

Dispersion-Corrected Density Functional for the Correct Description on Regioselectivity Trends in Heck-Mizoroki Reaction Catalyzed by Anionic (N-Heterocycle Carbene)-Palladium Complexes

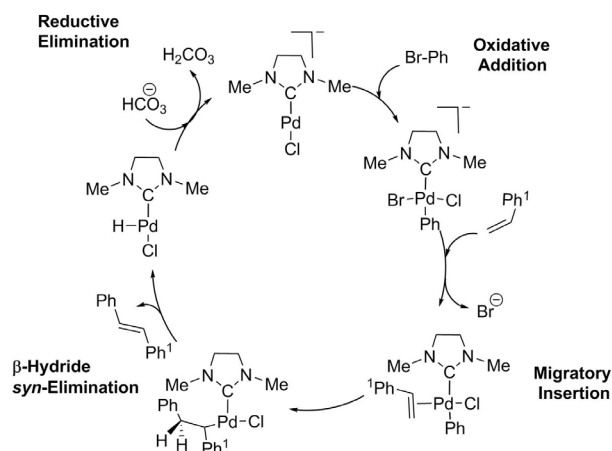
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Introduction

Palladium-catalyzed cross-coupling reactions are an important field in organic synthesis and organometallic chemistry. Its importance was recognized in 2010 by awarding Richard Heck, Ei-ichi Negishi and Arika Suzuki the Nobel Prize of Chemistry, for the prominent contribution to this field.¹ The Heck-Mizoroki (HM) reaction is an excellent tool for C-C sp^2 bond construction.² Historically, phosphines have been used as main ligands for palladium complexes furthering high catalytic activity in HM process, in particular cases, with excellent regio- and stereoselectivity control.³ In past decade, the N-heterocyclic carbenes (NHCs) emerged as new class of ligands in a number of cross-coupling reactions.⁴

The NHCs are strong σ -donors ligands, thus they are capable to provide better stability to transition metal complexes with highest oxidation state. Furthermore, NHCs are usually more sterically demanding than phosphines. The N-substituted pendants groups from central imidazole ring can play an important role in the reactivity and selectivity of catalyzed systems. Recently, density functional calculations were used to rationalize the role of the ionic (NHC)PdCl complex as pre-catalyst in a HM coupling reaction involving PhBr and styrene in the presence of HCO_3^- as base (Scheme 1).⁵ In this case, computational studies were applied to a

model system, in which the two SIPr groups (SIPr = 2,6-diisopropylphenyl) were replaced by Me groups (Me = methyl). Although this model system was able to provide new insights from the electronic influence of the NHC ligand in the reactivity and selectivity in HM coupling, the influence of the steric bulk from the real system over the selectivity of the catalyzed system still remains unclear.



Scheme 1. Plausible HM catalytic cycle for the (NHC)PdCl. The model system was constructed using Me groups as N-substituted in NHC ligand.

Computational studies have indicated that a correct description of dispersion interactions is crucial for modeling hindered phosphine (PPh_3) ligands in Pd-catalyzed cross-coupling reactions.⁶ Recently, Schoenebeck and collaborators showed that dispersion forces are key controlling factor to the correct description of the oxidative addition pathways involving crowded trialkyl substituent in palladium complexes.⁷ Norrby and Sigman performed theoretical calculations for the enantioselective Heck-Matsuda reaction using a *N,N*-PyOx ligand with *tert*-butyl substituent. Only dispersion-corrected density functionals were able to provide the correct stereochemistry of the product.⁸

Herein, we performed a computational study based on the density functional theory (DFT) to investigate how the real (NHC)PdCl- pre-catalyst influences the HM mechanism reaction. The main goal of this work is to analyze the regioselectivity trends by different exchange-correlation density functionals.

