies of other molecular species, as these are the TOF-determining transition state and intermediate, respectively.

Finally, some concluding remarks about the mechanism of the Sonogashira cross-coupling can be made. The overall reaction has many possible pathways,

which depend on a number of additives in the reaction mixture, as well as the reactants, catalyst, and solvent. The concentration of these species can change over the course of the reaction and influence which mechanistic pathways are active at any given moment. To assess which of these reaction routes are favored for a specific cross-coupling reaction, detailed study is necessary and the computational results described here can be used as a starting point.

SUMMARY IN ESTONIAN

Sonogashira ristkondensatisioonireaktsiooni arvutuslik uurimine

Käesolevas dissertatsioonis uuriti Sonogashira ristkondensatsiooni (bromobenseeni ja fenüülatsetüleemi vahel, mille saaduseks on difenüülatsetüleen) mehhanismi, kasutades tihedusfunktsionaali teooria meetodeid. Modelleeriti nii vase poolt katalüüsitud kui ka vasevaba Sonogashira reaktsiooni.

Vase kaasabil toimuv Sonogashira ristkondensatsiooni reaktsioon on tugevalt suunatud saaduste (difenüülatsetüleen ja regenereeritud pallaadiumkatalüsaator) tekke suunas. Kõrgeim punkt potentsiaalse energia pinnal on oksüdatiivsele liitumisele vastav aktiveeritud kompleks, mis viitab, et nimetatud etapp on summaarses reaktsioonis kõige aeglasem ja seega limiteerib reaktsiooni kiirust. Samas on vask(I)fenüületünüliidi teke CuBr-st ja fenüülatsetüleenist trietüülamiini juuresolekul endotermiline ning suunatud lähteainete tekke suunas. Seetõttu võib oletada, et vask(I)fenüületünüliidi kontsentratsioon reaktsioonisegus on madal, mis omakorda vähendab Sonogashira ristkondensatsiooni kiirust.

Arvutuste põhjal saab väita, et vasevaba Sonogashira reaktsiooni korral eksisteerib mitmeid võimalikke konkureerivaid reaktsiooniteid. Reaktsioonis kasutataval alusel võib olla oluline efekt reaktsiooni kiirusele, kuna koordineerub pallaadiumkatalüsaatoriga. Samas võib aluse struktuur olla tähtis oksüdatiivsel liitumisel ja deprotoneerumisel, sest nendes etappides esineb spetsiifiline koordinatsioon aluse ja pallaadiumikompleksi vahel. Oksüdatiivse liitumise korral esineb kaks konkureerivat reaktsiooniteed (kahe fosfaanligandiga ja soola poolt katalüüsitud reaktsiooniteed), mille produktid on erinevad (vastavalt *cis*-PdL_2RX ja *trans*-PdL_2RX). Mõlemad nimetatud saadused võivad deprotoneerumise etapis reageerida fenüülatsetüleeniga, kuid *cis*-PdL_2RX võib anda mitteaktiivse pallaadiumikompleksi, mis edasises katalüütilises tsüklis ei osale. Saadud tulemused näitavad, et reaktsioonisegule vastava aluse halogeensoola lisamine võib katalüüsida *trans*-PdL_2RX teket oksüdatiivsel liitumisel ning seeläbi vähendada mitteaktiivse pallaadiumikompleksi moodustumist. Deprotoneerumise etapp, mis lähtub *trans*-PdL_2RX kompleksist, toimib kontsertmehhanismi alusel ning *sec*-butüülamiini proton on suunatud pallaadiumikompleksi broomi aatomi poole. Seetõttu võib arvata, et primaarsete ja sekundaarsete amiinide korral, kus selline interaktsioon on võimalik, on vastav aktiveeritud kompleks stabiliseeritud ning deprotoneerumise etapp on kiirem kui tertsiaarsete amiinide korral. Redutseeriv elimineerumine toimub läbi aktiveeritud kompleksi, kus on kaks fosfaanligandi, ja see etapp ei ole mõjutatud halogeenioonide poolt. Samas võib ligandi väga madal kontsentratsioon suunata reaktsiooni rajale, mille aktiveeritud kompleksis on üks fosfaanligand. Vasevaba Sonogashira reaktsiooni katalüütilise tsükli kiirus on mõjutatud oksüdatiivse liitumise aktiveeritud kompleksi ja katalüütiliselt aktiivse

pallaadiumi kompleksi vabaenergiate erinevusest võrreldes teiste lahuses leiduvate osakeste vabaenergiatega.

