In silico rationalisation of selectivity and reactivity in Pd-catalysed C-H activation reactions

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Abstract

A computational approach has been developed to automatically generate and analyse the structures of the intermediates of palladium catalysed carbon-hydrogen (C-H) activation reactions as well as to predict the final products. Implemented as a high-performance computing cluster tool, it has been shown to correctly choose the mechanism and rationalise regioselectivity of chosen examples from open literature reports. The developed methodology is capable of predicting reactivity of various substrates by differentiation between two major mechanisms - proton abstraction and the electrophilic aromatic substitution. An attempt has been made to predict new C-H activation reactions. This methodology can also be used for the automated reaction planning, as well as a starting point for microkinetic modelling.

Introduction

Periodically, our knowledge of chemistry is enriched with new transformations that provide significant breakthroughs by enabling new synthetic strategies. Such examples in recent years include olefins metathesis [1] as well as C-C and C-N coupling reactions [2], among the most obvious examples. While these reactions undoubtedly had very significant impacts on the development of much cleaner and efficient chemical synthesis strategies, the early days of all new transformations are invariably challenging, with very slow and protracted paths from the

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initial discoveries to the demonstrations of broad substrate applicability and robustness, that are expected of industrial catalytic processes. Today, there exist a number of fairly recently (re)discovered transformations, that are of potential high industrial significance, and where one can observe the same problem of a lack of robustness. Thus, any approach that may speed-up the transition from a discovery of a new transformation to it becoming a robust synthetic strategy, is highly desired.

Recent years have seen the emergence of new methods of research in chemistry and process development, which include high-throughput experiments [3], autonomous self-optimising reactors [4], as well as predictions of reaction outcomes and of reaction conditions based on machine learning (ML) and artificial intelligence (AI) tools [5, 6]. Especially the methods of ML/AI for prediction of reaction outcomes are attracting a lot of attention. Prediction accuracies in the order of 70-80% for the reaction outcomes [6], and around 60-70% for reaction conditions [7], were recently demonstrated. While machine learning methods are showing great promise and continue to be improved upon, it is also clear that a ML model is unlikely to ever be able to compete in accuracy and interpretability with fully predictive mechanistic models, were it not for the prohibitively high cost of developing the mechanistic models based on accurate quantum chemical methods, such as the density functional theory (DFT) methods. Automation of DFT, as well as using results of DFT to develop less expensive predictive models, are the two approaches that may offer the alternatives to the fully data-driven statistical methods.

Here we demonstrate an approach that was developed to automate the DFT-level calculations of energies of the auto-generated reaction intermediates. These results were further used to generalize mechanistic knowledge of a class of reactions, and the developed models were used for *in silico* prediction of reactions outcomes. This approach was tested on the important for green chemistry class of C-H activation reactions. Whilst this study does not completely solve the problem of developing a robust chemical reaction, it offers an approach that is

complementary to efforts of developing machine learning models for predicting reaction outcomes.

C-H activation reactions allow conversion of relatively inexpensive and abundant hydrocarbons into the more sophisticated value-added molecules [8]. With the notion of step-economical and environmentally friendly synthesis, direct functionalization of C-H bonds is considered as a powerful strategy for the synthesis and derivatization of organic molecules [9]. Homogeneous catalysis employing transition metal complexes has been widely accepted as one of the most efficient ways to perform C-H activation-based synthesis with high selectivity under relatively mild conditions [10]. In particular, reactions involving palladium-catalyzed activation of sp^2 or sp^3 C-H bonds of arenes or alkanes have been extensively investigated due to their wide scope and functional group tolerance [11].

A number of different mechanisms are proposed in the literature, explaining the experimental observations on C-H activation reactions, depending on the nature of a ligand (L_n) and transition metal (M) in the catalytically active species (L_nM). These mechanisms include four elementary steps: oxidative addition, σ-bond metathesis, electrophilic substitution and 1,2-addition, respectively [12]. Even though the mechanisms are inherently different, three most important aspects should be primarily taken into account when classifying and rationalising C-H activation reactions:

1) the proximity of C-H bond to the transition metal;
2) the energy of C-H bond cleavage within the transition metal coordination sphere;
3) the energy of a new M-C bond formed and the thermodynamic stability of organometallic product.

With new developments in computational chemistry, mechanistic studies using density functional theory (DFT) provide valuable insights into the reactivity of organometallic complexes in C-H activation reaction. Along with the huge increase in computing power, this method becomes practically feasible to build model systems that provide parameters of the

actual experimental systems with acceptable accuracy [13]. Recently, a predictive tool using quantum mechanics descriptors was proposed for classifying whether the carbon atoms are active or inactive toward electrophilic aromatic substitution [14]. Also, a quantum mechanical approach was introduced to compute *ortho*-directing groups (DGs) in palladium-catalyzed aromatic C-H activation reaction [15]. However, there is a big challenge remaining which is to apply the computational analysis to a large number of mechanistically different transformations, both described and novel, in order to start generating accurate *in silico* reaction predictions. Here, we report an algorithm with high-performance computing (HPC) implementation, which has been developed to automatically generate and analyze the structures of the intermediates, and which allows prediction of the final products. The application of the developed methodology is in predicting reactivity for various substrates within a class of reactions. Using analysis of the computational data, a threshold to distinguish between two possible reaction mechanisms was established.

Computational methods

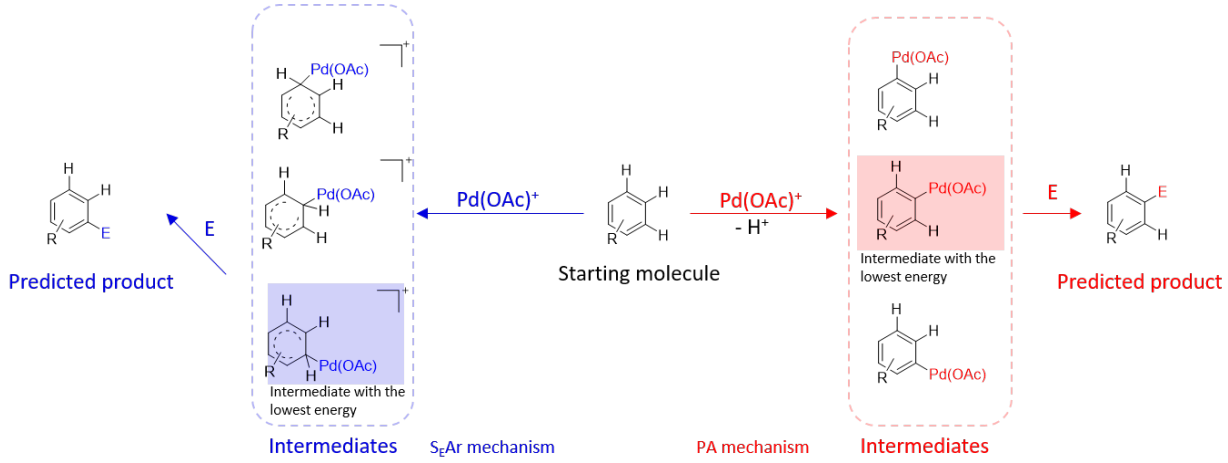
The NWChem, an open source software package, was used for the DFT calculations. It is easily scalable and designed to solve large scientific computational problems efficiently employing modern supercomputer clusters [16]. The structures were generated by the Python module developed in house and explained in detail elsewhere [17]. Electronic energies were evaluated using Becke's three-parameter hybrid B3LYP functional, while the molecular orbitals are expanded in triple-zeta all electron 6-31 set with added polarization and diffuse functions [6-31g(d,p)] [18]. B3LYP functional was proven to give accurate description of geometries, frequencies, relative stabilities of different conformers and the energy profile calculation [19]. Implementation of the tools is available at GitHub: https://github.com/sustainable-processes/Pd-catalysed_C-H_activation_reaction_prediction.

Results and Discussion

Computational approach to rationalise reactivity in Pd-catalyzed C-H bond activation reactions

Chemical reactivity is simultaneously influenced by many factors including catalyst, reactants, reaction conditions, and so on [20]. In order to achieve accurate and efficient reaction prediction, a mechanism-based method was chosen to direct quantum chemistry calculations and predictions, see Figure 1.

For the Pd(II)-catalysed C-H activation reactions, there are two main commonly accepted mechanisms: a) electrophilic aromatic substitution (S_EAr) mechanism and b) proton-abstraction (PA) mechanism. The key step for the electrophilic aromatic substitution is an electrophilic attack by Pd(II) onto the aromatic substrate that also defines the regioselectivity of the overall process [21]. The key feature of the proton abstraction (PA) mechanism [22] is that the formation of the metal-carbon bond (M-C) occurs simultaneously with the cleavage of the carbon-hydrogen (C-H) bond, while the hydrogen is being transferred to a basic center, Scheme 1.



Scheme 1. Schematic representation of the two mechanisms of Pd-catalyzed C-H activation reaction considered in this study.

Assuming the reaction proceeds through the formation of a relatively unstable intermediate (Figure 1) [23], Hammond postulate can be applied to the electrophilic substitution reactions. Hammond postulate states that a transition state will be structurally and energetically similar to the species (reactant, intermediate or product) nearest to it on the reaction path. In this case, the intermediates are likely to be close to, and resemble, transition states. Due to that, their

relative energy of formation can be translated to relative reaction kinetic barriers and thus be used, as the first approximation, to predict distributions of the final products, as well as the relative reactivity of the substrates [24]. For the PA mechanism, it has not been shown that the Hammond postulate can also be employed. Nevertheless, it is still reasonable to propose that the Hammond postulate can similarly be applied as a first approximation to produce *in silico* predictions.

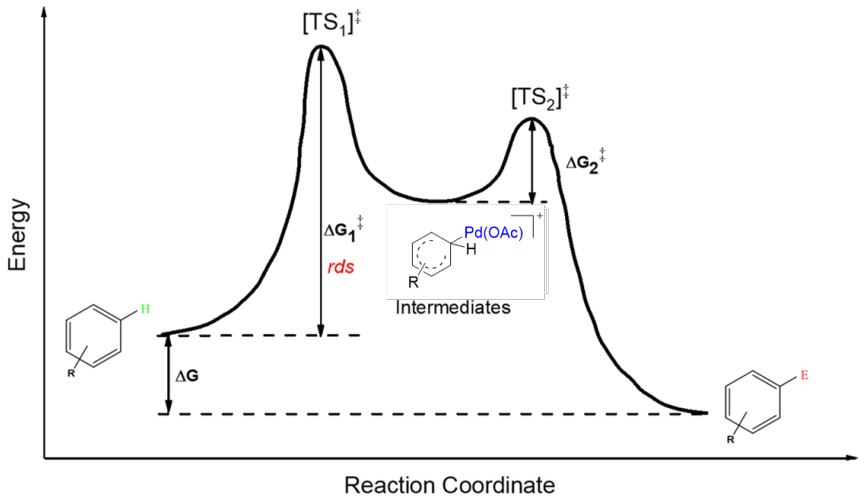


Figure 1. An approximate energy map for the electrophilic aromatic substitution mechanism.

Employing the Python module [17] and OpenBabel executables [25], the 3D structures of the most stable conformers were generated from 2D structure of a substrate. Subsequently, structures of all possible palladium intermediates representing both mechanisms (PA and S_EAr) were built for each conformer. A quick geometry optimization (maximum number of iteration steps was set to 5) was then applied to refine the intermediates and discard the ones with high energy (energy cut off of $10\ kcal \cdot mol^{-1}$). Full geometry optimisation followed by the frequency and thermochemistry analysis was then performed for the selected intermediates to obtain electronic energies. Multiple error handlers were implemented in order to automatically reprocess computational analysis for the intermediates when initial geometry optimisation failed, which include: erroneous optimisation to a saddle point where the final structure is changed by applying a move along imaginary coordinate followed by standard geometry optimisation, failed optimisation due to the need of updating Hessian in cases where significant geometry change occurred – standard resubmission starting from the last coordinate, failure to perform initial guess due to

particularly bad initial geometry – discard the conformer/intermediate, decomposed intermediate (no Pd-C bond determined by interatomic distance analysis) – discard intermediate.

Literature validation

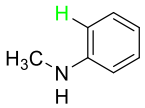
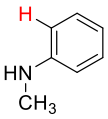
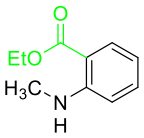
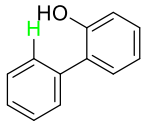
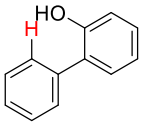
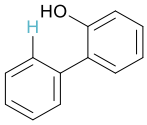
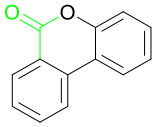
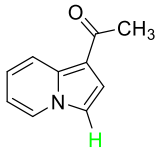
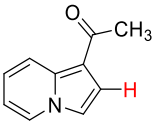
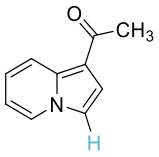
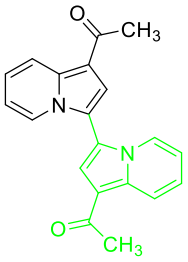
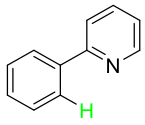
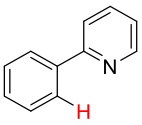
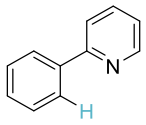
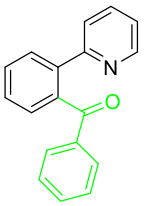
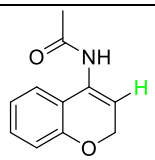
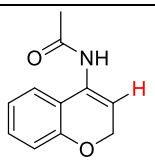
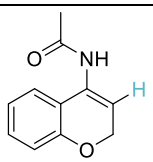
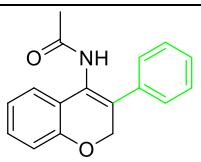
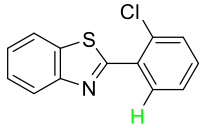
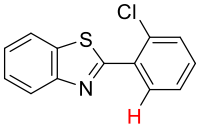
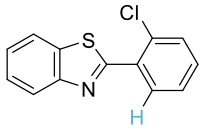
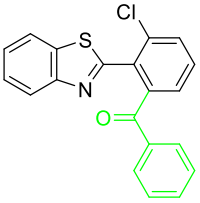
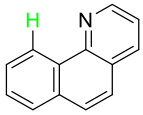
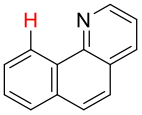
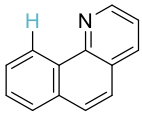
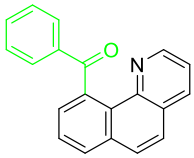
In order to test the developed algorithm, a representative literature data selection of Pd-catalyzed C-H activation reactions, consisting of reactant, reagents, and product structures as well as reaction conditions, was taken and analysed. Thus, twelve substrates shown in Table 1 were submitted to the algorithm, assuming that both mechanisms are possible. Using the relative energies of the intermediates obtained, the theoretically expected regioselectivity of the selected reactions was devised and then compared against the previously reported experimental data.