Methods

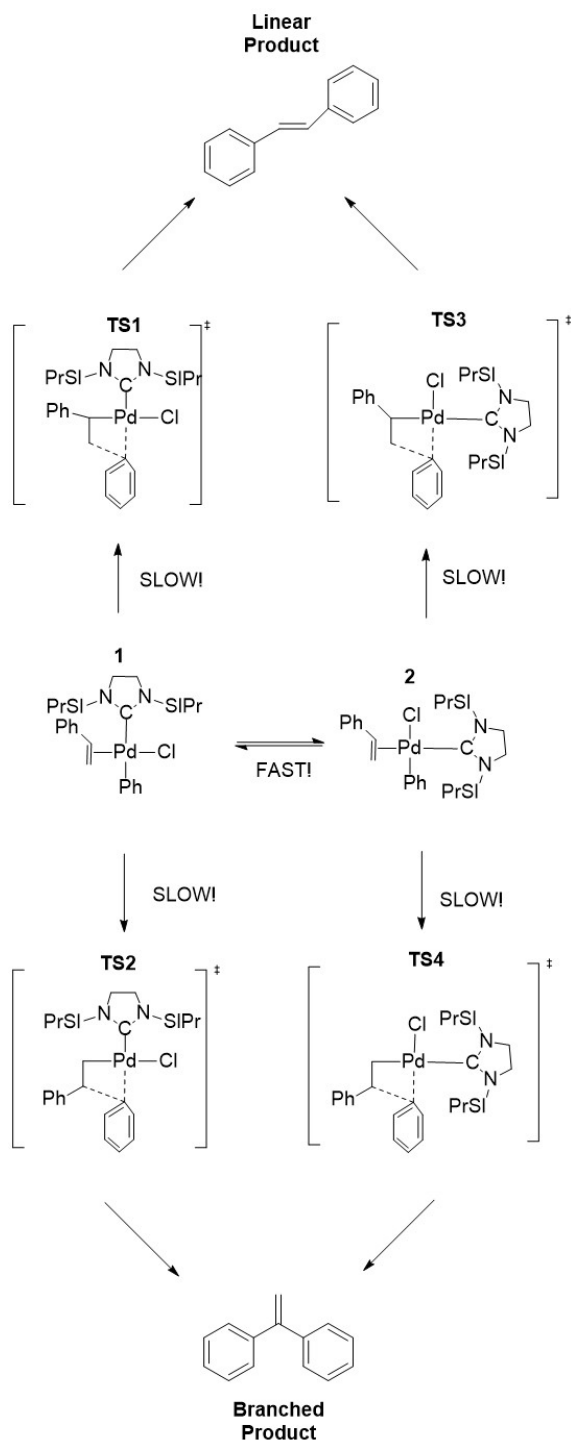
All electronic structure calculations were carried out within the DFT formalism using Gaussian09 suite of quantum chemical programs.⁹⁻¹⁰ Geometries optimizations, without any symmetry restriction were carried out in gas-phase using the GGA hybrid functionals PBE0¹¹ and B3LYP¹². The dispersion-corrected local and hybrid functional meta-GGAM06L¹³ and M06¹⁴ also were used in the current study, because these approaches have been proved to be reliable methods for transition metal kinetics-thermochemistry. The long-range-corrected hybrid GGA functional ω B97XD¹⁵ with the Grimme's empirical damped pair-wise dispersion terms (DFT-D2) was also explored.¹⁶ The SDD basis set was adopted to Pd¹⁷ and the 6-31G(d) basis set for the remaining atoms. This basis set approach is denoted as BS1 (6-31G(d), SDD (Pd)). Frequency calculations were performed in order to verify the nature of all stationary points on the potential energy surface (PES). The vibrational analysis was performed within the harmonic approximation with thermochemical data calculated at 298 K and 1 atm. Intrinsic reaction coordinate (IRC)¹⁸ calculations were used to connect reactants to products. Solvents effects were taken into account with the continuum solvation model SMD¹⁹ with DMF as the solvent. The

SMD calculations were performed as single-point energies calculations (SMD) on the optimized gas-phase geometries. In specific cases, single-point energies have been calculated using the SMD-6-311+G(d), SDD(Pd) level of theory. This basis set approaches denoted as BS2 (6-311+G(d), SDD (Pd)). All energies are presented in kcal/mol with respect to the lowest energy structure, unless otherwise specified.

Results and Discussion

The regioselective proposal for the catalyzed HM arylation is depicted in Scheme 2. The real (NHC)PdCl-complex is the catalyst. The starting aryl-palladium (II) complexes has two possible configurations, 1 and 2, with the Ph group (Ph=aryl) *trans* or *cis* to the NHC ligand, respectively. The stereoisomer 1 was found to be 10 kcal/mol higher than 2 at free energy surface, at SMD-PBE0/BS1 level of theory. It is noted the strongest NHC *trans* influence over the aryl group, increasing the energy of the intermediate 1. Besides the thermodynamic driving force in the isomerization of 1 towards to 2, we were unable to find the transition state for the isomerization via an associative or a dissociative process. A Berry pseudorotation mechanism was discarded, once a hindered steric bulk of the SiPr groups in imidazole ring is present.

