Closing report for

# "**Catalytic reactivity from QMMM simulations**"

OTKA project K116034

The main motif of the project was to address reactivity issues emerging in various research topics conducted by our experimental partners and also to study other, recent actual research questions from the literature. In the research plan we have set three directions: silver-catalyzed alkyne transformations; coupling reactions by hypervalent iodonium salts; and reactivity of Pd catalysts in homogeneous catalytic reactions. As the evolution of the project has shown (see yearly reports) divergencies from the original plan have occurred in terms of new, analogous systems/reactions and in terms of more general reactivity issues. In addition, the importance of QM/MM has been lessened in the simulations, mainly because of our experiences accumulated during the project and in particular on the basis of the criteria obtained in our New. J. Chem. paper in 2019 (studying Ag-catalyzed ring-closure process) where we have concluded that for a successful interpretation of experiment QMMM is not necessarily required in contrast to the original hypothesis; in fact implicit solvent models can often be employed at a fraction of cost. This helped to focus more on chemistry than methodology issues during the project. Nevertheless in several cases we have revealed important mechainstic insights employing QMMM simulations which otherwise could not have been obtained. On the other hand a topic pursued for a long time about the speciation and interconversion of Pd-acetate complexes in water was terminated without publication because considerations showed that the necessary further investment was unproportional to the expected value and impact of the results. Officially 5 participants have been in the project (T. Bihari, P. P. Fehér, K. T. Stenczel, B. Szathury, A. Stirling) but in one of the project Dr. J. Daru also participated, albeit without being in the official participation list. One PhD dissertation has been finished and successfully defended (Dr. T. Bihari). In the following we summarize all the projects conducted within the framework of the project. Note that a topical order is followed instead of a chronological order.

## A. Silver-catalyzed and analogous (Cu-catalyzed) coupling reactions [1,2]

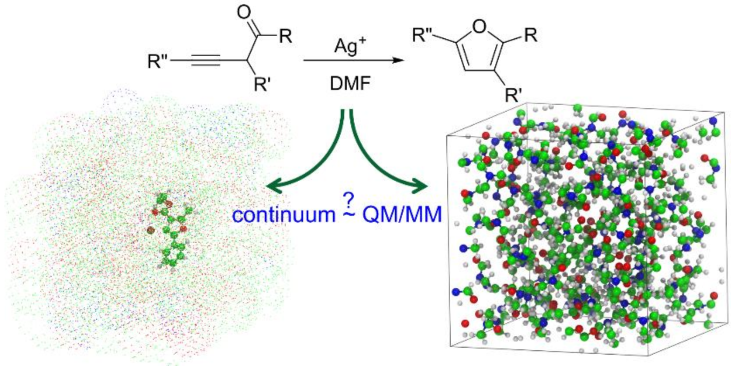

**Figure 1.** Illustration of the solvent concepts in modelling an Ag(I)-catalyzed ring-closing C-O coupling reaction.

1. QM/MM and cluster calculations have been performed to obtain the free energy barriers and reaction free energies of a silver-catalyzed C-O coupling reaction leading to the formation of furan ring (Figure 1). This reaction is a crucial step in a recently developed Ag-catalyzed oxidative furan formation from terminal alkyn precursors and beta-ketoesters. Three different potential pathways have been computed employing

both implicit (gas-phase) and explicit solvation (QM/MM) models combined with blue-moon samplings. The three pathways feature different charge states with bonding topologies characteristic of many silver- and copper-catalyzed reaction steps; hence they could serve as a blueprint for assessing the effects of solvents in a wider set of reactions. Comparison of the results showed that both methodologies could unequivocally determine the most favorable and least likely pathways. Analysis of the trajectories obtained from the QM/MM simulations indicated neither direct solvent participation in the reaction nor any site-specific interaction of the solvent with the reactant. These insights point to a sufficiently mobile, fluctuating solvent shell which can be efficiently described by implicit solvent models at a fraction of computational costs. This conclusion implies that it is important to double-check whether a given reactivity problem requires explicit inclusion of the solvent. The results was published in the New Journal of Chemistry [1].