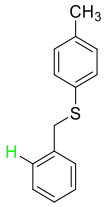
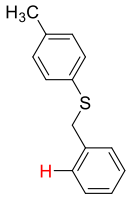
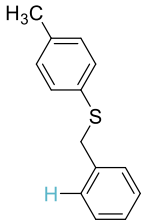
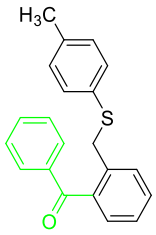
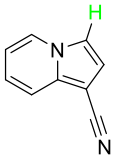
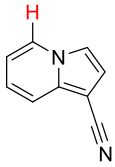
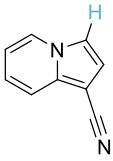
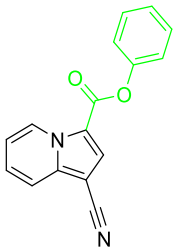
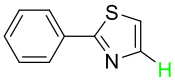
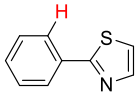
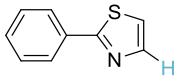
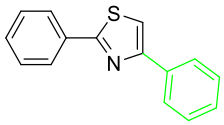
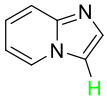
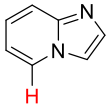
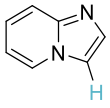
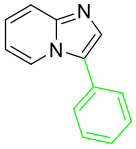
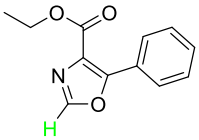
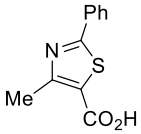
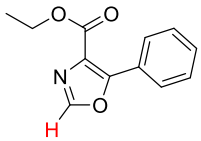
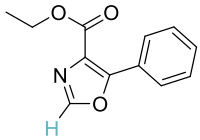
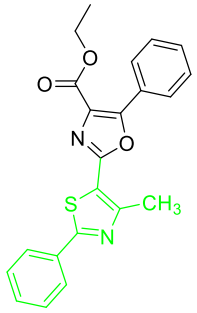
For all the examples regioselectivity predicted by at least one mechanism matched the previously reported experimental results, see Table 1. In the cases where only one product was predicted it is expected to be isolated in high yield without the need of further purification from any other regioisomer. For the examples where formation of multiple products was expected due to the close energies of the respective reaction intermediates, the ratio of products was calculated from the relative energies of these intermediates using the Boltzmann distribution equation.

Table 1. Comparison of the published experimental results with the computational predictions for the $Pd(OAc)_2$-catalysed reactions.

Protons marked green are those that react under the conditions reported in the literature. Protons marked red and blue are the predicted active centers via the acidity and the electrophilic mechanisms respectively.

No [ref]	Starting molecule	Exp. Cond.	Predicted active center		Experimentally isolated product
			Via acidity mechanism	*Via* electrophilic mechanism	

1 [26]		CO, EtOH, $Pd(OAc)_2$, $Cu(OAc)_2$, KOAc, DMF, KI, 100 °C, 13h		NO STABLE INTERMEDIATE	
2 [27]		CO, $Pd(OAc)_2$, $Cu(OAc)_2$, PivOH, mesitylene, 120 °C, 6h			
3 [28]		$Cu(OAc)_2$, $Pd(OAc)_2$, K_2CO_3, DMF, 60 °C, 0.6h			
4 [29]		$PhCOCO_2H$ $Pd(OAc)_2$, $K_2S_2O_8$, MeCN, 25 °C, 16h			
5 [30]		$PhSi(OMe)_3$, $Pd(OAc)_2$, AgF, dioxane, 80 °C, 16h			
6 [29]		Ph-CHO, $Pd(OAc)_2$, TBHP, toluene, 110 °C, 5h			
7 [31]		Ph-CHO, $Pd(OAc)_2$, Xylene, O_2 120 °C, 24h			

8 [32]		$PhCOCO_2H$, $Pd(OAc)_2$, Ag_2CO_3, DMF, 120 °C, 24h			
9 [33]		H-COOPh, $Pd(OAc)_2$, I_2, K_2CO_3, DMF, 100 °C, 12h			
10 [34]		$PhB(OH)_2$, $Pd(OAc)_2$, TEMPO, phen, DMAc, O_2 100 °C, 48h			
11 [35]		Benzene, $Pd(OAc)_2$, O_2, HOAc, DMA, 130 °C, 20h			
12 [36]		 , $Pd(OAc)_2$, $CuCO_3$, dioxane, DMSO, 140 °C, 16h			

Establishing the threshold between the two mechanisms

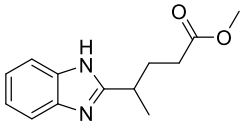
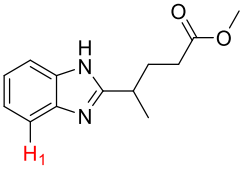
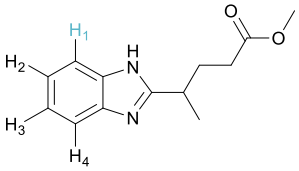
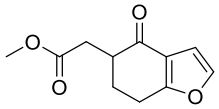
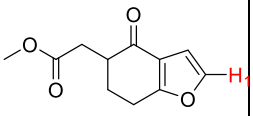
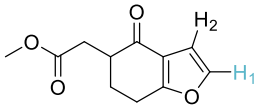
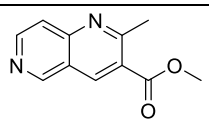
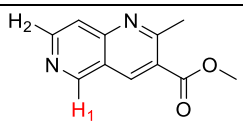
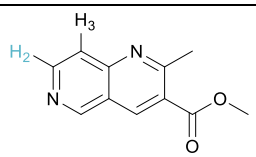
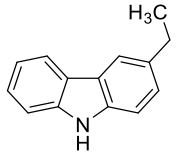
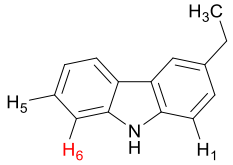
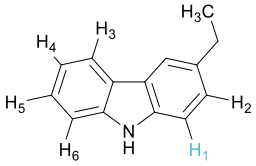
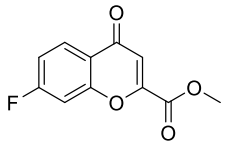
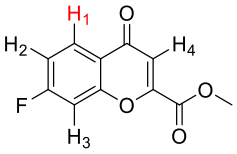
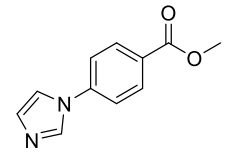
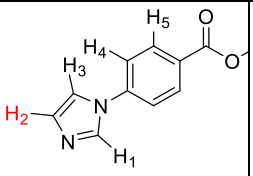
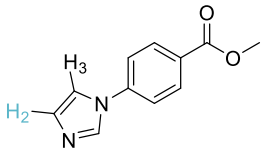
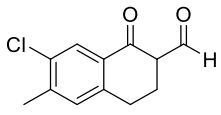
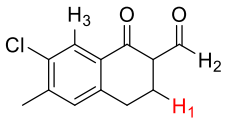
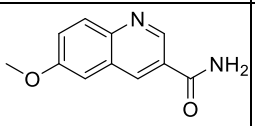
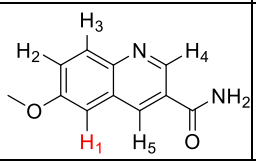
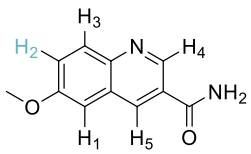
Although both, the proton-abstraction and the electrophilic aromatic-substitution, mechanisms are well established and described in the literature, it is not trivial to suggest the preferred mechanism for a given substrate based on a simple computational analysis. Through analysis of the results described above, the two-step evaluation algorithm was suggested.

Firstly, the optimized geometries were manually examined to ensure they represent the intermediates according to the particular mechanism. In particular, the bond length between the palladium atom and the corresponding carbon atom was given a maximum value of 2.4 Å to filter out inappropriate intermediates where there is no stable Pd-C bond [37].

Secondly, among the intermediates refined at the previous step, their relative Gibbs energies can be used to set a threshold establishing the likeliness of electrophilic aromatic substitution mechanism for C-H activation of a particular substrate. The more stable the ipso-complex between palladium acetate and the substrate is, the more likely the substrate is to follow the electrophilic mechanism. After performing the computational analysis of 12 examples which include five structures following the electrophilic mechanism, a threshold has been developed by choosing the example 6 as the reference, Table 1, and introducing the ipso-complex stability parameter. We define this parameter to be the energy difference between the most stable intermediate of the S_EAr mechanism and the one of the PA mechanism.

Table 2. *Predicting C-H activation bond for heteroaromatic compound. Most probable intermediates for each mechanism are shown, and relative Gibbs free energy are given in kcal* mol^{-1}*. If only one possible intermediate is given, it means that either the other intermediates are unstable or the other intermediates have 10 more kcal* mol^{-1} *Gibbs free energy than the most probable one. 'NO STABLE INTERMEDIATE' means instead of sitting on the corresponding*

carbon, the palladium sits on alternative atom. The predicted mechanism is given based on the threshold described in the previous section.

No.	Starting Molecule	Pred. Mec.	Computational prediction			
			Acidity mechanism		Electrophilic mechanism	
1		S_EAr		H1:0.0		H1:0.0
2		S_EAr		**H1:0.0**		**H1:0.0** H2:0.5
3		PA		**H1:0.0** H2:0.7		**H2:0.0** H3:0.9
4		PA		H1:1.9 H5:9.8 **H6:0.0**		**H1:0.0** H2:3.9 H3:2.9 H4:2.9 H5:4.2
5		PA		**H1:0.0** H2:2.7 H3:9.7 H4:6.2	NO STABLE INTERMEDIATE	
6		PA/ S_EAr		H1:0.2 **H2: 0.0** H3: 0.3 H4:0.9 H5:2.6		**H2:0.0** H3:2.7
7		PA		**H1:0.0** H2:2.8 H3:10.0	NO STABLE INTERMEDIATE	
8		PA		**H1:0.0** H2:0.8 H3:5.5 H4:4.3 H5:6.0		H1:0.1 **H2:0.0** H3:14.9 H4:15.0 H5:15.8

By comparing the computational results obtained to the literature experimental data, the two mechanisms can be segregated based on the following rules:

1) if the relative stability is below zero, the starting molecule will follow the proton abstraction mechanism.
2) If the relative stability is above five, the starting molecule will follow the electrophilic aromatic substitution mechanism.
3) If the relative stability is between zero and five, both mechanisms are regarded as plausible.

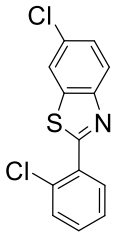
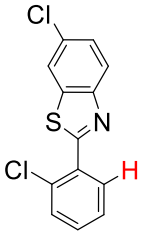
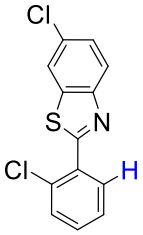
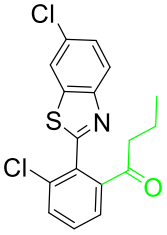
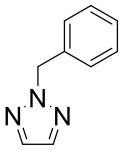
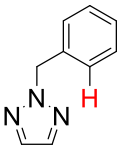
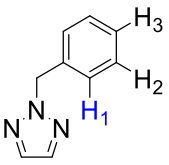
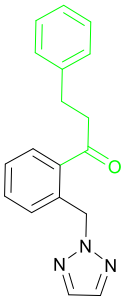
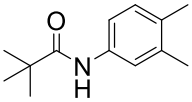
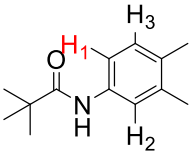
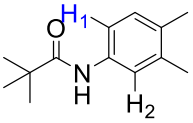
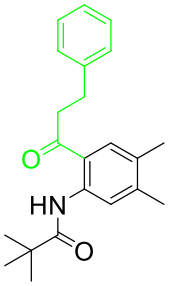
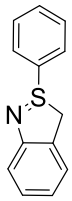
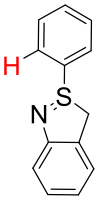
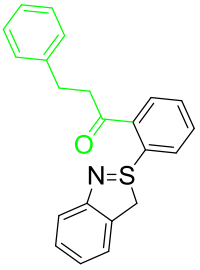
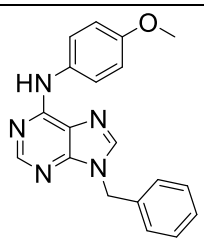
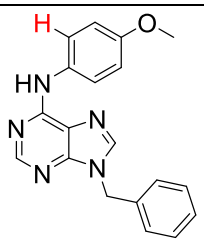
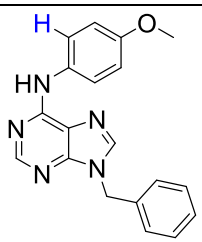
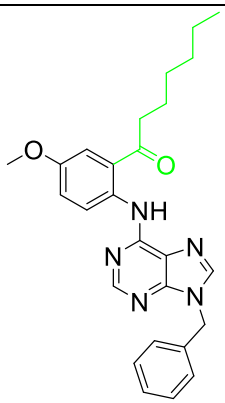
Although the rules set above seem rather approximate, they are consistent with the given examples, and further work aimed at increasing the accuracy and the scope of the algorithm is on-going. Based on the suggested rules, the predicted reactive centers for eight commercially available aromatic and heteroaromatic substrates as well as the most likely mechanisms are shown in Table 2.

In order to test the algorithm and the value of the threshold, an additional set of six examples was analysed, and the results are shown in Table 3. Both selectivity and mechanism were correctly identified by the algorithm applying the previously set threshold to the SnAr intermediate stability (intermediates 5), which is shown in Table 4.

Table 3. A comparison of the published experimental results with the computational predictions for the $Pd(OAc)_2$-catalysed reactions.

Protons marked green are those that react under the conditions reported in the literature. Protons marked red and blue are the predicted active centers via the acidity and the electrophilic mechanisms respectively.