In addition, it is well-known that a *cis-trans* isomerization is accelerated,^{1, 6b,8,21} when chlorine and basic ligands are present in HM catalyzed systems. Therefore, it is expected that the isomerization process would be faster than the migratory insertion of olefin into the starting intermediates 1 and 2. Consequently, the selectivity-determining step is the migratory insertion under Curtin-Hammett condition, in which the regioselectivity is determined solely by the relative energies of the competing insertion migratory transition states.²⁰ The transition states TS1 and TS3 are associated to the linear product, while the TS2 and TS4 yield the branched product. It is worthy to mention that only the linear product is detected by the experimental work, see the catalytic cycle in Scheme 1. The search for linear and branched transition states, having the full ligand SiPr, was made using DFT calculations. The dispersion-free density functional, PBE0 and B3LYP, and density functionals that take into account the dispersion forces (M06L, M06 and ω B97XD) were used.



Scheme 2. β - and γ - insertion migratory pathways starting through an isomerization between aryl-palladium (II) alkenes intermediates

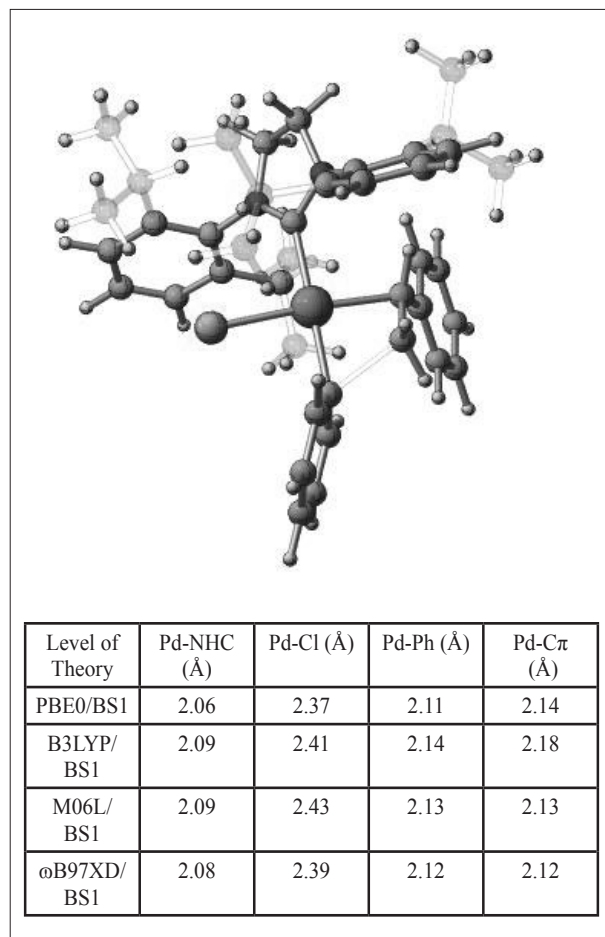


Figure 1. Crucial optimized features of TS1.

The optimized TS1 associated to linear products is illustrated in Figure 1. Its molecular structure clearly shows the C-C bond formation *via* four-membered arrangement. The dispersion has no significant impact on TS arrangement with respect to the calculations obtained using the model system. The Pd-NHC and Pd-C π bonds in NHC model (R = Me) were found to be 2.04 and 2.10 Å, respectively, at M06L/6-31+G(d), SDD (Pd) level of theory. For the real system, this bond distance is about 2.09 and 2.10 Å, respectively, at M06L/BS1. The geometries obtained using M06L and ω B97XD dispersion-corrected functionals are quite close; except in the case of Pd-Cl distance where the difference was 0.4 Å shorter using ω B97XD functional. Calculations

based on PBE0 and B3LYP showed larger differences compared to the dispersion-corrected methods.