2. In a a computational mechanistic study [2] we addressed a copper(III)-catalyzed carboarylation–ring closure reactions leading to the formation of functionalised heterocycles disclosed by our experimental partner group of Prof. Novák. We have performed DFT calculations along selected routes and compared their free energy profiles (Figure 2). The calculations considered two viable options for the underlying mechanism which differ in the order of the oxazoline ring formation and the aryl transfer steps. The calculations provided several new chemical insights: deprotonation can take place only after the tandem arylation–cyclisation sequence; the mechanism shows a very limited sensitivity in a wide range of substituents installed on the reactants; a crucial copper–oxygen interaction is responsible for the very high stereoselectivity of the reaction and it also excludes the formation of vinyl-cation intermediates. The obtained results could serve as a useful and more general description of the mechanism of the carboarylation–ring closure strategy based on the utilisation of alkynes and diaryliodonium salts, beyond the selected and studied oxazoline synthesis. The study appeared in the Beilstein Journal of Organic Chemistry [2].

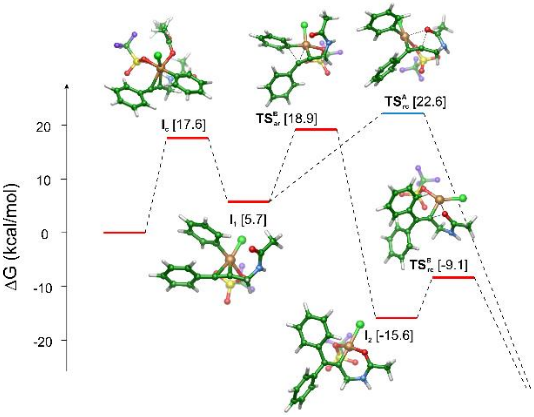

**Figure 2.** Free energy profiles for the possible reaction routes for the selected Cu-catalyzed arylation-cyclisation strategy.

## B. Studies on the reactivities of hypercoordinated iodine compounds

3. QM/MM simulations have been performed to sample the electronic structure of a number of different iodine compounds in dichloromethane. The QM/MM simulations have confirmed the limited effect of

temperature and solvent environment on the bonding patterns which enables simple gas-phase cluster calculations to describe the bonding situations in iodanes. A suitable criterion for the assignation of the localized electron pairs has been proposed to overcome the ambiguity hidden in the concept of valency. An important new physical insight is that in the majority of the cases iodine obeys the octet rule, but there are iodanes in which it is hypovalent (Figure 3). The hypovalencies can be associated with an enhanced reactivity. The employment of the centers of the localized orbitals has proved to be a very efficient and convincing method to interpret the bonding pattern around the cental iodine atom and can similarly provide additional guidance in the design of new iodane molecules. The study has been published as a "Hot paper" in Chemistry an European Journal [3].

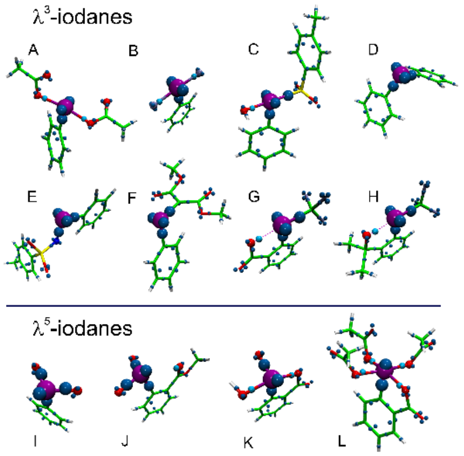

**Figure 3.** Wannier centers for a large set of different types of iodanes. Large blue balls are centers (centers of localized electron pairs) assigned to iodine.

4. One of our experimental partners, the Novak group has designed and developed a new synthetic route toward various aryl(trifloxyalkenyl)iodonium triflate salts. For this project we have provided theoretical data for the Z/E stabilities of the product salts which served in the assignation of the structures and the interpretation of the selectivities. We have found that the electronic energy differences indicated that the various intramolecular interactions in the Z and E isomers are very similar in magnitude, whereas the small solvation free energy differences showed that entropy and solvation (ie. longer-range interaction of the different charge distributions of the isomers with the solvent) represent a very limited effect as far as the stability differences are concerned. Still, our results could serve in the unambiguous assignation of the structures. The study was published in the ACS Omega [4].

