Dispersion-corrected density functional theory 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 Neigishi 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, excellent regio- and stereoselectivity control.[3] In past decade, the N-Heterocycle carbenes (NHCs) emerged as new class of ligands in a number of cross-coupling reactions.[4] The NHCs are stronger σ-donors ligands, thus is capable to provide greater stability to transition metal complexes with highest oxidation state. Furthermore, NHCs have steric bulks more complex in comparison to angle of the cone present into hindered phosphines. The *N*-substituted pendants groups from central imidazole ring can play an important role in the reactivity and selectivity into the catalytic system. Recently, we rationalize by DFT calculations the role of ionic (NHC)PdCl complex as pre-catalyst for the HM coupling reaction involving the PhBr and styrene in the presence of base HCO$_3^-$ (Scheme 1).[5] In this case, we perform the computational studies on model system, in which the two SlPr groups (SlPr = 2,6-diisoprophynel) were replaced by Me groups (Me = methyl). Besides the model system provide new insights from the electronic influence of the NHC ligand in the reactivity and selectivity in HM coupling, certainly the steric nature bulk of the real system influence the stereo- and regioselectivity of the system.
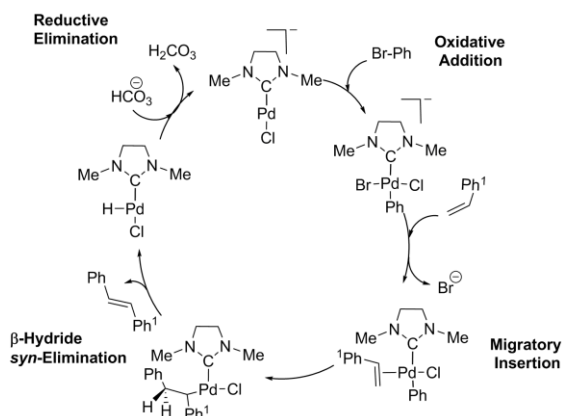
Scheme 1. Plausible HM catalytic cycle for the (NHC)PdCl$^-$. The model system was constructed using Me groups as *N*-substituted in NHC ligand.

Computational studies are indicated that correct describing of dispersion interactions is crucial in modeling hindered phosphine (PPh$_3$) ligands in the Pd-catalyzed cross-coupling reactions.[6] Recently, Schoenebeck and collaborators show the dispersion forces as key controlling factor to the correct theoretical description on oxidative oxidation 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 *terc*-butyl substituent. Only dispersed-corrected density funcionals were able to provide the correct stereochemistry of product.[8]

Herein, we performed the DFT calculation for the investigation of the real (NHC)PdCl$^-$ pre-catalysis influence in the HM mechanism reaction. The aim this work is analizing of the regioselectivity trends by different exchange-correlation density functionals.

METHODS

All electronic structure calculations were carried out within the Kohn–Sham Density Functional Theory (DFT) formalism with the Gaussian09 suite of quantum chemical programs.[9-10] Geometries optimization calculations were carried out in the gas-phase using the GGA hybrid functionals PBE0[11] and B3LYP[12]. The dispersion-corrected local and hybrid functionals *meta*-GGA M06L[13] and M06[14] also were used in the current study, because these approaches have been proved to be efficient and reliable methods for transition metal kinetics-thermochemistry. We also perform the long-range-corrected hybrid GGA functional ωB97XD[15] with the Grimme's empirical damped par-wise dispersion terms (DFT-D2).[16] The SDD basis set was adopted to Pd[17] and the 6-31G(d) basis set for the remaining atoms. Basis set approach denoted as BS1 (6-31G(d), SDD (Pd)). Full geometry optimizations without any symmetry restriction followed by frequency calculations on all stationary point were performed to verify their nature of the transition states (TS) 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 are given in kcal.mol^{-1}. Intrinsic reaction coordinate (IRC)[18] calculations were used to further authenticate the TSs. Solvents effects were take into account with the continuum solvation model SMD[19] 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 approach are denoted as BS2 (6-311G+(d), SDD (Pd)). All energies are presented with respect to the lowest energy structure, unless otherwise specified.

RESULTS AND DISCUSSION

The regioselectivy proposal HM arylation by the real pre-catalysis NHC-PdCl$^-$ are present at Scheme 2. The starting aryl-palladium (II) complexes has two possible configurations, **1** and **2**, with the Ph group (Ph=aryl) *trans* or *cis* to NHC ligand, respectively. The insertion of styrene in order to achieve **1** and **2**, in the model system, was computed with free energy in solution by -18.0 and -27.6 kcal.mol^{-1} in respect to separated reactants, respectively, at SMD-M06L/6-31G+(d), SDD (Pd) level of theory. Noted the stronger influence *trans* of the NHC-ligand to the ary group increasing the energy of **1** intermediate.