The electronic influence of NHC on the reaction regioselectivity was explored with Me groups in the NHC ligand.⁵ In the model system, the β -carbon addition was preferential, and the final product was in agreement with the experimental reports. The regioselectivity trends can be understood in terms of how metal-ligand bond changes during the course of the C-C bond formation.²⁰ As the new bond is forming, relative to the β -carbon ($C\pi$), a negative charge is generated in the neighbor carbon, which results in a stronger interaction with the palladium center. In the linear transition states, this carbanion is stabilized by conjugation with the styrene, decreasing its *trans* influence. On the other hand, in the branched transition state structures, the negative charge on alkyl group is free causing strongest *trans* influence over the ligands. The NHC ligand, a stronger σ -donor ligand and π -acceptor, once the *trans* to the localized carbanion, it is expect a destabilization more pronounced in the transition states structures than to exerted by chlorine moiety, ligand with weak *trans* influence. Therefore, it is expected that TS3 and TS4 have higher energy than the TS1 and TS2. In addition, the charge separation stabilized by conjugation into TS1 and TS3 transition states structures explains the electronic influence on regioselectivity trends to the linear product. However, into the real NHC catalyst, the dispersion forces are correlated with the electronic influence of ligand, thus both chemical properties

contributed to regioselectivity of the reaction.

The computed enthalpies and Gibbs free energies in DFM solution related to the insertion transition states are shown in Table 1. The PBE0 and B3LYP density functional favor the branched product via the transition state TS2, in total disagreement with the regioselectivity reported in the experimental work.⁵ The M06L method improves the energies, decreasing in 3 and 5 kcal/mol, the stability of TS2 as predicted by the PBE0 and the B3LYP functionals, however, the free energies barriers stills report the branched configuration as preferential product. Only the long-range-corrected ω B97XD method favors the linear transition state TS1, in agreement with the experimental data. M06 single-points calculations at the B3LYP optimized geometries are a common tool in computational studies involving metal transition catalyzed systems.¹⁴ In the preset study, the B3LYP/BS1/M06/BS2 approach failed in predicting the right regioselectivity. In contrast, the ω B97XD/BS1/M06/BS2 approach was able to properly describe the experimental regioselectivity. These results show the importance of using computational approaches that account for dispersion effects. Such approaches should be use in geometry optimizations, mainly for crowded organometallics catalysts. Importantly, no matter whether dispersion is included or not, the highest energies are obtained for TS3 and TS4 transition sates, showing that the strong electronic influence of NHC ligand can overcome the attractive intramolecular dispersion forces

Table 1. Relative enthalpies and free energies in DFM solution. The energies are computed with respect to the lowest energy transition state structure.

Level of Theory	ΔH_{DMF} (kcal/mol)				ΔG_{DMF} (kcal/mol)			
	TS1	TS2	TS3	TS4	TS1	TS2	TS3	TS4
PBE0/BS1	3.0	0.0	7.8	10.2	4.1	0.0	8.7	10.9
B3LYP/BS1	4.2	0.0	8.6	10.9	6.0	0.0	10.2	12.0
M06L/BS1	0.0	0.4	4.4	7.8	1.1	0.0	6.5	10.9
ω B97XD/BS1	0.0	0.6	5.5	6.7	0.0	0.8	7.2	7.7
ω B97XD/BS1// ω B97XD/BS2	0.0	0.8	5.8	7.6	0.0	1.0	7.5	8.5
B3LYP/BS1// M06/BS2	0.7	0.0	3.6	6.5	2.5	0.0	5.2	7.6
ω B97XD/BS1// M06/BS2	0.0	0.2	3.9	6.7	0.0	0.5	5.7	7.6

of real ligands. Furthermore, our results suggest that the regioselectivity in the present system follows a typical Harper mechanism²¹, wherein the major product, in this case the linear configuration, arises from a preceding minor intermediate, the alkene-palladium (II) complex 1.

Conclusions

In conclusion, density functionals that account for dispersion correction are fundamental to predict the correct regioselectivity in insertion migratory step of the NHC-catalyzed Heck-Mizoroki reaction discussed. Herein, we explored the influence of real NHC ligand bulk, an extension of computational studies on model NHC ligand with methyl ligands reported in the literature. The use of B3LYP and PBE0 functionals result in a strikingly different regioselectivity compared to the experimental prediction. Only hybrid dispersion-corrected ω B97XD and *meta*-GGA M06 functionals were capable to describe the influence of real ligand to the reaction regioselectivity. We expected with complete elucidation on the selectivity-controlling this catalyzed system, to start investigations based on theoretical design of new NHC ligands.

Acknowledgments

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