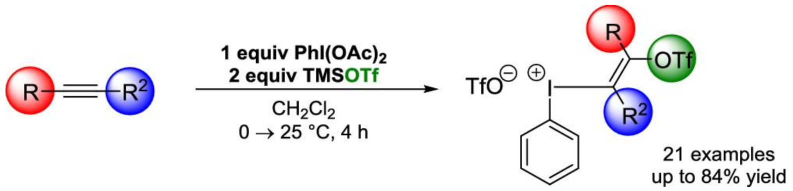

**Figure 4.** Synthetic route toward aryl(trifloxyalkenyl)iodonium triflate salts. Note that the development of the synthetic route is NOT the result of the present project; we have contributed with computational insights.

5. In another project we have exploited interesting neighbor-atom effects in N-arylation of heterocycles with diaryl-iodonium salts. In this combined theoretical-experimental work a theoretical model has been postulated which subsequently has been verified by experiment leading to an extension of the scope of the N-arylation. Our model featuring a tandem action of a nucleophilic N-site and a nearby acidic N-H moiety is effective in capturing the essence of the mechanism and it offers a new synthetic strategy as well. The free energy profiles have been calculated by a full quantum-chemical approach (Figure 5). The mechanistic pattern indicates that substrates featuring a strategically positioned Lewis base (nucleophilic) and Brønsted acidic centers in close vicinity can also undergo facile arylation with diaryliodonium salts under mild conditions with the same mechanism. This prediction has been tested on a limited set of substrates by calculations and also confirmed experimentally by the Novak group. The study was published in the Journal of Organic Chemistry [5].

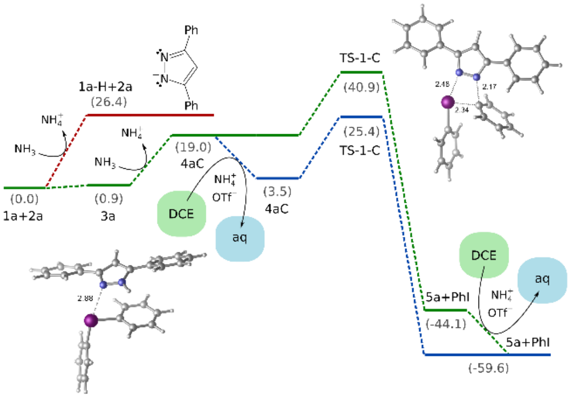

**Figure 5.** Free energy profiles for the best mechanistic proposals.

6. In collaboration with the Novak group we have undertaken a mechanistic study to understand a new and simple aziridination process that relies on the use of amines and novel alkenyl-iodonium reagents for the synthesis of strained, trifluoromethylated heterocycles (aziridines). As our earlier study revealed that implicit solvation models can sufficiently address reactivity issues of hypercoordinated iodanes here we studied the reaction with this computational strategy. The calculations have exposed the kinetic reasons responsible for the surprising observation that instead of the more stable amine and enamine products the strained three-membered ring formation occurs. Calculations also pointed out that among various potential C2-CF3 synthons, the iodonium reactant stands out with remarkably lower barriers for both the aromatic and the alkylamine reactants. The study has been published in Angewandte Chemie [6].

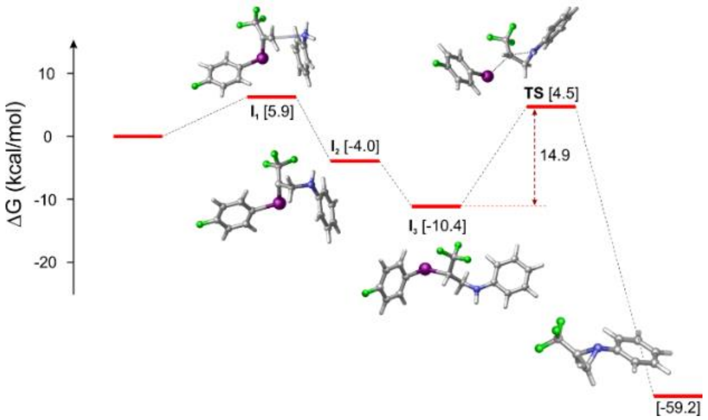

**Figure 6.** Free energy profile for the formation of the aziridine ring. Profiles for the thermodynamically far more favorable but experimentally not observed products are given in the SI of Ref. [6].