Kokkuvõtvalt võib öelda, et Sonogashira reaktsiooni korral esineb palju võimalikke reaktsiooniteid, mis oluliselt sõltuvad erinevatest reaktsioonisegus leiduvatest lisanditest ning ka lähteainetest, katalüsaatorist ja solvendist. Nende ainete sisaldused võivad reaktsiooni käigus muutuda ning seeläbi mõjutada millised reaktsiooniteed on antud ajahetkel aktiivsed. Eelistatud reaktsiooni-radade leidmiseks kindla ristkondensatsioonireaktsiooni puhul on vaja läbi viia põhjalikud uuringud ning antud töös toodud arvutuslikke tulemusi saab kasutada kui lähtepunkti edasiseks tööks.

REFERENCES

1. Barnard, C. Platinum Metals Rev. 2008, 52, 38–45.
2. Sonogashira, K.; Tohda, Y.; Hagihara, N. Tetrahedron Lett. 1975, 16, 4467–4470.
3. Dieck, H. A.; Heck, F. R. J. Organomet. Chem. 1975, 93, 259–263.
4. Cassar, L. J. Organomet. Chem. 1975, 93, 253–257.
5. Stephens, R. D.; Castro, C. E. J. Org. Chem. 1963, 28, 3313–3315.
6. Leadbeater, N. E.; Tominack, B. J. Tetrahedron Lett. 2003, 44, 8653–8656.
7. Kim, J.-H.; Lee, D.-H.; Jun, B.-H.; Lee, Y.-S. Tetrahedron Lett. 2007, 48, 7079–7084.
8. Chinchilla, R.; Nájera, C. Chem. Rev. 2007, 107, 874–922.
9. Negishi, E.-ichi; Anastasia, L. Chem. Rev. 2003, 103, 1979–2017.
10. Zalesskiy, S. S.; Ananikov, V. P. Organometallics 2012, 31, 2302–2309.
11. Fey, N.; Orpen, A. G.; Harvey, J. N. Coord. Chem. Rev. 2009, 253, 704–722.
12. an der Heiden, M. R.; Plenio, H.; Immel, S.; Burello, E.; Rothenberg, G.; Hoefsloot, H. C. J. Chem. Eur. J. 2008, 14, 2857–2866.
13. Jutand, A. Pure Appl. Chem. 2004, 76, 565–576.
14. Tougerti, A.; Negri, S.; Jutand, A. Chem. Eur. J. 2007, 13, 666–676.
15. Lee, M.-T.; Lee, H. M.; Hu, C.-H. Organometallics 2007, 26, 1317–1324.
16. Amatore, C.; Pflüger, F. Organometallics 1990, 9, 2276–2282.
17. Fauvarque J.-F.; Pflüger F.; Troupel M. J. Organomet. Chem. 1981, 208, 419–427.
18. Ahlquist, M.; Norrby, P. O. Organometallics 2007, 26, 550–553.
19. Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. J. Am. Chem. Soc. 2009, 131, 8141–8154.
20. Amatore, C.; Jutand, A. Acc. Chem. Res. 2000, 33, 314–321.
21. Amatore, C.; Azzabi, M.; Jutand, A. J. Am. Chem. Soc. 1991, 113, 8375–8384.
22. Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. J. Am. Chem. Soc. 2008, 130, 5842–5843.
23. Senn, H. M.; Ziegler, T. Organometallics 2004, 23, 2980–2988.
24. Ahlquist, M.; Fristrup, P.; Tanner, D.; Norrby, P.-O. Organometallics 2006, 25, 2066–2073.
25. Goossen, L. J.; Koley, D.; Hermann, H. L.; Thiel, W. Organometallics 2005, 24, 2398–2410.
26. Urata, H.; Tanaka, M.; Fuchikami, T. Chem. Lett. 1987, 751–754.
27. Casado, A. L.; Espinet, P. Organometallics 1998, 17, 954–959.
28. Álvarez, R.; Faza, O. N.; de Lera, A. R.; Cárdenas, D. J. Adv. Synth. Catal. 2007, 349, 887–906.
29. Meldal, M.; Tornøe, C. W. Chem. Rev. 2008, 108, 2952–3015.
30. Xue, L.; Lin, Z. Chem. Soc. Rev. 2010, 39, 1692–1705.
31. Dieck, H. A.; Heck, F. R. J. Organomet. Chem. 1975, 93, 259–263.
32. Soheili, A.; Albaneze-Walker, J.; Murry, J. A.; Dormer, P. G.; Hughes, D. L. Org. Lett. 2003, 5, 4191–4194.
33. Ljungdahl, T.; Bennur, T.; Dallas, A.; Emtenäs, H.; Mårtensson, J. Organometallics 2008, 27, 2490–2498.
34. García-Melchor, M.; Pacheco, M. C.; Nájera, C.; Lledos, A.; Ujaque, G. ACS Catal. 2012, 2, 135–144.
35. Brown, J. M.; Cooley, N. A. Chem. Rev. 1988, 88, 1031–1046.