No [ref]	Starting molecule	Exp. Cond.	Predicted active center		Experimentally isolated product
			Via acidity mechanism	*Via* electrophilic mechanism	

1 [38]		$Pd(OAc)_2$, TBHP, toluene, 120 °C, 6h			
2 [39]		$Pd(OAc)_2$, TBHP, DCE 80 °C, 16h		 **H1:0.0** H2:26.0 H3:27.5	
3 [40]		$Pd(OAc)_2$, TBHP, toluene, TFA, 40 °C, 3h	 **H1:0.0** H2:1.9 H3:7.6	 **H1:0.0** H2:3.2	
4 [41]		$Pd(OAc)_2$, Toluene, TBHP, 110°C, 5h		NO STABLE INTERMEDIATE	
5 [42]		$Pd(OAc)_2$, Dioxane, AcOH, DMSO, TBHP, 110°C, 24h			

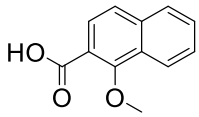
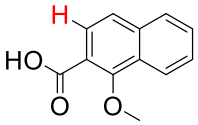
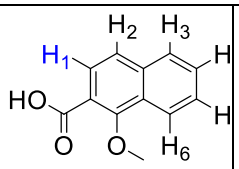
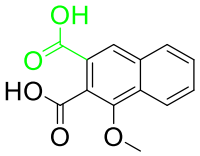
6 [43]		Ag_2CO_3, $Pd(OAc)_2$, NAoaC, CO, 1,4-dioxane, 130 °C, 18h		 **H1:0.0** H2:2.6 H3: 2.2 H4:2.5 H5:2.2 H6:2.8	

Table 4 A mechanism threshold tested based on the literature examples. Gibbs free energy of Pd-substrate is obtained by calculating the Gibbs free energy difference between starting molecule and the most probable intermediate in Hartree. The distance between palladium atom and the corresponding carbon are measured based on the web-based molecular structure virtualization, which can be accessed through https://leyscigateway.ch.cam.ac.uk/index.php.

Entry	Gibbs free energy of Pd-substrate / Hartree	d(Pd-C) / Å	Relative stability	Predicted mechanism	Reported mechanism
1	-355.5652	2.3005	3.0777	PA/ S_EAr	PA/ S_EAr
2	-355.5577	2.3778	-1.6369	PA	PA
3	-355.5626	2.1345	1.4558	PA/ S_EAr	PA/ S_EAr
4	No stable intermediate	-	-	PA	PA
5	355.5717	7.1781	2.2326	S_EAr	S_EAr
6	-355.5254	2.1680	-21.9298	PA	PA

Conclusions

A computational algorithm rationalising the existing palladium catalysed C-H activation reactions has been developed. Computational threshold to distinguish between the two main mechanisms, proton abstraction (PA) and electrophilic aromatic substitution (S_EAr) mechanism, has been proposed and tested against the literature experimental data. This model can give not only the most probable reactive site and the appropriate mechanism, but also provides information for further kinetic studies and process development, thus contributing to the development of robust new chemical transformations.

Acknowledgements

This project was in part supported by EPSRC grant EP/K009494/1 (ML) and the National Research Foundation, Prime Minister's Office, Singapore under its CREATE programme, project "Cambridge Centre for Carbon Reduction in Chemical Technology" (LC and AL).

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In silico rationalisation of selectivity and reactivity in Pd-catalysed C-H activation reactions

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Supporting Information

Table of Contents

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1. Computational approach to C-H reactivity analysis and prediction

Chemical reactivity is simultaneously influenced by many factors including catalyst, reactants, reaction conditions, etc.[10] The key idea is to achieve an accurate as well as efficient reaction prediction, and our approach is based on organic chemistry mechanism rules and molecular modelling, which leads to a mechanism-based method. In the following section, the technical details of how to achieve the result in the main article is explained and illustrated.

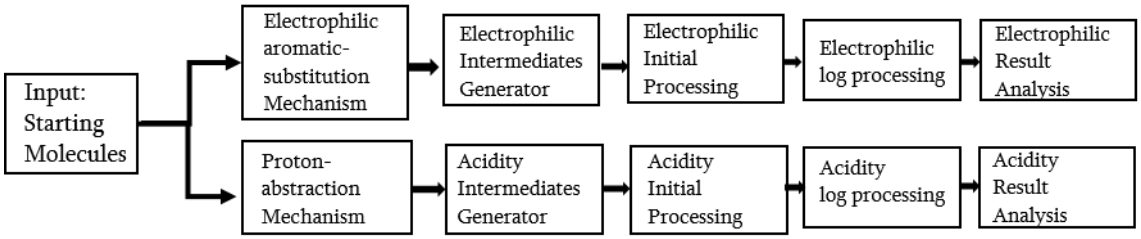
1.1 Computational methods

The software packages used in this research project include Python 2.7.9 for reaction prediction algorithm; Chemcraft, MarvinSketch (64bit), MarvinSpace (64bit) and OpenBabel 2.3.2 for starting molecular structure and its conformation generating; Gaussian 09 and NWChem 6.6 for DFT calculation.

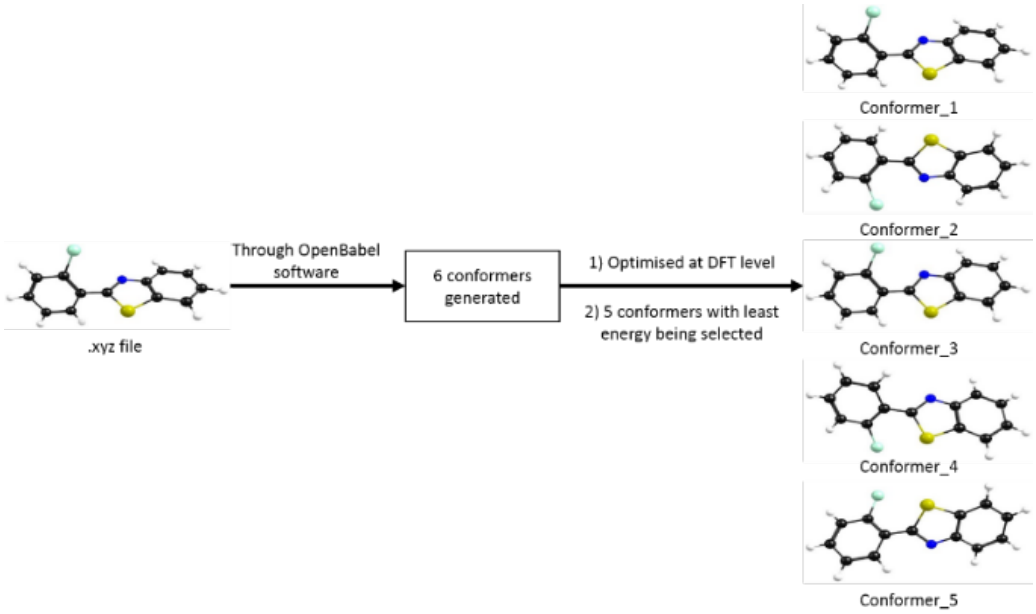
All the computational calculations were performed on either the Sustainable Reaction Engineering Group' machine *Gtuhanai* with 1 node containing 16 Intel® Xeon® E5-2650 cores (@2.60 GHz, 64GB RAM per node), or the Cambridge High Performance Computing Cluster *Darwin* with 600 nodes each containing 16 Intel® Xeon® E5-2670 cores (@2.60GHz, 64GB RAM per node).

1.2 Intermediates generation based on different mechanisms

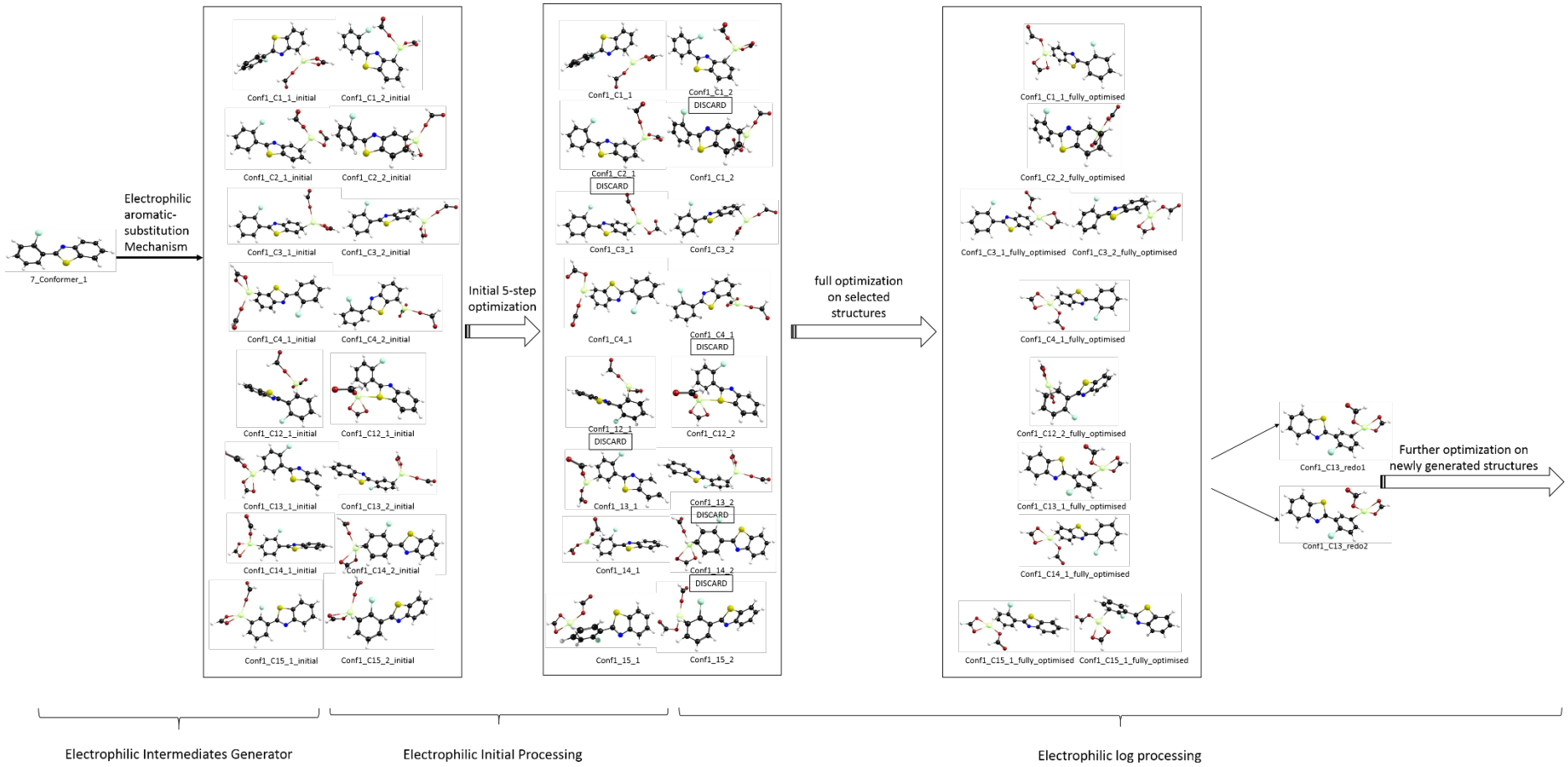
Within this algorithm, intermediates for different mechanisms will be automatically generated. At first, the structure of starting molecules will be drawn in MarvinSketch (64bit) software and will be saved as a xyz file. Also, with OpenBabel 2.3.2, an open source chemistry toolbox, the xyz format file will be converted into different file formats for further calculation: smiles format, mol2 format, sdf format as well as conf format which contains conformations of the starting structure. Next, the program will only pick five conformers of the starting molecule with lowest Gibbs free energy and save it as input for the follow-up calculation. And then, depending on mechanisms, the starting structures will go through different paths within this program to generate possible intermediates. The workflow is illustrated in the scheme below.



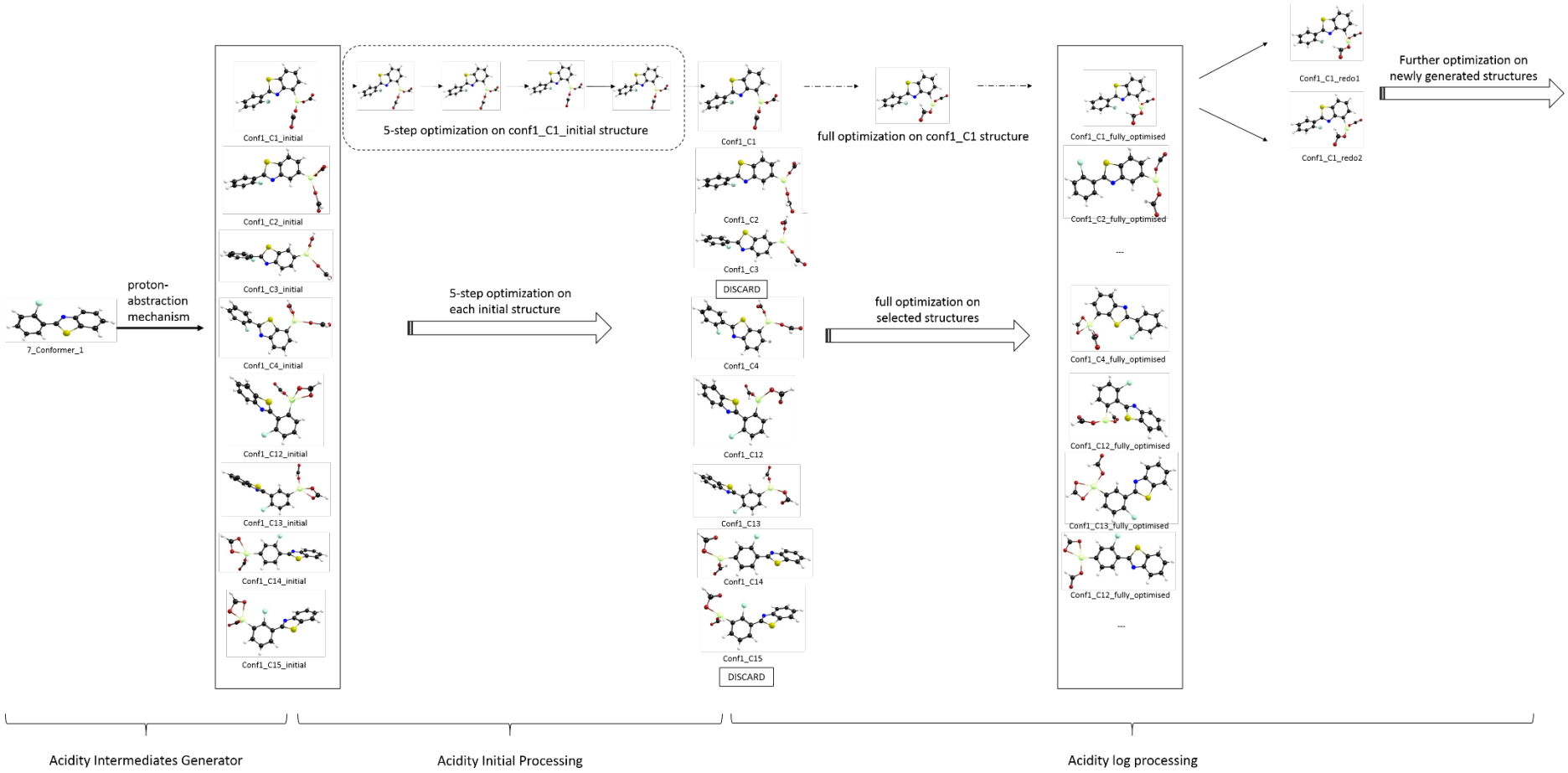
Scheme 1. Workflow for the computational algorithm.



Scheme 2. Illustration of starting structure automatic conformer generation.