Besides the thermodynamic driving force in the isomerization equilibrium 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 because of the hindered steric bulk of the SIPr groups in imidazole ring.
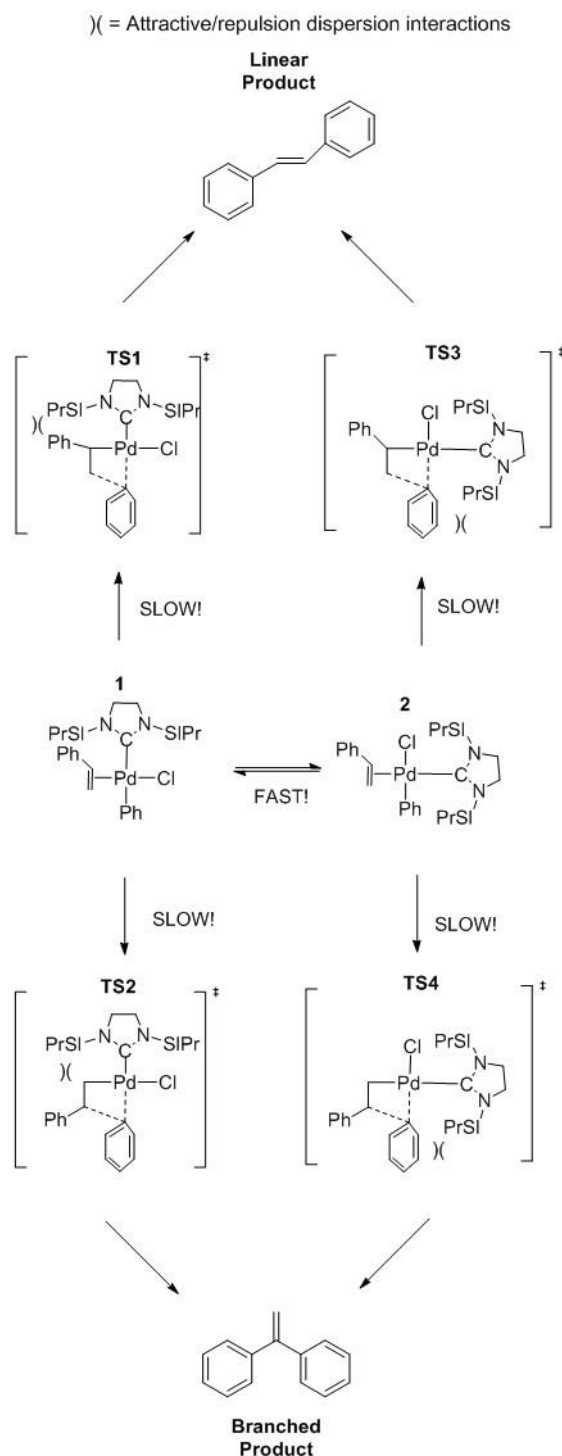
Scheme 2. β− and γ− insertion migratory pathways starting to fast isomerization between aryl-palladium (II) alkenes intermediates.
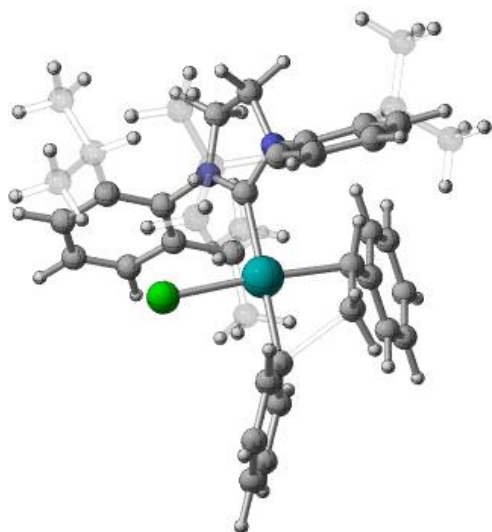
Figure 1. Crucial optimized features of **TS1**.

Level of Theory	Pd-NHC (Å)	Pd-Cl (Å)	Pd-Ph (Å)	Pd-Cπ (Å)
PBE0/BS1	2.06	2.37	2.11	2.14
B3LYP/BS1	2.09	2.41	2.14	2.18
M06L/BS1	2.09	2.43	2.13	2.13
ωB97XD/BS1	2.08	2.39	2.12	2.12

In addition, it is well-know that in presence of the chlorine and basic ligands in the HM catalytic system the *cis-trans* isomerization is accelerated.[1,6,20], thus is expected the isomerization process is faster than the insertion of olefin into starting intermediates **1** and **2**. Therefore, the determining-selectivity step is the migratory insertion under Curtin-Hammet condition, wherein the regioselectivity is determined solely by relative energies of the competing insertion migratory transition states. The transition states **TS1** and **TS3** are associated to linear product, while the **TS2** and **TS4** achieve to branched product. It is worth noted that solely linear product configuration is detected in experimental work, see the catalytic cycle at Scheme 1. The search for a linear and branched transition states for the full ligand SlPr, DFT calculations were performed applying dispersion-free methods (PBE0 and B3LYP) and that account well for dispersion forces (M06L, M06 and ωB97XD).