36. Pérez-Rodríguez, M.; Braga, A. A. C.; Garcia-Melchor, M.; Pérez-Temprano, M. H.; Casares, J. A.; Ujaque, G.; de Lera, A. R.; Álvarez, R. ; Maseras, F.; Espinet, P. J. Am. Chem. Soc. 2009, 131, 3650–3657.
37. Ananikov, V. P.; Musaev, D. G.; Morokuma, K. E. J. Inorg. Chem. 2007, 2007, 5390–5399.
38. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. (2003) Gaussian 03, Revision B.03. Gaussian Inc, Pittsburgh, PA.
39. Becke, A. D. J. Chem. Phys. 1993, 98, 5648–5652.
40. Lee, C.; Yang, W.; Parr, R. G. Phys. Rev. B 1988, 37, 785–798.
41. Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. Chem. Phys. Lett. 1989, 157, 200–206.
42. Dunning, T. H. J. Chem. Phys. 1989, 90, 1007–1023.
43. Schuchardt, K. L.; Didier, B. T.; Elsethagen, T.; Sun, L.; Gurumoorthi, V.; Chase, J.; Li, J.; Windus, T. L. J. Chem. Inf. Model. 2007, 47, 1045–1052.
44. Miertuš, S.; Scrocco, E.; Tomasi, J. Chem. Phys. 1981, 55, 117–129.
45. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09; Gaussian, Inc., Wallingford, CT, 2009.
46. Becke, A. D. J. Chem. Phys. 1997, 107, 8554–8560.
47. Grimme, S. J. Comput. Chem. 2006, 2007, 1787–1799.
48. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. J. Phys. Chem. B 2009, 113, 6378–6396.
49. Cramer, C. J. Essentials of Computational Chemistry: Theories and Models; Wiley: New York, USA, 2003.
50. Gonzalez, C.; Schlegel, H. B. J. Chem. Phys. 1989, 90, 2154–2161.
51. Gonzalez, C.; Schlegel, H. B. J. Chem. Phys. 1991, 95, 5853–5860.

52. Ardura, D.; López, R.; Sordo, T. L. J. Phys. Chem. B 2005, 109, 23618–23623.
53. Komáromi, A., Tolnai, G. L. and Novák, Z. Copper-free Sonogashira coupling in amine–water solvent mixtures. Tetrahedron Lett. 2008, 49, 7294–7298.
54. Rau, S.; Lamm, K.; Görls, H.; Schöffel, J.; Walther, D. J. Organomet. Chem. 2004, 689, 3582–3592.

ACKNOWLEDGEMENTS

I would like to thank my supervisors Peeter Burk and Jaana Tammiku-Taul for their guidance and time.

The author thanks the Estonian Academy of Sciences and the Hungarian Academy of Sciences for the Estonian-Hungarian Joint Research Project 2007–2009. This work was supported by Estonian Science Foundation (Grants No. 7199 and 8809), Estonian Ministry of Education and Research Targeted Financing project No. SF0180120s08, and Graduate School on Functional Materials and Technologies, EU Social Funds project 1.2.0401.09–0079.

I am thankful to our Hungarian partner András Kotschy, who guided us to the present topic.