Scheme 3. Illustration of intermediates generation of the S_EAr mechanism and the following optimization on DFT level procedures.



Scheme 4. Illustration of intermediates generation of the PA mechanism and the following optimization on DFT level procedures.

1.3 Exchange and correlation functionals evaluation for DFT calculation

As mentioned in the previous chapter, varying functionals and basis sets will cause changes in calculation of thermodynamic properties of molecules. In order to choose functionals suitable for transition metal catalysed intermediates calculation, palladium(II)-catalysed intermediates in particular, a crosscheck for different functionals need to be conducted.

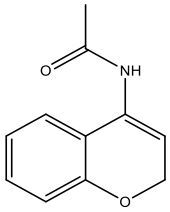
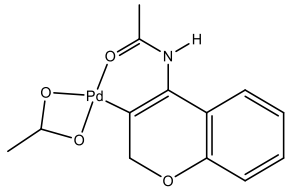
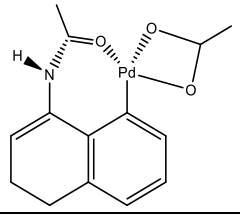
Four different exchange and correlation functionals have been chosen for testing, respectively wB97xD, B3LYP, TPSSh and M06-2X (Table1). Ten examples from Reaxys database were chose to check exchange and correlation functionals for the calculation at density functional theory level. For those ten examples[3], starting molecules, possible intermediates and final product were calculated with the four different functionals mentioned above.

Table 1. Introduction for four different exchange and correlation functionals

Functionals	Description
wB97xD[i]	The latest functional from Head-Gordon and co-workers, which includes the version of Grimme's D2 dispersion.
B3LYP[ii]	The hybrid functional using Becke 3 parameters and the Lee-Yang-Parr functional.
TPSSh[iii]	The hybrid functional using the TPSS functionals (The exchange functional of Tao, Perdew, Staroverov, and Scuseria, 2003).
M06-2X[iv]	The hybrid functional of Truhlar and Zhao (2008).

These four functionals were implemented for DFT calculation, and then results were compared. As can be seen in Table 2, in this palladium catalysed system, different exchange and correlation functionals only cause minor influence to the results. In this case, the most popular and well-developed functional B3LYP functional[v] was selected for further calculation in this project.

Table 2. Result for functionals evaluation of example_6[50g]. Uncorrected Gibbs free energy (E), corrected Gibbs energy (G) and enthalpy (H) were calculated based on different exchange and correlation functionals.

		Starting molecule	Intermediate 1	Intermediate 2
				
Thermal correction to enthalpy		0.2154	0.2644	0.2620
Thermal correction to Gibbs free energy		0.1641	0.1985	0.1938
WB97xD	E	-631.0114	-986.6362	-986.5765
	H	-630.7960	-986.3718	-986.3146
	G	-630.8473	-986.4377	-986.3828

[3] Examples selected here consistent with Table 3.

B3LYP	E	-631.1776	-987.0960	-987.0395
	H	-630.9622	-986.8317	-986.7775
	G	-631.0135	-986.8975	-986.8457
TPSSh	E	-631.2561	-987.1196	-987.0540
	H	-631.0407	-986.8552	-986.7920
	G	-631.0920	-986.9211	-986.8602
M06-2X	E	-630.9771	-986.6908	-986.6414
	H	-630.7616	-986.4264	-986.3794
	G	-630.8130	-986.4923	-986.4476

1.4 Geometry optimization and electronic structure determination at DFT level

Once the possible intermediates were generated based on the different mechanisms, a two-step optimization procedure was carried out in order to balance the computational time and the accuracy of the results.

At first, geometry of all generated intermediates was optimized over 5 iterations[4]. Then the structures having higher energy by a value of 10 $kcal \cdot mol^{-1}$ as compared to the least energy intermediate were crossed out, the remaining structure were then fully optimized and thermochemistry applied[5]. The geometry of the structures was considered stable and correct only if no negative vibrational frequencies were found after calculating force constants and vibrational frequencies. Moreover, for the unstable intermediates, the algorithm would automatically generate[6] another structure based on the former calculation as a starting point for further optimization.

All calculations were performed with the open source NWChem software package[vi] by using Becke's three-parameter hybrid B3LYP functional, while the molecular orbitals are expanded in triple-zeta all electron 6-31 set with added polarization and diffuse functions [6-31g(d,p)].[vii] B3LYP functional has been proven to give accurate description of geometries, frequencies, relative stabilities of different conformers and the energy profile calculation, not only in previous literatures,[viii] but also in the benchmarking studies done previously using Gaussian 09 software.

1.5 Selectivity analysis

Within the results analysis step, a text parsing and geometry operation module, coded in Python, has been developed to read and analyse the data from NWChem plain text outputs. By comparing Gibbs free energies of each intermediates, most reactive site for the given structure can be predicted which corresponds to the most stable intermediates. Moreover, the expected regioselectivity can be calculated based on the relative energy of intermediates using the Boltzmann distribution equation $ratio = e^{-\Delta E/RT}$.[48]

[4] As Initial Processing step shown in Scheme 3.

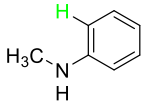
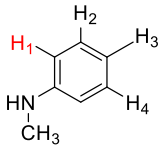
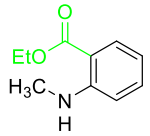
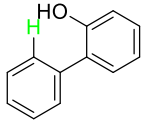
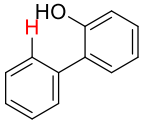
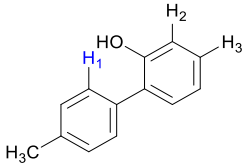
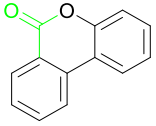
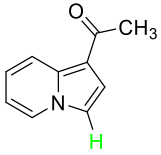
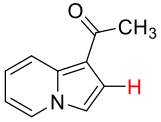
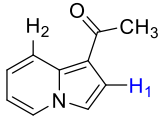
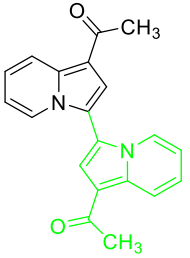
[5] As Log Process step shown in Scheme 3.

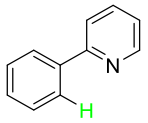
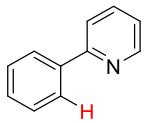
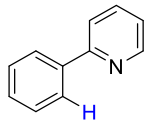
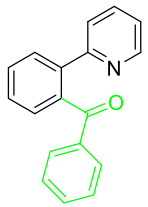
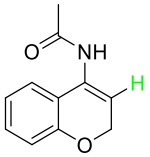
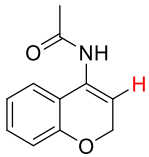
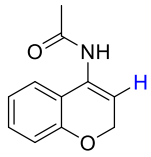
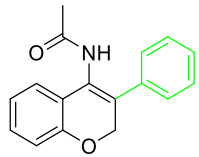
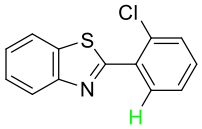
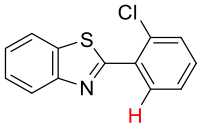
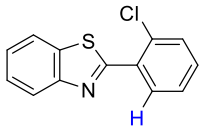
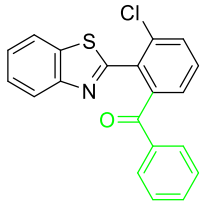
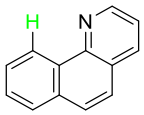
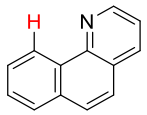
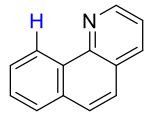
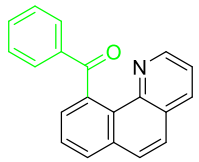
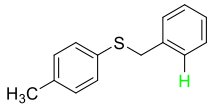
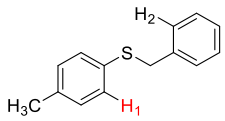
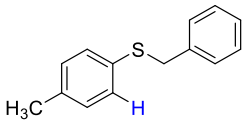
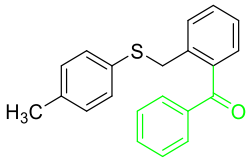
[6] The process of generating two new structure as starting point for further optimization is carried out within NWChem software.

2. Comparison of the published experimental results with the computational predictions for the $Pd(OAc)_2$-catalysed reactions

Table S3. Comparison of the published experimental results with the computational predictions for the $Pd(OAc)_2$-catalysed reactions.

Protons marked green are those that react under the conditions reported in the literature. Protons marked red and blue are the predicted active centers via the acidity and the electrophilic mechanisms respectively.

Entry [ref]	Starting molecule	Experimental conditions	Predicted active center				Experimentally isolated product
			Via acidity mechanism		*Via* electrophilic mechanism		
1 [23]		CO, EtOH, $Pd(OAc)_2$, $Cu(OAc)_2$, KOAc, DMF, KI, 100 °C, 13h		**H1:0.0** H2:1.2 H3:0.4 H4:2.1	NO STABLE INTERMEDIATE		
2 [24]		CO, $Pd(OAc)_2$, $Cu(OAc)_2$, PivOH, mesitylene, 120 °C, 6h				**H1:0.0** H2:1.2 H3:2.0	
3 [25]		$Cu(OAc)_2$, $Pd(OAc)_2$, K_2CO_3, DMF, 60 °C, 0.6h				**H1:0.0** H2:2.9	

4 [26]		$PhCOCO_2H$ $Pd(OAc)_2$, $K_2S_2O_8$, MeCN, 25 °C, 16h					
5 [27]		$PhSi(OMe)_3$, $Pd(OAc)_2$, AgF, dioxane, 80 °C, 16h					
6 [29]		Ph-CHO, $Pd(OAc)_2$, TBHP, toluene, 110 °C, 5h					
7 [28]		Ph-CHO, $Pd(OAc)_2$, Xylene, O_2 120 °C, 24h					
8 [29]		$PhCOCO_2H$, $Pd(OAc)_2$, Ag_2CO_3, DMF, 120 °C, 24h		**H1: 0.0** H2: 10.0			

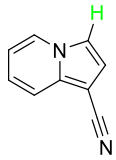
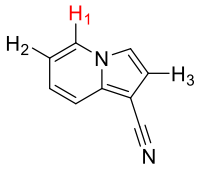
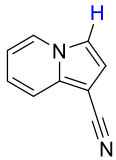
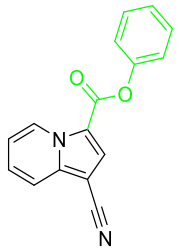
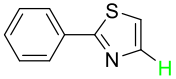
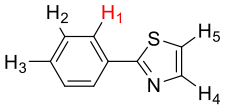
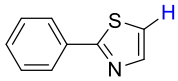
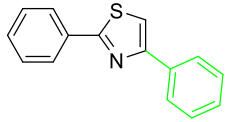
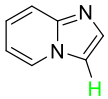
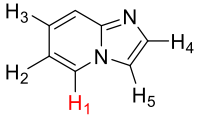
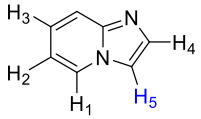
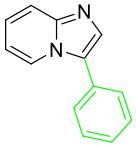
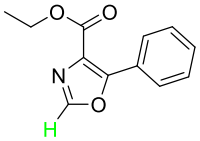
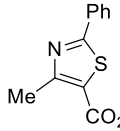
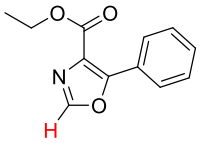
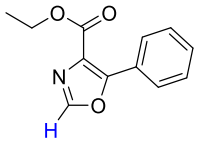
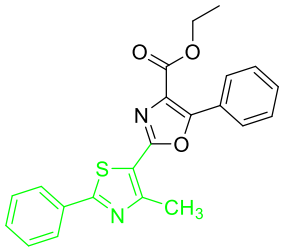
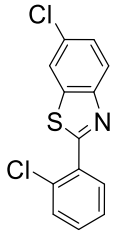
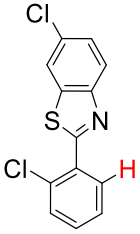
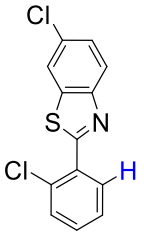
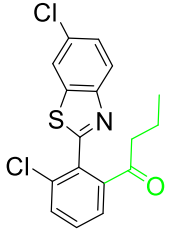
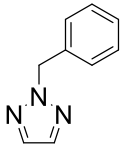
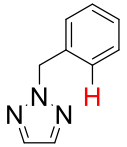
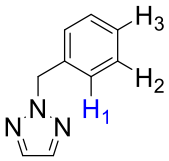
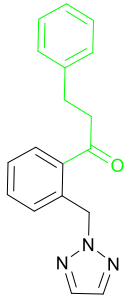
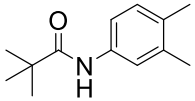
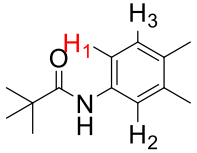
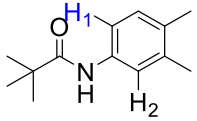
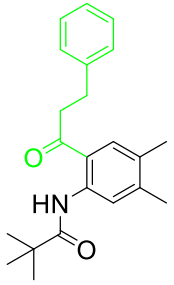
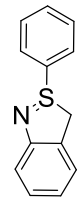
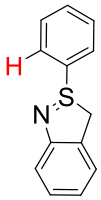
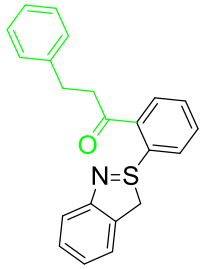
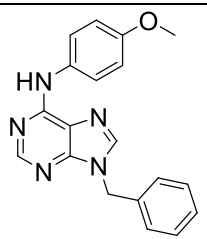
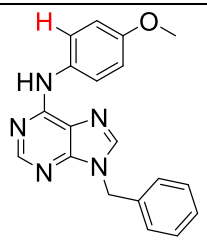
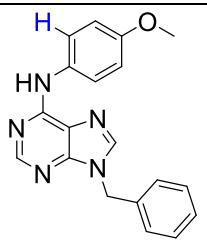
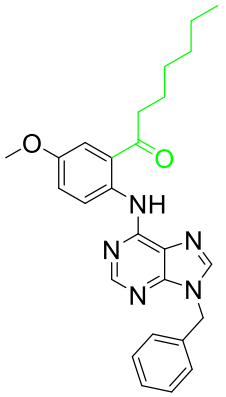
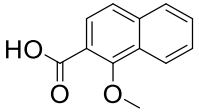
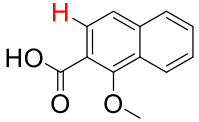
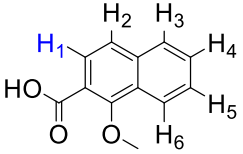
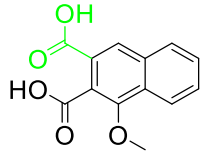
9 [30]		H-COOPh, $Pd(OAc)_2$, I_2, K_2CO_3, DMF, 100 °C, 12h		**H1:0.0** H2:1.3 H3:1.0			
10 [31]		$PhB(OH)_2$, $Pd(OAc)_2$, TEMPO, phen, DMAc, O_2 100 °C, 48h		**H1:0.0** H2:13.8 H3:13.8 H4:14.0		**H1:0.0** H2:5.8	
11 [32]		Benzene, $Pd(OAc)_2$, O_2, HOAc, DMA, 130 °C, 20h		**H1:0.0** H2:16.4 H3:12.9 H4:8.2 H5:14.2		H1:8.4 H2:11.1 H3:10.2 H4:1.4 **H5:0.0**	
12 [33]		 , $Pd(OAc)_2$, $CuCO_3$, dioxane, DMSO, 140 °C, 16h					

Table S2. Comparison of the published experimental results with the computational predictions for the $Pd(OAc)_2$-catalysed reactions.