## C. Studies on Pd- and Ni-catalyzed reactions

7. In collaboration with the group of Dr. Della Cà, we have successfully explored the mechanism of a Pd-catalyzed ring-closing/carbonylation reaction which takes place in a cascade fashion and leads to the formation of fused polyheterolytic structures via double or tetracyclization. My personal interest was boosted by the fact that this was a kind of total-synthetic project which I always find very fascinating and demanding. An interesting challenge in this project was to find the reason of the unexpected 6-endo-dig selectivity because the expected and highly possible 5-exo-dig route could not be observed. We traced back this selectivity to the asymmetric aryl-alkyl substitution on the triple bond where the first cyclization occurs; this asymmetric pattern favors the cyclization on the *sp* carbon closer to the aryl ring as this carbon becomes more electrophilic. Note that the selectivity of the first step strictly determines the selectivity of the final ring closing. The study has been published in Organic Letters [7].

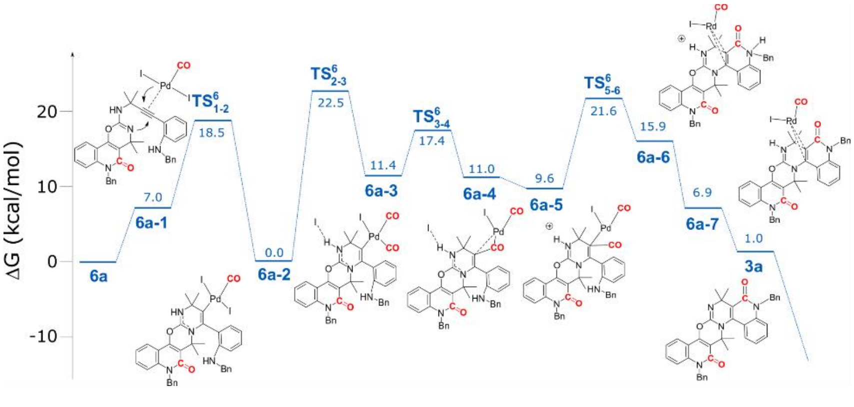

**Figure 7.** Free energy profile for the last two cyclization steps in the formation of compound **3**. Computations for the preceding steps are given in the SI of Ref. [7] whereas a summary of the full mechanism emerged from computation is given in the article.

8. Pd-catalyzed C-H activation and alkylation have been employed in a combined experimental-theoretical work where late-stage functionalization of aromatic ureas has been achieved successfully. The theoretical contributions were the identification of the rate-determining step (the oxidative alkyl-group transfer) and

the finding of an outer-sphere C-H insertion step. This step is notably different from the traditional CMD mechanism because a triflate anion plays the role of the base. The mechanistic studies also revealed that the formation of bimetallic palladium species is a crucial aspect of the reaction, playing an important role in the mild catalytic transformation. The study has been published in the Advanced Synthesis & Catalysis [8].

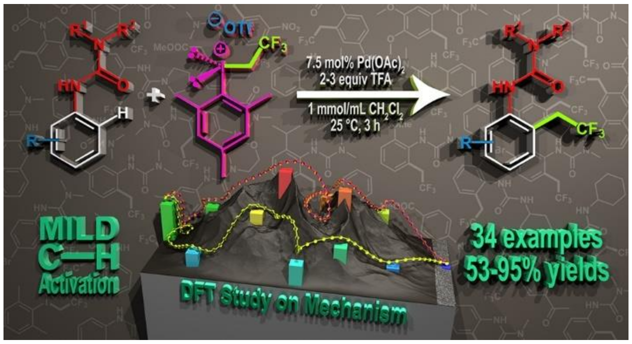

**Figure 8.** The eye-catching TOC figure of the study (Ref. [8]) by Balázs Tóth, the leading author of the study.

9. A Pd-analogous, Ni-catalyzed reaction has been studied within the framework of this project [9]. Very recently a base-free Suzuki-Miyaura coupling has been disclosed in two independent publications where the typical Pd-catalyst was replaced by Ni-catalysts. In this process acyl-fluorides are employed and an interesting decarbonylative coupling takes place. We have explored the reaction mechanism with static quantum chemical models and with QM/MM simulations with explicit solvent (THF) molecules. We have contrasted the effect of two typical phosphine ligands (P = $PCy_3$, $PPh_2Me$) and different experimental (stoichiometric and catalytic) conditions to elucidate the corresponding experimental observations. The free energy profiles of the most likely mechanisms supported the more facile formation of the transmetallation-active catalytic intermediate with $PPh_2Me$ and also justified why the intermediate of the oxidative addition cannot be observed for this ligand. A crucial ingredient of the mechanisms is the *cis-trans* rearrangement in the square planar ligand structure around the Ni(II) center to stabilize the complexes and to facilitate the Ni-insertion preceding the decarbonylation. Simulations also revealed that the smaller size of $PPh_2Me$ also enables the formation of highly fluxional five-coordinated species where the thermal fluctuations can remarkably simplify the mechanism predicted by static calculations and this implies a very fast decarbonylation. We could conclude that an enhanced level of statistical treatment was needed to describe properly this step.  The study has been published in Organometallics [9].