PUBLICATIONS

CURRICULUM VITAE

Name: Lauri Sikk
Born: 18.06.1983
Citizenship: Estonian
Phone: +372 737 5257; +372 5690 0440
E-mail: lauri.sikk@ut.ee

Education:

2008–present University of Tartu, Faculty of Science and Technology, Institute of Chemistry, PhD student

2006–2008 University of Tartu, Faculty of Science and Technology, Institute of Chemistry, *M.Sc* (theoretical and computational chemistry) 2008

2002–2006 University of Tartu, Department of Chemistry, *B.Sc.* (chemistry) 2006

Work Experience:

2006–2007 University of Tartu, Faculty of Science and Technology, Institute of Chemistry, Chair of Chemical Physics, chemist

Publications:

1. Burk, P.; Tammiku-Taul, J.; Tamp, S.; Sikk, L.; Sillar, K.; Mayeux, C.; Gal, J.-F.; Maria, P.-C. Computational study of cesium cation interactions with neutral and anionic compounds related to soil organic matter. *J. Phys. Chem. A,* **2009***, 113 (40), 10734–10744.*
2. Lorincz, K.; Kotschy, A.; Tammiku-Taul, J.; Sikk, L.; Burk, P. Computational study of azaphilic addition and nucleophilic substitution pathways of disubstituted tetrazines with methyllithium. *J. Org. Chem.* **2010,** *75(18),* 6196–6200.
3. Sikk, L.; Tammiku-Taul, J.; Burk, P. Computational Study of Copper-Free Sonogashira Cross-Coupling reaction. *Organometallics*, **2011,** *30,* 5656–5664.
4. Sikk, L.; Tammiku-Taul, J.; Burk, P.; Kotschy, A. Computational Study of the Sonogashira Cross-Coupling Reaction in the Gas Phase and in Dichloromethane Solution. *J. Mol. Mod.* **2012,** *18,* 3025–3033.
5. Sikk, L.; Tammiku-Taul, J.; Burk, P. Computational Study of Copper-Free Sonogashira Cross-Coupling Reaction: Shortcuts in the Reaction. *Proc. Est. Acad. Sci.* **2012***, accepted*.

ELULOOKIRJELDUS

Nimi: Lauri Sikk
Sündinud: 18.06.1983
Kodakondsus: Eesti
Telefon: 737 5257; 5690 0440
E-post: lauri.sikk@ut.ee

Hariduskäik:

2008–praegu	Tartu Ülikool, Loodus- ja tehnoloogiateaduskond, Keemia instituut, doktorant
2006–2008	Tartu Ülikool, Loodus- ja tehnoloogiateaduskond, Keemia instituut, *M.Sc* (teoreetiline- ja arvutikeemia) 2008
2002–2006	Tartu Ülikool, Füüsika-keemiateaduskond, Keemia instituut, *B.Sc* (keemia) 2006

Teenistuskäik:

2006–2007	Tartu Ülikool, Loodus- ja tehnoloogiateaduskond, Keemia instituut, Keemilise füüsika õppetool, keemik

Publikatsioonid:

1. Burk, P.; Tammiku-Taul, J.; Tamp, S.; Sikk, L.; Sillar, K.; Mayeux, C.; Gal, J.-F.; Maria, P.-C. Computational study of cesium cation interactions with neutral and anionic compounds related to soil organic matter. *J. Phys. Chem. A,* **2009***, 113 (40), 10734–10744.*
2. Lorincz, K.; Kotschy, A.; Tammiku-Taul, J.; Sikk, L.; Burk, P. Computational study of azaphilic addition and nucleophilic substitution pathways of disubstituted tetrazines with methyllithium. *J. Org. Chem.* **2010,** *75(18),* 6196–6200.
3. Sikk, L.; Tammiku-Taul, J.; Burk, P. Computational Study of Copper-Free Sonogashira Cross-Coupling reaction. *Organometallics*, **2011,** *30,* 5656–5664.
4. Sikk, L.; Tammiku-Taul, J.; Burk, P.; Kotschy, A. Computational Study of the Sonogashira Cross-Coupling Reaction in the Gas Phase and in Dichloromethane Solution. *J. Mol. Mod.* **2012,** *18,* 3025–3033.
5. Sikk, L.; Tammiku-Taul, J.; Burk, P. Computational Study of Copper-Free Sonogashira Cross-Coupling Reaction: Shortcuts in the Reaction. *Proc. Est. Acad. Sci.* **2012***, accepted*.