Protons marked green are those that react under the conditions reported in the literature. Protons marked red and blue are the predicted active centers via the acidity and the electrophilic mechanisms respectively.

Entry [ref]	Starting molecule	Experimental conditions	Predicted active center				Experimentally isolated product
			Via acidity mechanism		*Via* electrophilic mechanism		
1 [ix]		$Pd(OAc)_2$, TBHP, toluene, 120 °C, 6h					
2 [x]		$Pd(OAc)_2$, TBHP, DCE 80 °C, 16h				**H1:0.0** H2:26.0 H3:27.5	
3 [xi]		$Pd(OAc)_2$, TBHP, toluene, TFA, 40 °C, 3h		**H1:0.0** H2:1.9 H3:7.6		**H1:0.0** H2:3.2	

4 [xii]		$Pd(OAc)_2$, Toluene, TBHP, 110°C, 5h			NO STABLE INTERMEDIATE		
5 [xiii]		$Pd(OAc)_2$, Dioxane, AcOH, DMSO, TBHP, 110°C, 24h					
6[xiv]		Ag_2CO_3, $Pd(OAc)_2$, NAoaC, CO, 1,4-dioxane, 130 °C, 18h				**H1:0.0** H2:2.6 H3: 2.2 H4:2.5 H5:2.2 H6:2.8	

3. A mechanism threshold

3.1 A mechanism threshold calibrated based on literature examples

Entry	Gibbs free energy of Pd-substrate / Hartree	d(Pd-C) / Å	Relative stability	Predicted mechanism	Reported mechanism
1	No stable intermediate	-	-	PA	-
2	-355.5520	2.2246	-5.2968	PA	PA
3	-355.5715	2.1025	6.9666	S_EAr	S_EAr
4	-355.5547	2.3306	-3.5861	PA	PA
5	-355.5780	2.2049	11.0356	PA	PA
6	-355.5604	2.3097	0.0000	PA	PA
7	-355.5656	2.2591	3.2702	PA/ S_EAr	PA
8	-355.5506	2.2417	-6.1591	PA	PA
9	-355.5737	2.1199	8.3541	S_EAr	S_EAr
10	-355.5682	2.2210	4.8918	PA/ S_EAr	S_EAr
11	-355.5730	2.1240	7.9101	S_EAr	S_EAr
12	-355.5508	2.3204	-6.0532	PA	PA

3.2 A mechanism threshold tested on 6 literature examples

Entry	Gibbs free energy of Pd-substrate / Hartree	d(Pd-C) / Å	Relative stability	Predicted mechanism	Reported mechanism
1	-355.5652	2.3005	3.0777	PA/ S_EAr	PA
2	-355.5577	2.3778	-1.6369	PA	PA
3	-355.5626	2.1345	1.4558	PA/ S_EAr	PA
4	No stable intermediate	-	-	PA	PA
5	355.5717	7.1781	2.2326	S_EAr	S_EAr
6	-355.5254	2.1680	-21.9298	PA	PA

3.3 Using the mechanism threshold to predict on the new starting molecules

Entry	Gibbs free energy of Pd-substrate / Hartree	d(Pd-C) / Å	Relative stability	Predicted mechanism
1	-355.5795	2.2532	11.9884	S_EAr
2	-355.5740	2.2991	8.5297	S_EAr
3	-355.5480	2.1296	-7.7624	PA
4	-355.5560	2.2834	-2.7908	PA

5	No stable intermediate	-		PA
6	-355.5666	2.1634	-3.8766	PA/ S_EAr
7	No stable intermediate	-		PA
8	-355.5435	2.2045	-10.5740	PA

4. Cartesian coordinates, uncorrected electronic energies and screenshots of 3D representations of computed structures

4.1 Result of literature validation

No.	Cartesian coordinates, energies			
1	C	0.366954790	-1.596401070	-0.061240220
	C	1.166616020	-2.758535870	-0.017844030
	C	2.543138750	-2.620606200	0.274682630
	C	3.098252890	-1.375077300	0.536224960
	C	2.301879980	-0.219050880	0.527116250
	C	0.953235060	-0.363618240	0.197152990
	N	0.638630670	-4.018673480	-0.239707770
	C	-0.706607760	-4.226199520	-0.736990990
	H	-0.686214900	-1.649225120	-0.312534290
	H	3.168101100	-3.509576950	0.312829830
	H	4.155627630	-1.299082950	0.776216000
	H	2.734246490	0.747058770	0.791467530
	H	1.310831560	-4.728832260	-0.480709910
	H	-0.870780860	-5.297593100	-0.872159200
	H	-0.898663200	-3.722448610	-1.697357090
	H	-1.447483410	-3.866028340	-0.014366360
	Pd	0.097337040	1.356618410	0.008617660
	O	-1.410419960	3.051925890	-0.178470820
	C	-2.285528910	2.153860510	-0.089467230
	C	-3.761145430	2.456820370	-0.144728650
	O	-1.930575960	0.918170190	0.053503980
	H	-3.919397150	3.530791940	-0.245647790
	H	-4.247480850	2.089663060	0.763606930
	H	-4.212677390	1.932592020	-0.992282600
	Total DFT energy = -682.060622205886			
	One electron energy = -2704.074397721121			
	Coulomb energy = 1243.576182775515			
	Exchange-Corr. energy = -89.789822198948			
	Nuclear repulsion energy = 868.227414938667			
2	C	2.798697960	-0.271975490	-1.311267610
	C	2.549897200	-0.197307060	-2.677020580

	C	1.244714540	-0.033915360	-3.159313290
	C	0.205363010	0.067992830	-2.224290870
	C	0.441228430	0.008853030	-0.848162990
	C	1.757810520	-0.185837070	-0.365710870
	C	1.335442750	0.318748170	2.071105260
	C	2.069040000	-0.345585090	1.077554940
	C	3.104669160	-1.181144170	1.533009390
	C	3.378683360	-1.333610560	2.891523520
	C	2.618137410	-0.656414970	3.846207820
	C	1.583411030	0.182045250	3.429436860
	C	0.965060120	0.058494090	-4.640504510
	O	0.262663990	1.169558610	1.699847390
	H	3.822507390	-0.384231730	-0.965048650
	H	3.379058100	-0.267256600	-3.376733450
	H	-0.817305980	0.175993880	-2.576209260
	H	3.680024640	-1.743541110	0.805060420
	H	4.179116080	-1.997132650	3.204756950
	H	2.821739720	-0.780527670	4.905083580
	H	0.968538050	0.729178290	4.136222500
	H	1.690486270	-0.518943810	-5.221843620
	H	-0.036194370	-0.311112220	-4.880261590
	H	1.020962570	1.097312220	-4.990288800
	H	0.618009020	1.896951470	1.162763400
	Pd	-1.108364630	0.225853410	0.354093290
	O	-3.229305580	0.181814890	1.151918780
	C	-3.521163570	-0.365994480	0.056020240
	C	-4.923035210	-0.806220840	-0.274857670
	O	-2.592045960	-0.573423850	-0.819216990
	H	-5.610346920	-0.500318420	0.514363640
	H	-4.946597780	-1.894847200	-0.384904500
	H	-5.231611310	-0.374441520	-1.231298300
		Total DFT energy =	-933.019972849024	
		One electron energy =	-4393.738027331972	
		Coulomb energy =	2040.164476919358	
		Exchange-Corr. energy =	-125.178495785542	
		Nuclear repulsion energy =	1545.732073349132	
3	C	1.120776490	-0.015203040	-1.497026560
	C	2.446372220	-0.408383270	-1.644897820
	C	2.709467040	-1.646783190	-2.231625820
	C	1.661963360	-2.483409070	-2.648364000
	C	0.352987060	-2.073890610	-2.476156590
	N	0.115743740	-0.862576650	-1.922175120
	C	0.469754890	1.178855420	-0.936498310
	C	-0.917757170	1.079989300	-1.257713140
	C	-1.156105200	-0.270683530	-1.595817630

	C	1.241176980	2.383771000	-0.479605970
	C	0.469336310	3.610178930	-0.059537750
	O	2.457936840	2.323740620	-0.466056530
	H	3.226066260	0.261541720	-1.307364320
	H	3.737616690	-1.965609450	-2.368173900
	H	1.859102120	-3.445451460	-3.105824550
	H	-0.511027700	-2.661242880	-2.763227990
	H	-1.666262220	1.858962030	-1.196642240
	H	-2.059317970	-0.732993070	-1.969284250
	H	1.172113390	4.361578340	0.300370540
	H	-0.090950320	4.022417400	-0.907226820
	H	-0.249500120	3.373145860	0.732284260
	Pd	-0.790283760	-0.015037070	0.577278360
	O	-0.313447320	0.046189600	2.604757100
	C	-1.257818710	-0.781080210	2.864424610
	C	-1.586165840	-1.203607740	4.254043170
	O	-1.919631500	-1.212112050	1.850929600
	H	-0.785567480	-0.915632670	4.936618420
	H	-1.748689340	-2.284021700	4.284363340
	H	-2.517891540	-0.717984690	4.563897860
	Total DFT energy = -872.006968659128 One electron energy = -3949.954754955727 Coulomb energy = 1818.257383733277 Exchange-Corr. energy = -114.721854314071 Nuclear repulsion energy = 1374.412256877394			
4	N	-0.215679856	-1.489798583	-0.041262231
	C	-1.126365204	-2.474898174	-0.050081721
	C	-0.760776117	-3.815616995	-0.090532157
	C	0.599574968	-4.130665898	-0.123100815
	C	1.541802048	-3.107770192	-0.114047937
	C	1.119900987	-1.773264547	-0.072254803
	C	1.962611628	1.845808874	0.014617903
	C	1.256018605	0.643845514	-0.007371174
	C	1.964944506	-0.580490403	-0.055663970
	C	3.367685335	-0.585116311	-0.082223757
	C	4.062567031	0.621813166	-0.060468137
	C	3.361581699	1.831968825	-0.011979845
	H	-2.164014055	-2.158115210	-0.024018681
	H	-1.524400213	-4.584759669	-0.096596983
	H	0.922680172	-5.166769234	-0.155360746
	H	2.601455623	-3.334234506	-0.138604867
	H	1.423109232	2.787762263	0.052483131
	H	3.918759991	-1.521312093	-0.119978976
	H	5.148150767	0.621646581	-0.081339401
	H	3.909036465	2.770883626	0.005308086

	Pd	-0.700926435	0.488833003	0.017842429
	O	-2.907432311	0.865450128	0.036111311
	C	-2.616338151	2.097123246	0.069765850
	C	-3.685174962	3.159129755	0.105716147
	O	-1.382486940	2.459725075	0.074754462
	H	-4.675523410	2.704393139	0.067765174
	H	-3.553909265	3.841609176	-0.739086359
	H	-3.583023433	3.750075112	1.021029880
	Total DFT energy = -834.556592550964			
	One electron energy = -3747.570940083952			
	Coulomb energy = 1735.537245742924			
	Exchange-Corr. energy = -111.486631416948			
	Nuclear repulsion energy = 1288.963733207012			
5	C	-0.553029702	1.873053829	0.159595598
	C	-1.208795568	2.875308183	-0.569750750
	C	-1.728448473	2.666634808	-1.856601709
	C	-1.591128300	1.401757565	-2.435818911
	C	-0.940229171	0.381610241	-1.736503874
	C	-0.432441420	0.623875687	-0.463276330
	C	-0.017486397	2.150760387	1.543548121
	C	-0.751362371	-1.014675731	-2.316255809
	C	-2.401297133	3.795130903	-2.603907354
	H	-1.319854050	3.857093538	-0.112422458
	H	-1.993296765	1.208625755	-3.429287970
	H	-0.223895307	3.183067140	1.839617765
	H	-0.464122209	1.481233743	2.284634399
	H	1.062861606	1.985081658	1.592400707
	H	-0.335055703	-1.772344837	-1.599938942
	H	-1.701412701	-1.460873278	-2.627711969
	H	-0.063446087	-1.022568093	-3.167368092
	H	-1.664283033	4.442442316	-3.095878997
	H	-2.987270923	4.428395518	-1.930286307
	H	-3.072658329	3.417052016	-3.380588952
	Pd	0.372702436	-1.058988505	0.125753332
	O	1.414211804	-2.759727881	1.197572353
	C	1.593922620	-1.934371820	2.130099244
	C	2.315374518	-2.296694719	3.401387205
	O	1.150650736	-0.724928063	2.008009109
	H	2.636491179	-3.338080937	3.366181572
	H	1.653897770	-2.138660961	4.258313241
	H	3.182466365	-1.642545966	3.531753142
	Total DFT energy = -705.355170165722			
	One electron energy = -3004.492695650592			
	Coulomb energy = 1390.105675109587			

	Exchange-Corr. energy = -94.851709755349			
	Nuclear repulsion energy = 1003.883560130632			
6	C	-2.944905099	-0.801838578	0.794034272
	C	-4.003727495	-1.690138527	0.932004645
	C	-3.879523615	-3.039079916	0.551000307
	C	-2.689524740	-3.531014623	0.021978095
	C	-1.620532351	-2.643005245	-0.119289686
	C	-1.742889508	-1.290701940	0.261678949
	N	-0.585825991	-0.561232267	0.050311444
	S	-0.006044828	-2.948569334	-0.745877661
	C	0.407335558	-1.270988024	-0.465655823
	C	1.647429849	-0.553496224	-0.706122691
	C	2.855148594	-1.025556304	-1.235602735
	C	1.558645231	0.817689500	-0.329850684
	C	2.658334504	1.655826039	-0.491205707
	C	3.848983949	1.150066101	-1.023214694
	C	3.954072994	-0.191631746	-1.398049567
	Cl	3.038533541	-2.748150647	-1.733144604
	H	-3.023855010	0.241330210	1.083070621
	H	-4.944990361	-1.337180742	1.341540898
	H	-4.724947983	-3.709474199	0.670859959
	H	-2.596649794	-4.571761647	-0.270891522
	H	2.584098927	2.699644832	-0.202070492
	H	4.708231962	1.803012193	-1.149868400
	H	4.873676900	-0.589281465	-1.810752892
	Pd	-0.173967830	1.399300224	0.404175825
	O	-1.867585841	2.555082868	1.267861856
	C	-1.094063696	3.558670854	1.252623192
	C	-1.558551037	4.916604023	1.706996580
	O	0.107895103	3.420765623	0.816753756
	H	-2.448576422	4.823277847	2.330709651
	H	-1.804794409	5.522766825	0.828453442
	H	-0.759745333	5.426403119	2.250245234
	Total DFT energy = -1323.316594257154			
	One electron energy = -5596.401108171238			
	Coulomb energy = 2546.842361824607			
	Exchange-Corr. energy = -150.610293229781			
	Nuclear repulsion energy = 1876.852445319258			
7	C	0.921424699	-0.851710359	-0.374906179
	C	1.643342007	-1.981622321	-0.724112865
	C	2.985139768	-1.852759088	-1.158313011
	C	3.614048301	-0.619161882	-1.248814015
	C	2.908975286	0.555207637	-0.901239709
	C	1.569341702	0.403337227	-0.469943873
	C	0.807928085	1.545888831	-0.106747640