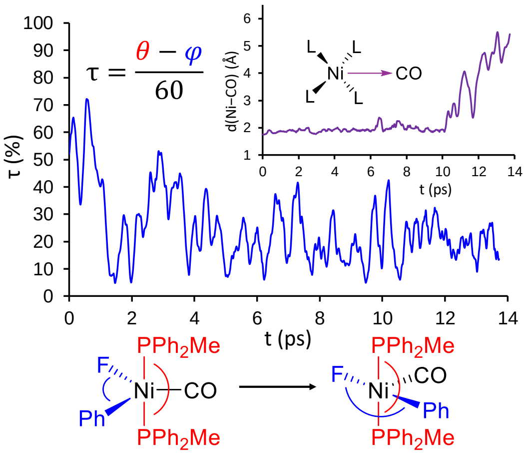

**Figure 9.** Time evolution of the trigonal bipyramidal (τ ≈ 100%) and square pyramidal (τ ≈ 0%) structures in the QM/MM trajectory of a crucial Ni-carbonyl intermediate. As the inset shows, the fluxional rearrangements assist the decarbonylation.

## D. Additional reactivity studies

A study has been conducted in order to introduce the various free energy methods to Dr. Fehér, the principal coworker of the project. In this study, where the formation of various chloramine species was scrutinized, his earlier computational models have been improved with a large number of explicit water molecules and QM MD and free energy calculations have been performed. In close collaboration with the experimental group of Prof. Fábián (Uni Debrecen) we have provided a mechanism for the acid-catalyzed dimer formation and also excluded kinetically unfavorable hypotheses. The mechanism involves the reaction between the protonated and unprotonated forms of monochloramine, with a rate constant k = 335.3 ± 11.8 $M^{-1}$ $s^{-1}$, corresponding to an activation free energy barrier of 14.1 kcal/mol. The simulations predicted a barrier of 14.9 kcal/mol and revealed a key short-lived chlorine-bridged intermediate which yields dichloroamine and ammonium ion through a deprotonation-coupled chlorine shift.The work has been published in Dalton Transactions [10]. The study sparked some interest inland and a request arrived to write an article in "Vízmű Panoráma" a specialized journal for water industry experts. This article appeared in the 5. issue of the XXVIII volume (2020) of Vízmű Panoráma [15].

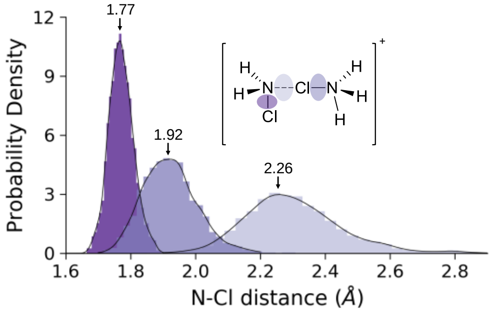

**Figure 10.** Distance distributions of the three N–Cl bond types in the elusive chlorine-bridged intermediate observed in the simulations [10]. The envelope curves are the approximate probability density functions obtained via kernel density estimation.

11. In collaboration with organic chemists of the Technical University, Bp. a combined MM and QM simulation study of stereoselectivity in enantioselective synthesis of substituted a-aminophosphonates catalyzed by D-glucose-based crown ethers has been conducted. The study has revealed that suitable side arms on the crown ether beneficially affect the position of the central sodium cation, which in turn helps enhance the stereocontrol by allowing a closer contact between substrate and catalyst. A simple model has been designed which can efficiently rationalize the observed selectivities including the decline in stereoselectivity when Na+ is replaced by K+. The study has been published in the New Journal of Chemistry [11].