DISSERTATIONES CHIMICAE UNIVERSITATIS TARTUENSIS

1. **Toomas Tamm.** Quantum-chemical simulation of solvent effects. Tartu, 1993, 110 p.
2. **Peeter Burk.** Theoretical study of gas-phase acid-base equilibria. Tartu, 1994, 96 p.
3. **Victor Lobanov.** Quantitative structure-property relationships in large descriptor spaces. Tartu, 1995, 135 p.
4. **Vahur Mäemets.** The ^{17}O and ^{1}H nuclear magnetic resonance study of H_2O in individual solvents and its charged clusters in aqueous solutions of electrolytes. Tartu, 1997, 140 p.
5. **Andrus Metsala.** Microcanonical rate constant in nonequilibrium distribution of vibrational energy and in restricted intramolecular vibrational energy redistribution on the basis of slater's theory of unimolecular reactions. Tartu, 1997, 150 p.
6. **Uko Maran.** Quantum-mechanical study of potential energy surfaces in different environments. Tartu, 1997, 137 p.
7. **Alar Jänes.** Adsorption of organic compounds on antimony, bismuth and cadmium electrodes. Tartu, 1998, 219 p.
8. **Kaido Tammeveski.** Oxygen electroreduction on thin platinum films and the electrochemical detection of superoxide anion. Tartu, 1998, 139 p.
9. **Ivo Leito.** Studies of Brønsted acid-base equilibria in water and non-aqueous media. Tartu, 1998, 101 p.
10. **Jaan Leis.** Conformational dynamics and equilibria in amides. Tartu, 1998, 131 p.
11. **Toonika Rinken.** The modelling of amperometric biosensors based on oxidoreductases. Tartu, 2000, 108 p.
12. **Dmitri Panov.** Partially solvated Grignard reagents. Tartu, 2000, 64 p.
13. **Kaja Orupõld.** Treatment and analysis of phenolic wastewater with microorganisms. Tartu, 2000, 123 p.
14. **Jüri Ivask.** Ion Chromatographic determination of major anions and cations in polar ice core. Tartu, 2000, 85 p.
15. **Lauri Vares.** Stereoselective Synthesis of Tetrahydrofuran and Tetrahydropyran Derivatives by Use of Asymmetric Horner-Wadsworth-Emmons and Ring Closure Reactions. Tartu, 2000, 184 p.
16. **Martin Lepiku.** Kinetic aspects of dopamine D_2 receptor interactions with specific ligands. Tartu, 2000, 81 p.
17. **Katrin Sak.** Some aspects of ligand specificity of P2Y receptors. Tartu, 2000, 106 p.
18. **Vello Pällin.** The role of solvation in the formation of iotsitch complexes. Tartu, 2001, 95 p.

19. **Katrin Kollist.** Interactions between polycyclic aromatic compounds and humic substances. Tartu, 2001, 93 p.
20. **Ivar Koppel.** Quantum chemical study of acidity of strong and superstrong Brønsted acids. Tartu, 2001, 104 p.
21. **Viljar Pihl.** The study of the substituent and solvent effects on the acidity of OH and CH acids. Tartu, 2001, 132 p.
22. **Natalia Palm.** Specification of the minimum, sufficient and significant set of descriptors for general description of solvent effects. Tartu, 2001, 134 p.
23. **Sulev Sild.** QSPR/QSAR approaches for complex molecular systems. Tartu, 2001, 134 p.
24. **Ruslan Petrukhin.** Industrial applications of the quantitative structure-property relationships. Tartu, 2001, 162 p.
25. **Boris V. Rogovoy.** Synthesis of (benzotriazolyl)carboximidamides and their application in relations with *N*- and *S*-nucleophyles. Tartu, 2002, 84 p.
26. **Koit Herodes.** Solvent effects on UV-vis absorption spectra of some solvatochromic substances in binary solvent mixtures: the preferential solvation model. Tartu, 2002, 102 p.
27. **Anti Perkson.** Synthesis and characterisation of nanostructured carbon. Tartu, 2002, 152 p.
28. **Ivari Kaljurand.** Self-consistent acidity scales of neutral and cationic Brønsted acids in acetonitrile and tetrahydrofuran. Tartu, 2003, 108 p.
29. **Karmen Lust.** Adsorption of anions on bismuth single crystal electrodes. Tartu, 2003, 128 p.
30. **Mare Piirsalu.** Substituent, temperature and solvent effects on the alkaline hydrolysis of substituted phenyl and alkyl esters of benzoic acid. Tartu, 2003, 156 p.
31. **Meeri Sassian.** Reactions of partially solvated Grignard reagents. Tartu, 2003, 78 p.
32. **Tarmo Tamm.** Quantum chemical modelling of polypyrrole. Tartu, 2003. 100 p.
33. **Erik Teinemaa.** The environmental fate of the particulate matter and organic pollutants from an oil shale power plant. Tartu, 2003. 102 p.
34. **Jaana Tammiku-Taul.** Quantum chemical study of the properties of Grignard reagents. Tartu, 2003. 120 p.
35. **Andre Lomaka.** Biomedical applications of predictive computational chemistry. Tartu, 2003. 132 p.
36. **Kostyantyn Kirichenko.** Benzotriazole – Mediated Carbon–Carbon Bond Formation. Tartu, 2003. 132 p.
37. **Gunnar Nurk.** Adsorption kinetics of some organic compounds on bismuth single crystal electrodes. Tartu, 2003, 170 p.
38. **Mati Arulepp.** Electrochemical characteristics of porous carbon materials and electrical double layer capacitors. Tartu, 2003, 196 p.