	C	3.449447242	1.889136955	-0.953022031
	C	2.709130122	2.984687057	-0.601577481
	C	1.346132781	2.851107796	-0.160876350
	N	-0.472117564	1.290468573	0.294793797
	C	-1.256745377	2.305796991	0.652780089
	C	-0.801105932	3.635150196	0.628150699
	C	0.496178449	3.909361909	0.222917541
	H	1.187443689	-2.965896713	-0.667071791
	H	3.536596490	-2.749946252	-1.428240663
	H	4.644898176	-0.550213738	-1.585324390
	H	4.477290596	2.018262818	-1.282729461
	H	3.143345985	3.979296651	-0.650767152
	H	-2.264820998	2.051040639	0.963689186
	H	-1.474955531	4.429977546	0.927946544
	H	0.861551574	4.932619837	0.199085847
	Pd	-0.943877372	-0.716985059	0.261455678
	O	-3.036055721	-1.135222785	0.923503942
	C	-2.768670183	-2.356019881	0.721963400
	C	-3.780234405	-3.439552685	0.991082681
	O	-1.601296599	-2.688468185	0.294958154
	H	-4.772571289	-3.007396645	1.125317010
	H	-3.496950425	-3.978618987	1.901315122
	H	-3.784926355	-4.160098155	0.169377196
	Total DFT energy = -910.785828638370 One electron energy = -4286.683389188997 Coulomb energy = 1990.265481243157 Exchange-Corr. energy = -122.380694558873 Nuclear repulsion energy = 1508.012773866344			
8	C	1.787571489	1.140436663	-1.897550661
	C	2.246580311	0.174798850	-2.791739983
	C	1.399765530	-0.318497768	-3.787879164
	C	0.092454589	0.159425859	-3.885765049
	C	-0.366690025	1.127454992	-2.991340508
	C	0.474933903	1.628417568	-1.989970198
	C	-0.020412723	2.669471357	-1.031194634
	S	-0.624983096	2.050091454	0.637041776
	C	-1.827022341	0.753563801	0.263571890
	C	-3.133511014	0.829182278	-0.207997711
	C	-1.207641379	-0.439603966	0.614113743
	C	-1.907037116	-1.637600434	0.479192187
	C	-3.228934954	-1.609573355	-0.000460435
	C	-3.822293254	-0.379378330	-0.341069559
	C	-4.022188584	-2.891117406	-0.116904187
	H	2.448508634	1.513308922	-1.119590095
	H	3.265841522	-0.191241096	-2.711858507

	H	1.758986657	-1.069956656	-4.484931704
	H	-0.570455350	-0.218365256	-4.658648794
	H	-1.385394399	1.497178806	-3.071326125
	H	0.768373038	3.371864883	-0.747103076
	H	-0.854009316	3.242539625	-1.444715380
	H	-3.601310370	1.775517995	-0.465541542
	H	-1.442764833	-2.585189614	0.739249821
	H	-4.844079487	-0.370782512	-0.711873472
	H	-4.768041585	-2.831170144	-0.915250735
	H	-3.371138058	-3.745890696	-0.321728454
	H	-4.558784475	-3.106752267	0.815558451
	Pd	0.608293005	0.046601900	1.193059318
	O	2.742271118	0.150577302	1.854301957
	C	2.686538487	-1.107959097	1.971558005
	C	3.874700429	-1.911042617	2.435972160
	O	1.594153342	-1.727142146	1.692539140
	H	4.728566285	-1.256851265	2.615502527
	H	4.130056445	-2.660940543	1.681387894
	H	3.617870548	-2.447056677	3.354603544
	Total DFT energy = -1295.302914717103 One electron energy = -5498.334435838654 Coulomb energy = 2502.619977254335 Exchange-Corr. energy = -148.468842627926 Nuclear repulsion energy = 1848.880386495142			
9	C	1.813607530	-2.200189880	-1.051155410
	C	1.170951140	-0.979629330	-1.206941980
	N	-0.053720090	-0.926591970	-1.838529220
	C	-0.679439030	-2.028620850	-2.315730790
	C	-0.059715080	-3.256592350	-2.185806640
	C	1.191219760	-3.342541480	-1.552647310
	C	-0.532745380	0.431179740	-1.810422290
	C	1.505171760	0.392539050	-0.811345090
	C	0.546964700	1.256420240	-1.429810070
	C	2.770337780	0.753322840	-0.269789500
	N	3.811708030	1.015135540	0.176015320
	H	2.777206840	-2.240100830	-0.556309890
	H	-1.643672140	-1.880537500	-2.786755260
	H	-0.548965980	-4.138832070	-2.580124830
	H	1.679261940	-4.306352650	-1.454784490
	H	-1.418501440	0.686517320	-2.374702220
	H	0.613554280	2.330594690	-1.541287930
	Pd	-0.441414040	0.714838720	0.395714640
	O	-0.409521060	0.751097830	2.472643960
	C	-1.676413900	0.942351140	2.503423420
	C	-2.422725290	1.155198250	3.771823890

	O	-2.262232820	0.956170100	1.358037880
	H	-1.782418600	0.939764170	4.627915790
	H	-3.313271770	0.521314050	3.787295680
	H	-2.756607090	2.197198840	3.818386520
	Total DFT energy = -811.193021369581			
	One electron energy = -3366.425576437523			
	Coulomb energy = 1547.477503449683			
	Exchange-Corr. energy = -106.330579417900			
	Nuclear repulsion energy = 1114.085631036159			
10	N	-2.950914400	-0.649699220	0.020924690
	C	-3.061637510	-2.011087330	0.139192340
	C	-2.047126760	-2.760590860	-0.399001900
	S	-0.927608760	-1.743893480	-1.239566540
	C	-1.911508000	-0.307522300	-0.665871880
	C	-1.268502550	1.000887310	-0.728864370
	C	-1.714404990	2.049900400	0.116998120
	C	-0.141682790	1.214374770	-1.588597770
	C	0.518744600	2.464404480	-1.569399550
	C	0.077057690	3.467145400	-0.724812610
	C	-1.048985780	3.260420880	0.106033840
	H	-3.925303590	-2.430564770	0.642159750
	H	-1.949754120	-3.836962960	-0.432139830
	H	-2.568952000	1.874682900	0.760615300
	H	0.066359360	0.531915960	-2.409546430
	H	1.352936430	2.632884650	-2.241770030
	H	0.581136910	4.427937110	-0.712947280
	H	-1.391827660	4.064265910	0.749721630
	Pd	0.612978870	-0.289521060	0.047261590
	O	1.787970390	-1.425849220	1.316571570
	C	2.446441590	-0.378340280	1.654649560
	C	3.585224700	-0.420321070	2.608003090
	O	2.062627630	0.714486180	1.091138840
	H	3.535295780	-1.326778590	3.213488000
	H	3.575780410	0.470501780	3.240476330
	H	4.522925420	-0.423113870	2.040732840
	Total DFT energy = -1155.637075612617			
	One electron energy = -4358.364095572560			
	Coulomb energy = 1946.910568726199			
	Exchange-Corr. energy = -125.636760062229			
	Nuclear repulsion energy = 1381.453211295973			
11	N	-1.024033930	-3.685910700	-0.346903440
	C	-2.218137880	-3.704491860	0.242983430
	C	-2.653524440	-2.725033720	1.163730830
	C	-1.805498840	-1.680355460	1.452574960

	N	-0.592677680	-1.665582860	0.841049420
	C	-0.218050280	-2.683309470	-0.032509350
	N	1.061431910	-2.497774810	-0.490677210
	C	0.494010500	-0.723210880	0.903106410
	C	1.502615870	-1.411529910	0.100492840
	H	-2.869506360	-4.534506720	-0.019286500
	H	-3.629112480	-2.786966490	1.629763470
	H	-2.035311790	-0.868748370	2.134208820
	H	0.707367240	-0.299593980	1.882996040
	H	2.514805400	-1.051698180	-0.050229150
	Pd	0.118034520	0.902767600	-0.369200340
	O	0.047709400	2.836992420	-1.216530690
	C	0.812395200	3.247301170	-0.289869130
	C	1.276508680	4.652010370	-0.151715650
	O	1.170985680	2.342739830	0.577453540
	H	1.107344480	5.188287860	-1.086970770
	H	2.334492770	4.674134670	0.121581440
	H	0.710852110	5.138721750	0.650640290
	Total DFT energy = -751.399959035685 One electron energy = -3015.372896705027 Coulomb energy = 1374.195903413361 Exchange-Corr. energy = -96.714448665475 Nuclear repulsion energy = 986.491482921455			
12	C	-0.926757440	3.987274610	0.891859010
	C	-1.582916440	2.763591590	0.985003920
	C	-0.905588610	1.609669550	0.567744600
	C	0.417037390	1.650687270	0.058794250
	C	1.052795800	2.888342000	-0.025697090
	C	0.380283680	4.044778270	0.389467950
	C	-1.413531480	0.266149670	0.583315920
	N	-0.648736830	-0.731246310	0.147978300
	C	-1.391465040	-1.876916840	0.285130870
	C	-2.604347600	-1.529494270	0.807949730
	O	-2.609667560	-0.157582040	0.994723650
	C	-3.811317420	-2.269882220	1.172894760
	O	-4.821367690	-1.778526630	1.626482340
	O	-3.647026160	-3.593399180	0.933181980
	H	-1.427469740	4.896770840	1.208655220
	H	-2.596075460	2.696814370	1.371023770
	H	2.065729410	2.951188930	-0.412151860
	H	0.882464770	5.006452320	0.320874230
	H	-1.023549580	-2.852131440	0.007358580
	H	-4.480688800	-4.021496860	1.189359440
	Pd	1.208338850	-0.087379800	-0.470516930
	O	2.589788320	-1.679589330	-1.183771290

	C 3.427900580 -0.752969750 -1.380750060 C 4.798552760 -1.026309420 -1.939352910 O 3.099719690 0.461981840 -1.102698180 H 4.936036600 -2.095885690 -2.100635820 H 5.559250330 -0.650990750 -1.248569790 H 4.921476000 -0.489039450 -2.884603260 Total DFT energy = -1020.904411819450 One electron energy = -4494.346351043626 Coulomb energy = 2070.040913660952 Exchange-Corr. energy = -131.095333526886 Nuclear repulsion energy = 1534.496359090110

4.2 Literature test

No.	Cartesian coordinates, energies
1	['C', 2.30133782, 1.44348591, -0.03963458, conf1], ['C', 3.63911371, 1.56853988, -0.38985525, conf1], ['C', 4.28754305, 0.52465496, -1.06720957, conf1], ['C', 3.6492455, -0.65791611, -1.41624558, conf1], ['C', 2.3039187, -0.7760592, -1.06055282, conf1], ['C', 1.63114359, 0.25930172, -0.37958668, conf1], ['N', 0.30750096, -0.03756023, -0.1126917, conf1], ['S', 1.20979335, -2.12184474, -1.34597522, conf1], ['C', -0.0703119, -1.23140463, -0.54656903, conf1], ['C', -1.45253243, -1.59612716, -0.29350031, conf1], ['C', -2.1636537, -0.5707437, 0.39442964, conf1], ['C', -2.13148714, -2.77479024, -0.62898644, conf1], ['C', -3.46977631, -2.95973113, -0.30701958, conf1], ['C', -4.15189752, -1.94358166, 0.36764298, conf1], ['C', -3.50520444, -0.75359642, 0.71819695, conf1], ['Cl', -1.29201435, -4.11093753, -1.49878355, conf1],

	['Cl', 6.01540307, 0.7262328, -1.50113866, conf1], ['H', 1.77544226, 2.23552394, 0.48446683, conf1], ['H', 4.19004915, 2.46910267, -0.14386772, conf1], ['H', 4.17934177, -1.44511992, -1.93976345, conf1], ['H', -3.96604574, -3.88366632, -0.58092768, conf1], ['H', -5.1993865, -2.08733999, 0.61982559, conf1], ['H', -4.04332994, 0.03074856, 1.24224166, conf1], ['Pd', -1.13226175, 1.05145666, 0.82652535, conf1], ['O', -0.45180057, 3.04343045, 1.53584521, conf1], ['C', -1.62948941, 3.2087811, 1.97448317, conf1], ['C', -2.02909694, 4.46055334, 2.70976585, conf1], ['O', -2.49940034, 2.27670344, 1.80551826, conf1], ['H', -1.27310723, 5.23701856, 2.57985165, conf1], ['H', -2.13315191, 4.23381943, 3.77717406, conf1], ['H', -3.00239937, 4.8103102, 2.35356162, conf1]]; Total DFT energy = -1337.668163472253 One electron energy = -5797.271109806028 Coulomb energy = 2647.005077803946 Exchange-Corr. energy = -153.129626237135 Nuclear repulsion energy = 1965.518043390692
2	['C', -1.20127034, 3.90897974, 0.225632, conf1], ['C', -2.06617401, 2.8876962, -0.1668913, conf1], ['C', -1.6588337, 1.54800304, -0.11453308, conf1], ['C', -0.36526124, 1.2233689, 0.32861178, conf1], ['C', 0.49625978, 2.25479046, 0.72226983, conf1], ['C', 0.08096629, 3.58901667, 0.67300936, conf1],