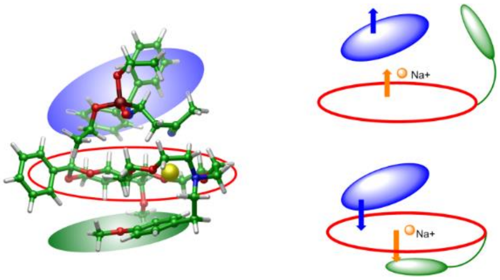

**Figure 11.** TOC figure of Ref. [11] illustrating the concept of the catalytic effect.

12. We have finished a study which has only partial overlap with the topics of the present project (free energy simulations) where $H_2$-activation by frustrated Lewis pairs (FLPs) has been investigated with a very powerful arsenal of the free energy methodologies (MD, metaMD, umbrella sampling, committor analysis, description the mechanism in terms of reaction path CV, decomposing reactive trajectories to different degrees of freedom). The computed free energy surfaces derived for the reactions with three different intramolecular FLPs suggest that the heterolytic $H_2$ splitting process takes place in a single concerted step as described previously. We find no computational evidence for the stepwise mechanism, not even for transient reaction intermediates. The statistical analysis carried out for a large number of reaction trajectories launched from the transition state regions points to a notable asynchronicity in the formations of the donor-H and acceptor-H bonds with the latter being ahead in development. An important consequence of the asynchronicity is that most of the excess kinetic energy (i.e., reaction heat) released upon $H_2$ cleavage is accumulated in the form of donor-H bond vibrations, resulting in enhanced reactivity of this site in a subsequent event, for instance, in a possible catalytic proton transfer step. The study has been published in ACS Catalysis [12].

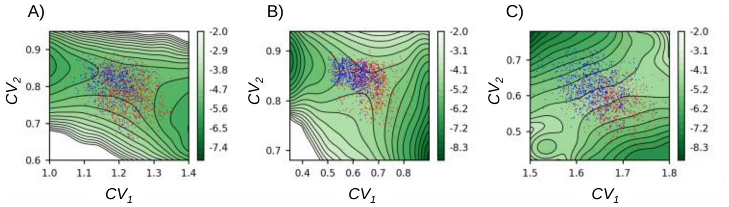

**Figure 12.** TS regions of the free energy surfaces obtained from umbrella samplings for thres reactions between FLPs and $H_2$. Positions from where trajectories were initiated are indicated by dots. Blue and red colors refer to trajectories that reached reactant and product states in the simulations. For further details see Ref [12].

13. A methodological study has been conducted where new hidden properties of the continuous symmetry measure (CSM) quantity has been derived and applied. We have shown that if the temperature dependence of CSM of a given molecule is available from simulations (either full quantum, QMMM or MM) then temperature effects (ie the effects of thermal fluctuations) can be separated from other sources of distortions, such as Jahn-Teller distortion and the distortions can be analyzed in a more detailed level. We demonstrate the potential of the method by studying two highly symmetric molecules: adamantane and the cyclopentadienyl anion and their cationic states. We concluded that an ensemble-averaged CSM is a suitable measure to characterize the extent of the JT effect on the molecular geometry and efficiently grasps the perception behind it. The study appeared in the Israel Journal of Chemistry [13].

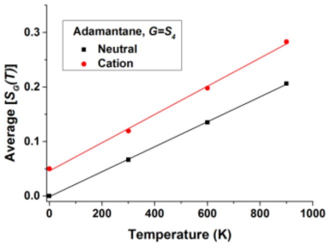

**Figure 13.** Average CSM(T, symmetry= $S_4$) values for the neutral adamantane (black squares) and its cation (red circles) with G=$S_4$. Based on 40,000 data points. The difference seen at O K is due to JT distortion and it persists at higher temperatures to a good approximation. The derivation is given in Ref. [13].

## E. Ongoing studies

Two studies have not been finished and published within the project timeframe. One is a step forward in the field of aziridin-chemistry where the peculiar reactivity of a new iodonium salt has been studied [6]. The main issue here is that the amine formation and aziridin ring formation are competitive reaction routes and now secondary amines are scrutinized in their reactions with trifluoropropenyl iodonium salt. Here the computational parts have been finished but the results are not yet published because of some issues are being resolved at experimental front. Another study is however at the revision phase: this is the work of one of the secondary students (Mr. Szathury) participated earlier in the project. In this study we have scrutinized the so-called chelation-assisted metallation (palladation) topic. We have built a model from computations to provide a solid framework for experiment to explain and predict reactivities of substrates with different substituents of varying steric demands installed in one of the two ortho positions relative to various ortho-directing groups. This has been a longer project than we expected it would be, but with time it has matured significantly. The manuscript is now under revision in Chemical Science [14].