39. **Dan Cornel Fara.** QSPR modeling of complexation and distribution of organic compounds. Tartu, 2004, 126 p.
40. **Riina Mahlapuu.** Signalling of galanin and amyloid precursor protein through adenylate cyclase. Tartu, 2004, 124 p.
41. **Mihkel Kerikmäe.** Some luminescent materials for dosimetric applications and physical research. Tartu, 2004, 143 p.
42. **Jaanus Kruusma.** Determination of some important trace metal ions in human blood. Tartu, 2004, 115 p.
43. **Urmas Johanson.** Investigations of the electrochemical properties of polypyrrole modified electrodes. Tartu, 2004, 91 p.
44. **Kaido Sillar.** Computational study of the acid sites in zeolite ZSM-5. Tartu, 2004, 80 p.
45. **Aldo Oras.** Kinetic aspects of dATPαS interaction with $P2Y_1$ receptor. Tartu, 2004, 75 p.
46. **Erik Mölder.** Measurement of the oxygen mass transfer through the air-water interface. Tartu, 2005, 73 p.
47. **Thomas Thomberg.** The kinetics of electroreduction of peroxodisulfate anion on cadmium (0001) single crystal electrode. Tartu, 2005, 95 p.
48. **Olavi Loog.** Aspects of condensations of carbonyl compounds and their imine analogues. Tartu, 2005, 83 p.
49. **Siim Salmar.** Effect of ultrasound on ester hydrolysis in aqueous ethanol. Tartu, 2006, 73 p.
50. **Ain Uustare.** Modulation of signal transduction of heptahelical receptors by other receptors and G proteins. Tartu, 2006, 121 p.
51. **Sergei Yurchenko.** Determination of some carcinogenic contaminants in food. Tartu, 2006, 143 p.
52. **Kaido Tämm.** QSPR modeling of some properties of organic compounds. Tartu, 2006, 67 p.
53. **Olga Tšubrik.** New methods in the synthesis of multisubstituted hydrazines. Tartu. 2006, 183 p.
54. **Lilli Sooväli.** Spectrophotometric measurements and their uncertainty in chemical analysis and dissociation constant measurements. Tartu, 2006, 125 p.
55. **Eve Koort.** Uncertainty estimation of potentiometrically measured ph and pK_a values. Tartu, 2006, 139 p.
56. **Sergei Kopanchuk.** Regulation of ligand binding to melanocortin receptor subtypes. Tartu, 2006, 119 p.
57. **Silvar Kallip.** Surface structure of some bismuth and antimony single crystal electrodes. Tartu, 2006, 107 p.
58. **Kristjan Saal.** Surface silanization and its application in biomolecule coupling. Tartu, 2006, 77 p.
59. **Tanel Tätte.** High viscosity $Sn(OBu)_4$ oligomeric concentrates and their applications in technology. Tartu, 2006, 91 p.