	['C', -2.66087408, 0.47181243, -0.46910601, conf1], ['N', -2.10208637, -0.56191975, -1.34721579, conf1], ['N', -0.93769659, -1.15767336, -1.08920796, conf1], ['C', -0.80713478, -2.10764592, -2.02703656, conf1], ['C', -1.94539295, -2.0432876, -2.83448048, conf1], ['N', -2.7466105, -1.06743608, -2.38348073, conf1], ['H', -1.52721592, 4.94438751, 0.17927251, conf1], ['H', -3.06931391, 3.13049482, -0.51269147, conf1], ['H', 1.49172451, 2.01173935, 1.08232718, conf1], ['H', 0.76333719, 4.37634427, 0.9840973, conf1], ['H', -3.02949691, -0.0383832, 0.43042988, conf1], ['H', -3.51871019, 0.87221535, -1.01055529, conf1], ['H', 0.06477649, -2.7426098, -2.05540415, conf1], ['H', -2.2169853, -2.63122264, -3.69825025, conf1], ['Pd', 0.34495957, -0.62744055, 0.39651335, conf1], ['O', 1.61851686, -2.39421399, 0.93000998, conf1], ['C', 2.19052003, -1.6277235, 1.75774357, conf1], ['C', 3.30926937, -2.11155152, 2.64410006, conf1], ['O', 1.80811608, -0.40211505, 1.85681791, conf1], ['H', 3.56750194, -3.14417894, 2.40265232, conf1], ['H', 3.00029749, -2.0448494, 3.69299997, conf1], ['H', 4.18556825, -1.46699623, 2.52031527, conf1] total DFT energy = -867.798334014867 One electron energy = -3905.501801747304 Coulomb energy = 1806.797996591963

	Exchange-Corr. energy = -114.436644094880 Nuclear repulsion energy = 1344.4455669
3	['C', -1.7220706, -0.1288945, 1.26378046, conf1], ['C', -0.43822612, -0.13401945, 0.71110744, conf1], ['C', 0.65901354, 0.1447396, 1.53374165, conf1], ['C', 0.43807567, 0.41362376, 2.89306233, conf1], ['C', -0.84065962, 0.41719612, 3.45250601, conf1], ['C', -1.94689443, 0.14213704, 2.61935513, conf1], ['C', -3.35234515, 0.12674614, 3.17243412, conf1], ['C', -1.02616358, 0.70855535, 4.9232287, conf1], ['N', 2.01640731, 0.05555114, 1.07517879, conf1], ['C', 2.82190297, 0.84671851, 0.27882551, conf1], ['C', 2.23342265, 2.04881997, -0.50203492, conf1], ['O', 4.00891993, 0.55722041, 0.18043212, conf1], ['C', 1.53516967, 3.06203511, 0.4300035, conf1], ['C', 3.39932373, 2.75298047, -1.22405409, conf1], ['C', 1.26041504, 1.53271462, -1.58618574, conf1], ['H', -2.57324951, -0.36770213, 0.6305484, conf1], ['H', 1.30043435, 0.62314291, 3.52296463, conf1], ['H', -3.4633891, -0.6143807, 3.97469782, conf1], ['H', -4.0803484, -0.11507436, 2.39241875, conf1], ['H', -3.63072014, 1.09870852, 3.60063888, conf1], ['H', -1.50586312, -0.12964253, 5.44530816, conf1], ['H', -0.06630735, 0.89942075, 5.41274065, conf1], ['H', -1.66432979, 1.5868906, 5.08624521, conf1], ['H', 2.57870421, -0.66068413, 1.52427013, conf1],

	['H', 1.18954652, 3.92293691, -0.15489722, conf1], ['H', 2.23603788, 3.43408958, 1.18561237, conf1], ['H', 0.673013, 2.63599211, 0.94785828, conf1], ['H', 3.01916105, 3.6120593, -1.78907879, conf1], ['H', 4.14051847, 3.10922191, -0.5037932, conf1], ['H', 3.91202955, 2.07492442, -1.91085725, conf1], ['H', 0.99439616, 2.32125904, -2.2993357, conf1], ['H', 1.70186034, 0.7125516, -2.1626215, conf1], ['H', 0.26473607, 1.28570422, -1.11990599, conf1], ['Pd', -0.23580393, -0.54503323, -1.20789314, conf1], ['O', -0.42696519, -1.58990692, -3.18150564, conf1], ['C', -1.08983093, -2.46307319, -2.55646803, conf1], ['C', -1.64330658, -3.68850749, -3.23353481, conf1], ['O', -1.29567082, -2.31519105, -1.28932207, conf1], ['H', -1.50911565, -3.61460839, -4.31422666, conf1], ['H', -2.70416869, -3.80328978, -2.99062013, conf1], ['H', -1.12222287, -4.57718571, -2.86043416, conf1]]; Total DFT energy = -991.963771763584 One electron energy = -4971.255833761329 Coulomb energy = 2318.276526498318 Exchange-Corr. energy = -134.741739549086 Nuclear repulsion energy = 1795.757275048513
4	['C', -2.46492633, -1.73587212, -0.17761153, conf1], ['C', -3.22225775, -1.24800424, 0.85787209, conf1], ['C', -3.26033621, 0.14132733, 1.18538526, conf1], ['C', -2.49080285, 1.03411524, 0.48635834, conf1], ['C', -1.58844999, 0.56638137, -0.53830527, conf1],

	['C', -1.70801098, -0.82168768, -0.97951062, conf1], ['N', -1.19866561, -1.17448409, -2.17453049, conf1], ['C', -1.2342277, 1.42347646, -1.7410749, conf1], ['S', -0.41854873, 0.16362955, -2.818778, conf1], ['C', 1.2489932, 0.2537623, -2.1188282, conf1], ['C', 1.47721073, 0.29526987, -0.74257531, conf1], ['C', 2.27286517, 0.28744247, -3.07605708, conf1], ['C', 3.59302593, 0.38784862, -2.64665206, conf1], ['C', 3.85847482, 0.44706656, -1.27569719, conf1], ['C', 2.82198925, 0.40085545, -0.33936248, conf1], ['H', -2.48043754, -2.78361979, -0.45786571, conf1], ['H', -3.82370677, -1.93789192, 1.44411343, conf1],['H', -3.88247789, 0.47828918, 2.00789579, conf1],['H', -2.51290292, 2.09382713, 0.72575244, conf1],['H', -2.1274945, 1.7746727, -2.27374277, conf1],['H', -0.54875671, 2.25311089, -1.56817957, conf1],['H', 2.03430008, 0.24089217, -4.13609866, conf1],['H', 4.40230919, 0.41788929, -3.37038503, conf1],['H', 4.88586294, 0.52301459, -0.9274796, conf1],['H', 3.05591618, 0.42911534, 0.72004928, conf1],['Pd', 0.14917222, 0.14171261, 0.73683999, conf1],['O', -0.61453545, -0.19890851, 2.81446689, conf1],['C', 0.58768574, -0.2909001, 3.20200246, conf1],['C', 0.92688822, -0.5549313, 4.64875901, conf1],['O', 1.53921054, -0.16122368, 2.3540076, conf1],['H', 0.01869591, -0.6121226, 5.25192276, conf1],['H', 1.57542108, 0.24204341, 5.02777993, conf1],['H', 1.48344808, -1.49489703, 4.72989558, conf1]]; Total DFT energy = -1310.068341737213 One electron energy = -5634.944500191906 Coulomb energy = 2566.540394617571 Exchange-Corr. energy = -148.831612646038 Nuclear repulsion energy = 1905.642309180845

5	['N', -0.46972902, -0.22338131, -0.09497911, conf1],['C', -0.27739137, 0.36147258, 1.11510552, conf1],['C', -0.88570032, 1.62474959, 1.31585105, conf1],['C', -1.62619965, 2.15309035, 0.26346321, conf1],['N', -1.82228974, 1.58247696, -0.94207082, conf1],['C', -1.22245157, 0.41197769, -1.04510232, conf1],['N', -0.88601725, 2.46691979, 2.40541693, conf1],['C', -1.61625841, 3.48651659, 2.00852901, conf1],['N', -2.10327796, 3.35876754, 0.72389918, conf1],['C', -2.91275398, 4.32052202, -0.03681303, conf1],['C', -2.08868796, 5.3898243, -0.727407, conf1],['N', 0.44776643, -0.20068799, 2.09398649, conf1],['C', 1.14054275, -1.43216592, 2.12505439, conf1],['C', 2.5637327, -3.82679991, 2.36328021, conf1],['C', 2.5247099, -2.92752649, 3.44041743, conf1],['C', 1.81864611, -1.74319981, 3.31740735, conf1],['C', 1.17045137, -2.31948301, 1.0424652, conf1],['C', 1.88952975, -3.5179159, 1.17749207, conf1],['O', 3.28340239, -4.96950877, 2.57215299, conf1],['C', 3.35765271, -5.91377403, 1.51618733, conf1],['C', -1.33701409, 5.07373019, -1.86785779, conf1],['C', -0.56961641, 6.0532162, -2.49710473, conf1],['C', -0.54894214, 7.35865906, -1.99785909, conf1],['C', -1.29955333, 7.68118316, -0.86677499, conf1],['C', -2.0654883, 6.69889624, -0.23483085, conf1],['H', -1.31814998, -0.13286917, -1.97880995, conf1],['H', -1.8407319, 4.35972398, 2.60718324, conf1],['H', -3.62810798, 4.77126525, 0.65755404, conf1],['H', -3.47605629, 3.73047467, -0.76479053, conf1],['H', 0.49525921, 0.36397566, 2.93468697, conf1],['H', 3.05125809, -3.17693423, 4.35568809, conf1],['H', 1.78868672, -1.04572598, 4.15313196, conf1],['H', 1.90938767, -4.20053273, 0.33632895, conf1],['H', 3.97154587, -6.73494719, 1.89188053, conf1],['H', 2.36466699, -6.29590385, 1.24522381, conf1],['H', 3.83047833, -5.48475009, 0.62297585, conf1],['H', -1.35673243, 4.05862539, -2.25673161, conf1],['H', 0.00913144, 5.79910393, -3.38088649, conf1],['H', 0.04734848, 8.12113942,

	-2.49151331, conf1],['H', -1.29167819, 8.69512996, -0.47624731, conf1],['H', -2.65365585, 6.95560541, 0.64397189, conf1],['Pd', 0.27401003, -2.02492113, -0.68570712, conf1],['O', -0.44961723, -2.32345516, -2.78072908, conf1],['C', 0.16426007, -3.43140521, -2.76215363, conf1],['C', 0.13249913, -4.36526242, -3.94566602, conf1],['O', 0.81010452, -3.78151083, -1.70919596, conf1],['H', -0.23163921, -3.84388732, -4.83314774, conf1],['H', -0.53728147, -5.20484824, -3.72570435, conf1],['H', 1.12933021, -4.77695753, -4.12817599, conf1] Total DFT energy = -1438.483434407151 One electron energy = -7873.011443280018 Coulomb energy = 3680.188553568017 Exchange-Corr. energy = -194.315164224758 Nuclear repulsion energy = 2947.235264116937
6	['C', -0.24896286, -1.01395028, 3.58267421, conf1],['C', -0.59265438, -0.60774369, 2.26535982, conf1],['C', -1.95310196, -0.24204769, 1.99799875, conf1],['C', -2.90794984, -0.27983399, 3.05036105, conf1],['C', -2.5375359, -0.6766206, 4.31530025, conf1],['C', -1.19685698, -1.04985202, 4.58137761, conf1],['C', 0.37257367, -0.55422698, 1.22004302, conf1],['C', 0.01475613, -0.1412581, -0.0384571, conf1],['C', -1.34380342, 0.2151119, -0.32463543, conf1],['C', -2.31648279, 0.15610208, 0.67834543, conf1],['C', -1.6541131, 0.6748025, -1.67847294, conf1],['O', -2.68555851, 0.96883882, -2.227948, conf1],['O', -0.45131642, 0.76016996, -2.41753397, conf1],['O', -3.61225524, 0.52899451, 0.46165776, conf1],['C', -4.45801516, -0.44423048, -0.16736031, conf1],['H', 0.78111903, -1.29329774, 3.78825799, conf1],['H', -3.92652244, 0.02410071, 2.83631379, conf1],['H', -3.27196881, -0.70082632, 5.11537797, conf1],['H', -0.91601839, -1.36171885, 5.58385691, conf1],['H', 1.40076072, -0.83463173, 1.43229373, conf1],['H', -0.64868636,

	1.00473954, -3.34050659, conf1],['H', -5.44947308, 0.00999008, -0.21245503, conf1],['H', -4.11699777, -0.6675389, -1.18128177, conf1],['H', -4.49932557, -1.36207621, 0.43226577, conf1],['Pd', 1.30381414, 0.00689531, -1.5126726, conf1],['O', 3.18381822, -0.0805382, -2.73294128, conf1],['C', 3.72276077, -0.56050001, -1.69829768, conf1],['C', 5.17496173, -0.95520772, -1.65590113, conf1],['O', 3.00654809, -0.72491328, -0.63534649, conf1],['H', 5.65746755, -0.72230649, -2.60669252, conf1],['H', 5.25875644, -2.02799644, -1.45134271, conf1],['H', 5.67919223, -0.42574339, -0.84091608, conf1] Total DFT energy = -1044.158088294759 One electron energy = -4834.841126912455 Coulomb energy = 2237.255996027257 Exchange-Corr. energy = -136.184545343106 Nuclear repulsion energy = 1688.779213376769

4.3 New reactions predictions

No.	Cartesian coordinates, energies
1	C 0.859175700 -2.574717800 -1.497186220 C 0.325734300 -3.853633640 -1.599078790 C -1.003243520 -4.139960970 -1.218970590 C -1.849216100 -3.154238730 -0.725913930 C -1.315204040 -1.866932380 -0.628507240 C 0.013413990 -1.576233290 -0.999834670 N 0.221041120 -0.216560140 -0.757008390 N -1.868558910 -0.668266110 -0.192859780 C -0.923625640 0.286681610 -0.278320080 C -1.094989540 1.748205580 0.021223090

	S -2.407331190 2.192520690 1.235844930 C 0.258568430 2.398359300 0.338855250 C -2.129282520 1.093964080 2.684672700 C -3.241665990 0.056494830 2.825082770 O -3.656760950 -0.028558520 4.079870060 O -3.681599300 -0.618344060 1.906907310 C -4.695035500 -1.003793530 4.357425830 H 1.879274380 -2.356712210 -1.788907180 H 0.947128420 -4.656332130 -1.982270770 H -1.373488450 -5.155004230 -1.317889340 H -2.871932020 -3.368663290 -0.435701540 H -2.746456030 -0.567133390 0.338442160 H -1.497870490 2.225444920 -0.882428830 H 0.162928410 3.470130900 0.532138590 H 0.901824270 2.435762510 -0.601764170 H 0.764677570 1.948473360 1.196248310 H -2.078215450 1.709705710 3.582970560 H -1.175200640 0.567834310 2.580577350 H -4.899008200 -0.907527960 5.421794210 H -4.338330330 -2.006874220 4.117123910 H -5.583610320 -0.777441250 3.765955860 Pd 1.897335340 0.889641160 -0.910799720 O 3.314107910 -0.350077590 -1.699190450