A representative geometry of located **TS1** for linear product 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 model system calculated. The Pd-NHC and Pd-Cπ with Me groups were calculated 2.04 and 2.10 Å, respectively, at M06L/6-31G+(d), SDD (Pd) level of theory. For real system this bond distance is 2.09 and 2.10 Å, respectively, at M06L/BS1. The geometries obtained by M06L and wB97XD dispersion-corrected functionals are correlated, except for the Pd-Cl distance is 0.4 Å shorter obtained with wB97XD method. Moreover, shorter distances resulted with PBE0, and larger distances were obtained with B3LYP, when are compared with dispersion-correct methods. When we computed the catalytic cycle with the Me groups in NHC ligand, it could be explored the electronic influence in regioselectivity.[5] For the system model we obtained the β-carbon addition as preferential in agreement with product detected in experimental reports. The regioselectivity trends can be understood in terms how metal-ligand bond changes during the course of the C-C bond formation.[20] With the new bond is forming to the β-carbon (Cπ), a negative charge is generated in the neighbor carbon, that results in strongest interaction to palladium center. In the linear transition states, this carbanion is stabilized by conjugation with the styrene, decreasing its *trans* influence. In the branched transition states **TS2**, this negative charge on alkyl group is free causing a charge separation in the structure. Thus, we can expect that the **TS1** has lower energy that **TS2**, and the **TS3** and **TS4** with higher energy because the NHC ligand, a strongest σ-donor ligand and modest π-acceptor, *trans* to the localized carbanion causing the a high charge separation in the structures. However, into the real NHC catalysis, the dispertion 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 at 298,15 k in DFM solution for the insertion transition states is shown in Table 1. Our results show that PBE0 and B3LYP calculations favor the branched product via the transition state **TS2**, in total disagreement with the regioselectivity shown in experimental work.

Table 1. Relative enthalpies and free energies in solution at 298K and 1 atm. The energies are computed relative with the lowest energy transition state structure.

Level of Theory	ΔH_{DMF} (kcal.mol^{-1})				ΔG_{DMF} (kcal.mol^{-1})			
	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
ωB97XD/BS1	0.0	0.6	5.5	6.7	0.0	0.8	7.2	7.7
ωB97XD/BS1//ωB97XD/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
ωB97XD/BS1//M06/BS2	0.0	0.2	3.9	6.7	**0.0**	**0.5**	**5.7**	**7.6**

The M06L method improves the energies, decreasing in 3 and 5 kcal.mol^{-1} the stability of **TS2** predicted by PBE0 and B3LYP functionals, besides the free energies barriers stills towards to the branched configuration as preferential product. Only the long-range-corrected ωB97XD method favors the linear transition state **TS1** in ωB97XD/BS1 at level of theory, in agreement with experimental data. The single-points M06 in B3LYP optimized geometries is widely used in computational studies for predicted the dispersion in metal transition catalyzed systems.[14] For this system, the B3LYP//M06 approach failed in the prediction of regioselectivity selectivity trend at B3LYP/BS1//M06/BS2 level of theory. In contrast, the ωB97XD/BS1//M06/BS2 approach computed the free energies barriers with a correct regioselectivity. These results show the importance of inclusion the dispersion effects in optimization geometry calculations for crowded organometallics catalysis. Importantly, no matter whether dispersion is included or not, the **TS3** and **TS4** have highest energies, shown the strongest electronic influence of NHC ligand overcome the repulsive intramolecular dispersion forces of real ligand. Furthermore, our results are suggested that regiosselectivity follows a typical Harpern mechanism[21], 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, only using DFT methods that account well the dispersion successfully predict the correct regioselectivity in insertion migratory step of the Heck-Mizoroki reaction by N-Heterocycle carbenes (NHC) catalysis. Herein, we explored the real bulk hydrocarbon (R=SlPr) of NHC ligand, an extension of computational studies to the smaller methyl ligands reported by us in the literature. The B3LYP and PBE0, dispersion-free methods, not correctly described the correlated electronic influence and the repulsive/attractive steric intramolecular dispersion forces in the real ligand providing a strikingly different regioselectivity against the experimental prediction. Only hybrid dispersion-corrected ωB97XD and *meta*-GGA M06 functionals were capable to describe the influence of real ligand and predicted the correct regioselectivity trends. With complete understanding of selectivity-control this catalytic system, we expected starting a theoretical design of new NHC ligands.

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