60. **Dimitar Atanasov Dobchev**. Robust QSAR methods for the prediction of properties from molecular structure. Tartu, 2006, 118 p.
61. **Hannes Hagu**. Impact of ultrasound on hydrophobic interactions in solutions. Tartu, 2007, 81 p.
62. **Rutha Jäger.** Electroreduction of peroxodisulfate anion on bismuth electrodes. Tartu, 2007, 142 p.
63. **Kaido Viht.** Immobilizable bisubstrate-analogue inhibitors of basophilic protein kinases: development and application in biosensors. Tartu, 2007, 88 p.
64. **Eva-Ingrid Rõõm.** Acid-base equilibria in nonpolar media. Tartu, 2007, 156 p.
65. **Sven Tamp.** DFT study of the cesium cation containing complexes relevant to the cesium cation binding by the humic acids. Tartu, 2007, 102 p.
66. **Jaak Nerut.** Electroreduction of hexacyanoferrate(III) anion on Cadmium (0001) single crystal electrode. Tartu, 2007, 180 p.
67. **Lauri Jalukse.** Measurement uncertainty estimation in amperometric dissolved oxygen concentration measurement. Tartu, 2007, 112 p.
68. **Aime Lust.** Charge state of dopants and ordered clusters formation in CaF_2:Mn and CaF_2:Eu luminophors. Tartu, 2007, 100 p.
69. **Iiris Kahn**. Quantitative Structure-Activity Relationships of environmentally relevant properties. Tartu, 2007, 98 p.
70. **Mari Reinik.** Nitrates, nitrites, N-nitrosamines and polycyclic aromatic hydrocarbons in food: analytical methods, occurrence and dietary intake. Tartu, 2007, 172 p.
71. **Heili Kasuk.** Thermodynamic parameters and adsorption kinetics of organic compounds forming the compact adsorption layer at Bi single crystal electrodes. Tartu, 2007, 212 p.
72. **Erki Enkvist.** Synthesis of adenosine-peptide conjugates for biological applications. Tartu, 2007, 114 p.
73. **Svetoslav Hristov Slavov**. Biomedical applications of the QSAR approach. Tartu, 2007, 146 p.
74. **Eneli Härk.** Electroreduction of complex cations on electrochemically polished Bi(*hkl*) single crystal electrodes. Tartu, 2008, 158 p.
75. **Priit Möller.** Electrochemical characteristics of some cathodes for medium temperature solid oxide fuel cells, synthesized by solid state reaction technique. Tartu, 2008, 90 p.
76. **Signe Viggor.** Impact of biochemical parameters of genetically different pseudomonads at the degradation of phenolic compounds. Tartu, 2008, 122 p.
77. **Ave Sarapuu.** Electrochemical reduction of oxygen on quinone-modified carbon electrodes and on thin films of platinum and gold. Tartu, 2008, 134 p.
78. **Agnes Kütt.** Studies of acid-base equilibria in non-aqueous media. Tartu, 2008, 198 p.

79. **Rouvim Kadis.** Evaluation of measurement uncertainty in analytical chemistry: related concepts and some points of misinterpretation. Tartu, 2008, 118 p.
80. **Valter Reedo.** Elaboration of IVB group metal oxide structures and their possible applications. Tartu, 2008, 98 p.
81. **Aleksei Kuznetsov.** Allosteric effects in reactions catalyzed by the cAMP-dependent protein kinase catalytic subunit. Tartu, 2009, 133 p.
82. **Aleksei Bredihhin.** Use of mono- and polyanions in the synthesis of multisubstituted hydrazine derivatives. Tartu, 2009, 105 p.
83. **Anu Ploom.** Quantitative structure-reactivity analysis in organosilicon chemistry. Tartu, 2009, 99 p.
84. **Argo Vonk.** Determination of adenosine A_{2A}- and dopamine D_1 receptor-specific modulation of adenylate cyclase activity in rat striatum. Tartu, 2009, 129 p.
85. **Indrek Kivi.** Synthesis and electrochemical characterization of porous cathode materials for intermediate temperature solid oxide fuel cells. Tartu, 2009, 177 p.
86. **Jaanus Eskusson.** Synthesis and characterisation of diamond-like carbon thin films prepared by pulsed laser deposition method. Tartu, 2009, 117 p.
87. **Marko Lätt.** Carbide derived microporous carbon and electrical double layer capacitors. Tartu, 2009, 107 p.
88. **Vladimir Stepanov.** Slow conformational changes in dopamine transporter interaction with its ligands. Tartu, 2009, 103 p.
89. **Aleksander Trummal.** Computational Study of Structural and Solvent Effects on Acidities of Some Brønsted Acids. Tartu, 2009, 103 p.
90. **Eerold Vellemäe.** Applications of mischmetal in organic synthesis. Tartu, 2009, 93 p.
91. **Sven Parkel.** Ligand binding to 5-HT_{1A} receptors and its regulation by Mg^{2+} and Mn^{2+}. Tartu, 2010, 99 p.
92. **Signe Vahur.** Expanding the possibilities of ATR-FT-IR spectroscopy in determination of inorganic pigments. Tartu, 2010, 184 p.
93. **Tavo Romann**. Preparation and surface modification of bismuth thin film, porous, and microelectrodes. Tartu, 2010, 155 p.
94. **Nadežda Aleksejeva.** Electrocatalytic reduction of oxygen on carbon nanotube-based nanocomposite materials. Tartu, 2010, 147 p.
95. **Marko Kullapere.** Electrochemical properties of glassy carbon, nickel and gold electrodes modified with aryl groups. Tartu, 2010, 233 p.
96. **Liis Siinor.** Adsorption kinetics of ions at Bi single crystal planes from aqueous electrolyte solutions and room-temperature ionic liquids. Tartu, 2010, 101 p.
97. **Angela Vaasa.** Development of fluorescence-based kinetic and binding assays for characterization of protein kinases and their inhibitors. Tartu 2010, 101 p.