	C 4.186888440 0.599847960 -1.661580510 C 5.573798260 0.417618970 -2.161036240 O 3.756059890 1.708244010 -1.185286720 H 5.852491510 -0.637185520 -2.131469680 H 6.263696250 1.019969350 -1.565994950 H 5.623902120 0.765510270 -3.199205710 Total DFT energy = -1479.446622737764 One electron energy = -6374.542679658208 Coulomb energy = 2890.662380886692 Exchange-Corr. energy = -168.751556455525 Nuclear repulsion energy = 2173.185232489278
2	C -1.361539020 0.875830480 -0.247062000 C -2.130847620 -0.039354000 0.700702410 C -1.380776720 -1.364517810 0.984776510 C -1.046598840 -2.168118810 -0.292260500 C -0.452503230 -1.260465300 -1.292547890 C -0.546035240 0.142335380 -1.274058250 C 0.110130420 0.606979000 -2.468724290 O 0.200275790 -1.691142120 -2.391726320 C 0.681810400 -0.540097720 -3.024206890 O -1.402828180 2.087785840 -0.253564300 C -2.555962680 0.695895310 1.975297130 C -3.712028400 -0.013876450 2.662912820 O -4.037384330 0.596811760 3.804994900

	O -4.266207670 -1.002850700 2.222748140 C -5.142578110 0.022416790 4.539528570 H -3.053686860 -0.306472350 0.158606370 H -2.014133290 -1.978849850 1.626330920 H -0.453115350 -1.157232180 1.532779490 H -0.386318510 -3.019354710 -0.095750080 H -1.964158250 -2.586826530 -0.736349790 H 0.142086040 1.616015660 -2.857988480 H 1.228322770 -0.709970920 -3.941062060 H -2.864343170 1.717932470 1.733434790 H -1.723245200 0.793168040 2.681505420 H -6.050776570 0.044519860 3.933996300 H -4.917815620 -1.009877460 4.815442320 H -5.254392470 0.644056680 5.426187440 Pd 1.787351550 0.151611820 -1.130745820 O 2.943801000 0.259894560 0.572043330 C 3.980103780 0.530223650 -0.134730010 C 5.308052200 0.832480770 0.453405380 O 3.773724720 0.539037420 -1.407087980 H 5.324750410 0.552984100 1.507972380 H 5.503059400 1.906691540 0.359557790 H 6.087641740 0.301865910 -0.099790970 Total DFT energy = -1082.816402106921

	One electron energy = -5036.751017741624 Coulomb energy = 2318.823847388187 Exchange-Corr. energy = -140.155232576514 Nuclear repulsion energy = 1775.266000823030
3	C -1.073381780 0.068021510 -0.220112990 N -2.347800100 0.181121360 -0.444047370 C -3.140415500 1.083589970 0.191639280 C -2.578869440 1.924743670 1.125790900 C -1.185873260 1.839849250 1.411028000 C -0.389202160 0.874973030 0.715141730 C 0.985962060 0.807648340 1.009989590 N -0.645267280 2.676401520 2.335775790 C 0.649574670 2.608316250 2.609660850 C 1.523232940 1.664104260 1.952419540 C 1.137719120 3.581539640 3.649470930 C 2.981909350 1.597320450 2.269501460 O 3.563529090 2.297910680 3.074946680 O 3.608556560 0.645042520 1.543312740 C 5.018759910 0.513477880 1.786835640 H -4.192888840 1.099824250 -0.068281050 H -3.175008740 2.657920020 1.655860930 H 1.611278970 0.086539530 0.497112910 H 1.592836330 3.060972850 4.496420300 H 0.289561320 4.177774420 3.987203640

	H 1.918890200 4.232184230 3.247209380 H 5.205087750 0.255965170 2.832236740 H 5.354755150 -0.286468910 1.127847210 H 5.536758240 1.447246110 1.555195700 Pd -1.320633580 -1.287670000 -1.570756850 O -1.731987650 -2.803594700 -3.116570080 C -0.502910050 -3.100508130 -3.070438970 C 0.082578360 -4.193795700 -3.923532120 O 0.264059220 -2.457276990 -2.263222190 H -0.656499240 -4.550015330 -4.641843190 H 0.399050860 -5.023361160 -3.283230490 H 0.969965460 -3.824035920 -4.444251040 Total DFT energy = -1040.334639275808 One electron energy = -4689.221434419004 Coulomb energy = 2164.567828529027 Exchange-Corr. energy = -135.971068541066 Nuclear repulsion energy = 1620.290035155235
4	C -0.097352870 0.109624890 -1.731640360 C -0.694118870 1.215061480 -1.005063810 C -0.075291090 2.426422000 -1.521789030 C 0.850827620 2.013971100 -2.506042010 N 0.802173870 0.603618380 -2.594122670 C -2.013171680 -0.445664900 0.253291220 C -1.597523470 0.923395630 -0.014056490

	C -0.464109730 -1.247216550 -1.474825520 C -1.573163080 -1.479903860 -0.616704440 C -0.219511490 3.787909480 -1.245416000 C 0.563760390 4.697383020 -1.958825690 C 1.474480850 4.262824130 -2.932828080 C 1.634655360 2.904869100 -3.226188220 C -3.116098380 -0.652929120 1.275306720 C -3.406472310 -2.098511120 1.683650030 H 1.364113430 0.048998910 -3.227404520 H -2.020560080 1.711417180 0.603219760 H -0.064776580 -2.049673900 -2.085832530 H -1.997349530 -2.474244100 -0.548319520 H -0.923721040 4.136674810 -0.496769420 H 0.465803060 5.758887950 -1.758001060 H 2.068808140 4.993253730 -3.471691330 H 2.339860810 2.571272610 -3.980425110 H -2.864835730 -0.061018190 2.163387110 H -4.027920730 -0.195997280 0.864155170 H -4.178213340 -2.112652020 2.456898610 H -2.516444600 -2.586532110 2.093894160 H -3.779244150 -2.698449630 0.847538320 Pd 0.132108900 -1.213141280 0.729084380 O 0.578581430 -1.291471800 2.757335590

	C 1.781942870 -1.651602430 2.495420180 C 2.756285460 -1.993811100 3.569169550 O 2.084357360 -1.725546740 1.251667680 H 2.464016040 -1.522754510 4.509076590 H 3.760902950 -1.682356260 3.275039630 H 2.764229600 -3.080719230 3.707607540 Total DFT energy = -951.658713276782 One electron energy = -4689.511750449346 Coulomb energy = 2173.743715291785 Exchange-Corr. energy = -129.430308302289 Nuclear repulsion energy = 1693.539630183068
5	C 0.254879100 -1.457562110 -0.037564740 C -0.550836070 -0.353862540 -0.022945440 C -1.953707170 -0.529325240 -0.030191270 C -2.501088370 -1.806958820 -0.049100780 C -1.622806670 -2.905838130 -0.061329070 C -0.204706220 -2.771752590 -0.056781850 C 0.289197000 -4.109033420 -0.075945920 N -1.844629750 -4.257312700 -0.080972710 N -0.701456990 -4.984310390 -0.090024310 Cl 2.048525070 -0.974151380 -0.044898380 H -2.599806520 0.342667890 -0.017821040 H -3.577176170 -1.951214640 -0.054340660 H 1.314809470 -4.448990770 -0.079592730

	H -2.726619140 -4.741827660 -0.089796850 Pd 0.572385850 1.247504130 0.002594550 O 1.332754670 3.356490830 0.109294280 C 0.119818210 3.693039460 0.133331730 C -0.321940620 5.129011120 0.194279220 O -0.789576640 2.771324680 0.092899470 H 0.547401610 5.785121770 0.244041910 H -0.959097280 5.283575640 1.069881950 H -0.917922740 5.366410550 -0.691987150 Total DFT energy = -749.352928108988 One electron energy = -3110.007622738734 Coulomb energy = 1434.629780425167 Exchange-Corr. energy = -98.071499036013 Nuclear repulsion energy = 1024.096413240591
6	C -1.035873140 0.039488670 0.555079170 C -1.740511770 0.551511510 1.635007160 C -1.067533430 1.390365910 2.540609740 C 0.272696550 1.753042520 2.435982880 C 0.968664950 1.232323620 1.347241620 C 0.331167250 0.394145410 0.426225750 C 1.031587310 -0.146325480 -0.695972970 O 2.293595000 1.548597310 1.181638140 C 2.962122650 1.040707010 0.122768250 C 2.418761620 0.220370270 -0.818139090

	F -1.761161360 1.879127410 3.581773420 O 0.409541200 -0.901130480 -1.504597570 C 4.403851890 1.452593340 0.041059380 O 4.761447370 2.256094220 1.047930540 O 5.133294100 1.079037710 -0.852439360 C 6.136845680 2.687978720 1.026206130 H -2.788498020 0.325554940 1.800857430 H 0.739802290 2.403579820 3.164153750 H 3.039415540 -0.134181880 -1.630874390 H 6.345734270 3.242438440 0.108583950 H 6.253123240 3.327011970 1.900167400 H 6.805675210 1.826247510 1.083137620 Pd -1.597236660 -1.143957110 -0.907577010 O -2.750724860 -2.461669000 -2.281672780 C -3.730621860 -2.259563010 -1.512537580 C -5.076283550 -2.890121860 -1.743064370 O -3.569446230 -1.495921330 -0.481845460 H -5.112384120 -3.347546550 -2.732344470 H -5.863546270 -2.138803750 -1.640652740 H -5.251121440 -3.657538960 -0.981938550 Total DFT energy = -1179.301553709704 One electron energy = -5236.766564466325 Coulomb energy = 2409.543133165935 Exchange-Corr. energy = -148.672461073728

	Nuclear repulsion energy = 1796.594338664414
7	N -3.518801540 -0.226613770 -1.123711850 C -4.252034880 -0.493165880 0.026571610 C -5.555612020 -0.232360030 -0.297904490 N -5.659987800 0.203673960 -1.604083880 C -4.435201000 0.192431190 -2.068752330 C -2.118357570 -0.330282380 -1.286437900 C 0.108109950 -0.200972340 -0.358143120 C -1.269497670 -0.092419270 -0.194287620 C -1.594908910 -0.673516710 -2.548561750 C -0.221833640 -0.766042380 -2.723219630 C 0.625627800 -0.533236370 -1.630931590 C 2.076224860 -0.603337910 -1.648492630 O 2.733523890 -0.371823360 -0.606121470 O 2.678654920 -0.916654120 -2.784924390 C 4.122347840 -0.976577540 -2.763730550 H -3.786323940 -0.875763660 0.920441830 H -6.428032900 -0.336650790 0.332032400 H -4.128701050 0.512248440 -3.054464720 H -1.680669060 0.197418150 0.766875860 H -2.267262120 -0.893562570 -3.369801850 H 0.194140350 -1.032202400 -3.689976870 H 4.458086400 -1.733937240 -2.052716590

	H 4.412104970 -1.242561560 -3.778994970 H 4.536084620 -0.006080990 -2.482959450 Pd 1.465333430 0.083881870 1.023627830 O 2.478551210 0.496773480 2.987918400 C 1.313343380 0.620742870 3.451544540 C 1.051058070 0.949037860 4.896167130 O 0.301106800 0.461553600 2.660251310 H 1.993059850 1.066582910 5.432397170 H 0.459153420 0.150440260 5.353377380 H 0.464951600 1.870322070 4.963342430 Total DFT energy = -1040.333081732739 One electron energy = -4750.732148288092 Coulomb energy = 2195.300602758361 Exchange-Corr. energy = -135.983710832294 Nuclear repulsion energy = 1651.082174629286
8	C 2.584779520 -1.065563600 -0.362058430 C 3.911066940 -1.082098640 -0.740592480 C 4.612102460 0.084378550 -1.127418150 C 3.909035040 1.287877030 -1.115989540 C 2.567465770 1.321922230 -0.734711630 C 1.883946240 0.153646920 -0.354184690 C 0.488022330 0.261224350 0.037269760 O 1.951281010 2.549968840 -0.751833540 C 0.659150340 2.642537570 -0.394594370

	C -0.088309180 1.578707700 -0.009175000 Cl 4.772703670 -2.652692760 -0.735136210 C 6.059231180 0.043997320 -1.535071410 O -0.212557640 -0.717986580 0.400691340 C -1.546030850 1.668241130 0.398047950 O -2.139134910 2.720244480 0.397206870 H 2.067002830 -1.971654060 -0.069858640 H 4.395607530 2.213309030 -1.404619690 H 0.279159300 3.655961480 -0.450934860 H 6.686423250 -0.310391790 -0.710308020 H 6.407599080 1.033854240 -1.836708110 H 6.211605050 -0.649946080 -2.367613830 Pd -2.195767610 -0.106242580 0.866244250 O -3.513168810 -1.848218270 1.488268410 C -4.421976440 -0.985123900 1.627998120 C -5.810085910 -1.356065720 2.083440480 O -4.172004040 0.255142820 1.379500040 H -5.887642010 -2.435249660 2.220243920 H -6.542367380 -1.018768280 1.344126190 H -6.037006330 -0.844239930 3.023491300 Total DFT energy = -1019.208176852926 One electron energy = -4621.786047057436 Coulomb energy = 2137.097544822834 Exchange-Corr. energy = -132.481687397838

	Nuclear repulsion energy = 1597.962012779514
9	C 0.252185210 -2.172224420 0.336474690 C 0.748163090 -3.431650780 0.604854150 C 2.145547620 -3.676063730 0.569881380 C 3.013384420 -2.653341280 0.275154080 C 2.541179380 -1.340264050 0.002059190 C 1.130819830 -1.094302940 0.031247520 C 0.659699620 0.231096240 -0.251963130 N 3.461085600 -0.372355230 -0.285951450 C 2.992761670 0.832148110 -0.528420570 C 1.617227740 1.207163330 -0.501901590 O -0.021539030 -4.525426380 0.920965980 C -1.423194780 -4.333224750 0.985679280 C 1.357216590 2.663242100 -0.796049380 O 2.096172790 3.298572480 -1.554212900 N 0.308561540 3.236052150 -0.151313080 H -0.808264110 -1.959544070 0.368812820 H 2.498379460 -4.681436080 0.782795450 H 4.087300780 -2.813690220 0.242092590 H 3.716432970 1.608668510 -0.770499780 H -1.848962860 -5.301361000 1.262252160 H -1.695415380 -3.583466250 1.740447180 H -1.834244610 -4.018203590 0.016642210

	H 0.186083510 4.227066600 -0.307699090 H -0.174336780 2.801969270 0.642602630 Pd -1.276100850 0.552746160 -0.459135660 O -1.324809210 0.820091740 -2.552268800 C -2.588246300 0.994466960 -2.580355090 O -3.310143500 0.946759700 -1.554978370 O -1.628941950 0.194509500 1.524925730 C -1.433565440 1.118266320 2.400204850 O -0.957076780 2.247276580 2.256898170 H -1.762024560 0.798249630 3.412868960 H -3.043945350 1.195739400 -3.568389250 Total DFT energy = -1190.262614463902 One electron energy = -5721.460522287092 Coulomb energy = 2662.404926802650 Exchange-Corr. energy = -153.055256733222 Nuclear repulsion energy = 2021.848237753763

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