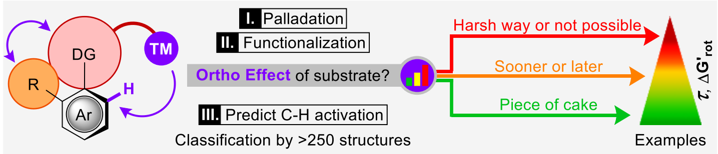

**Figure 14.** TOC figure of Ref. [14]. The term and concept of Ortho Effect (OE) was introduced for the description of steric effects in transition metal catalyzed directed *ortho* C-H activation reactions. With the aid of the developed model the general reactivity

of substrates can be explained and predicted. The applicability of the theoretical model was demonstrated with the interpretation of various experimental studies.

The results of the studies have been presented also in various conferences: ACS meeting, COST workshops, KeMoMo-QSAR, Molecular Quantum Mechanics conf., in-house meetings in ELKH-TTK, etc. and for many of them required the support of the budget of the present project. In addition we have participated workshops showcasing and discussing the state-of-the-art of simulations (e.g. CECAM workshops, COST tutorial).

The present OTKA project has provided young scientists with the opportunity to master in quantum chemical modeling and free energy simulations. Tamás Bihari has sucessfully defended his PhD thesis and presently he works in industry. Both secondary-school participants (Mr. Tamás Károly Stenczel and Mr. Bálint Szathury) are now the in Cambridge and they pursue their studies. I hope that soon not only Mr. Stenczel, but also Mr. Szathury will have his publication from the topic undertaken within the framework of this project which can be important in boosting his competitiveness. Dr. Fehér is now in our new, photocatalytic project and all the subprojects heavily rely on his vast experience and skills in computations and simulations obtained by participating in this finished project.

Finally I wish to thank the NKFIH for the funding of the present K116034 project. It has contributed to build successful research directions, helped to maintain and improve our existing collaborations and helped to establish new ones. It also helped the young participants to obtain deep theoretical and practical knowledge in the field of computational chemistry and simulations.

**Publications of the project**

[1] P. P. Fehér, A. Stirling*, *Assessment of reactivities with explicit and implicit solvent models: QM/MM and gas-phase evaluation of three different Ag-catalysed furan ring formation routes*, **New J. Chem.** 2019, 43, 15706-15713.

[2] T. K. Stenczel, A. Sinai, Z. Novak*, A. Stirling*, *DFT calculations on the mechanism of Copper-Catalysed Tandem Arylation-Cyclization Reaction of Alkynes and Diaryliodonium Salts*, **Beilstein J. Org. Chem.** 2018, 14,1743-1749.

[3] A. Stirling*: *Assessing Hypervalency in Iodanes*, **Chem. Eur. J.** 2018, 24, 1709-1713.

[4] B. L. Tóth, F. Béke, O. Egyed, A. Bényei, A. Stirling, Z. Novák*, *Synthesis of Multifunctional Aryl(trifloxyalkenyl)iodonium Triflate Salts*, **ACS OMEGA**, 2019, 4, 9188-9197.

[5] T. Bihari, B. Babinszki, Zs. Gonda, Sz. Kovács, Z. Novák*, A. Stirling*, *Understanding and Exploitation of Neighboring Heteroatom Effect for the Mild N-Arylation of Heterocycles with Diaryliodonium Salts under Aqueous Conditions: A Theoretical and Experimental Mechanistic Study*, **J. Org. Chem.**, 2016, 81, 5417-5422.

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[7] F. Pancrazzi, N. Sarti, P. P. Mazzeo, A. Bacchi, C. Carfagna, R. Mancuso, B. Gabriele, M. Costa, A. Stirling*, N. Della Ca*, *Site-Selective Double and Tetra Cyclization Routes to Fused Polyheterocyclic Structures by Pd-Catalyzed Carbonylation Reactions*, **Organic Letters**, 2020, 4, 1569-1574.

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