98. **Indrek Tulp.** Multivariate analysis of chemical and biological properties. Tartu 2010, 105 p.
99. **Aare Selberg.** Evaluation of environmental quality in Northern Estonia by the analysis of leachate. Tartu 2010, 117 p.
100. **Darja Lavõgina.** Development of protein kinase inhibitors based on adenosine analogue-oligoarginine conjugates. Tartu 2010, 248 p.
101. **Laura Herm.** Biochemistry of dopamine D_2 receptors and its association with motivated behaviour. Tartu 2010, 156 p.
102. **Terje Raudsepp.** Influence of dopant anions on the electrochemical properties of polypyrrole films. Tartu 2010, 112 p.
103. **Margus Marandi.** Electroformation of Polypyrrole Films: *In-situ* AFM and STM Study. Tartu 2011, 116 p.
104. **Kairi Kivirand.** Diamine oxidase-based biosensors: construction and working principles. Tartu, 2011, 140 p.
105. **Anneli Kruve.** Matrix effects in liquid-chromatography electrospray mass-spectrometry. Tartu, 2011, 156 p.
106. **Gary Urb.** Assessment of environmental impact of oil shale fly ash from PF and CFB combustion. Tartu, 2011, 108 p.
107. **Nikita Oskolkov.** A novel strategy for peptide-mediated cellular delivery and induction of endosomal escape. Tartu, 2011, 106 p.
108. **Dana Martin.** The QSPR/QSAR approach for the prediction of properties of fullerene derivatives. Tartu, 2011, 98 p.
109. **Säde Viirlaid.** Novel glutathione analogues and their antioxidant activity. Tartu, 2011, 106 p.
110. **Ülis Sõukand.** Simultaneous adsorption of Cd^{2+}, Ni^{2+}, and Pb^{2+} on peat. Tartu, 2011, 124 p.
111. **Lauri Lipping.** The acidity of strong and superstrong Brønsted acids, an outreach for the "limits of growth": a quantum chemical study. Tartu, 2011, 124 p.
112. **Heisi Kurig.** Electrical double-layer capacitors based on ionic liquids as electrolytes. Tartu, 2011, 146 p.
113. **Marje Kasari.** Bisubstrate luminescent probes, optical sensors and affinity adsorbents for measurement of active protein kinases in biological samples. Tartu, 2012, 126 p.
114. **Kalev Takkis.** Virtual screening of chemical databases for bioactive molecules. Tartu, 2012, 122 p.
115. **Ksenija Kisseljova**. Synthesis of aza-β^3-amino acid containing peptides and kinetic study of their phosphorylation by protein kinase A. Tartu, 2012, 104 p.
116. **Riin Rebane.** Advanced method development strategy for derivatization LC/ESI/MS. Tartu, 2012, 184 p.

117. **Vladislav Ivaništšev.** Double layer structure and adsorption kinetics of ions at metal electrodes in room temperature ionic liquids. Tartu, 2012, 128 p.
118. **Irja Helm.** High accuracy gravimetric Winkler method for determination of dissolved oxygen. Tartu, 2012, 139 p.
119. **Karin Kipper.** Fluoroalcohols as Components of LC-ESI-MS Eluents: Usage and Applications. Tartu, 2012, 164 p.
120. **Arno Ratas.** Energy storage and transfer in dosimetric luminescent materials. Tartu, 2012, 163 p.
121. **Reet Reinart-Okugbeni**. Assay systems for characterisation of subtype-selective binding and functional activity of ligands on dopamine receptors. Tartu, 2012, 159 p.