This article is published as part of the *Dalton Transactions* themed issue entitled:

Computational Chemistry of Molecular Inorganic Systems

Guest Editor: Professor Stuart MacGregor
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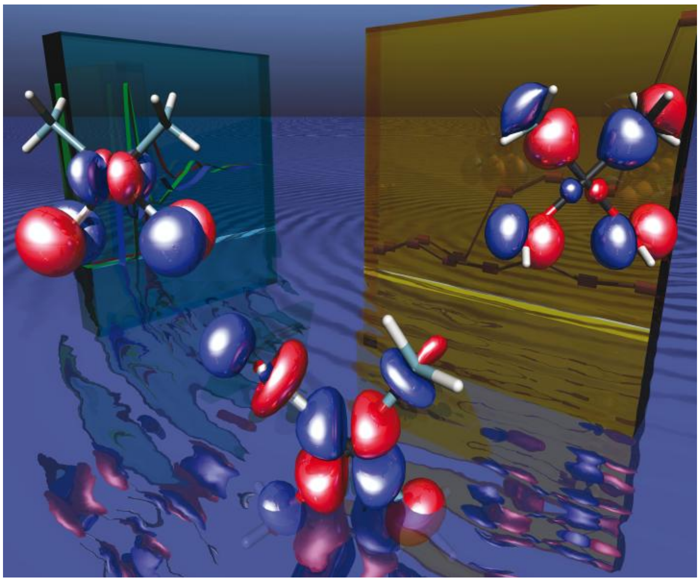
Published in issue 42, 2011 of *Dalton Transactions*



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PAPER

A DFT comparison of the neutral and cationic Heck pathways†

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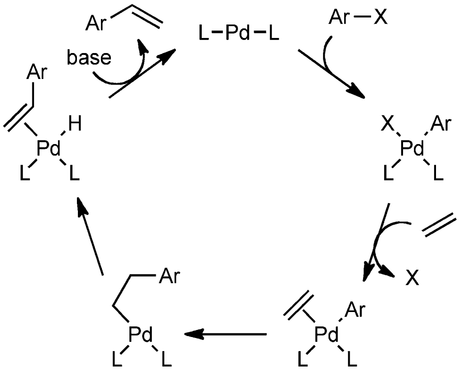
Received 1st April 2011, Accepted 25th May 2011
DOI: 10.1039/c1dt10558b

The two distinct mechanistic pathways of the Heck reaction, cationic and neutral, are characterized computationally using DFT calculations with corrections for solvation and dispersion. The selectivity in each type of reaction is discussed in terms of the detailed reaction paths, and the two types are compared to each other. The geometries and energies of the selectivity-determining transitions states are analyzed in detail.

Introduction

Palladium-catalyzed arylation or vinylation of alkenes has been used for more than 30 years in organic synthesis. This methodology, known as the Heck or the Mizoroki–Heck reaction,[1,2] was recognized together with other palladium-catalyzed reactions with the Nobel Prize in chemistry 2010.[3] The basic reaction cycle is schematically depicted in Scheme 1.



Scheme 1 A simplified catalytic cycle for the title reaction.

Much knowledge about the performance for different ligands, substrates, and reaction conditions has been built up over the years.[4] For example, the selectivity difference obtained by running the reaction with or without coordinating anions, termed neutral or anionic Heck from the nature of the pre-insertion complex (Scheme 2), has been studied in detail.[5,6] Computational techniques have been applied to the title reaction.[7,8] Examples include elucidation of observed reaction selectivities, including regioselectivity in initial carbopalladation[9] and subsequent hydride elimination,[10] as well as stereoselectivity in asymmetric Heck reactions.[11] However, the complex nature of the reaction still leaves many questions to be answered, like the balance between neutral and cationic paths under conditions where both could be possible.

The aim of the present study has been to investigate model reactions for the two different Heck versions, a cationic and a neutral reaction. For the cationic reaction, two triphenylphosphines (PPh_3) were used as ligands. For the neutral reaction one of the triphenylphosphines was replaced by a chloride. In both cases styrene was used as the substrate. Phenyl chloride was used in the oxidative addition step in both of these reactions. We note that experimentally for aryl chlorides the oxidative addition tends to be rate limiting, but subsequent steps are not very sensitive to the nature of the halide ion. We also modeled halide-free cationic reaction conditions, in which phenyl triflate was used as the model electrophile; the triflate anion was assumed to be non-coordinating after oxidative addition. In all cases ammonia was used as base. Experimentally, bulkier bases are preferred to avoid coordination of the base to palladium, but the pK_a, and therefore the thermodynamics of deprotonation, are similar.

Computational details

All calculations herein were performed with the Jaguar 7.0 program package[12] using the hybrid functional B3LYP.[13] For geometry optimization and vibrational analysis, we used the LACVP* basis set which combines the 6-31G* basis set for light elements with the Hay–Wadt ECP and accompanying basis set[14] for Pd. Final electronic energies were computed using LACV3P**+, which augments the basis set to 6-311+G** for light elements. All optimized geometries were characterized and their minima or saddle points were verified. Harmonic vibrational frequencies have been used to calculate the thermodynamic contributions to the enthalpies and free energies, including zero point energy corrections, using the default temperature of 298.15 K. We have also verified the connectivity between a given transition state (TS) with the corresponding reactant and product by following the intrinsic reaction coordinate (IRC). The dispersion energy has been computed with the DFT-D3 method using the program of Grimme *et al.*[15] The solute–solvent interaction was modeled

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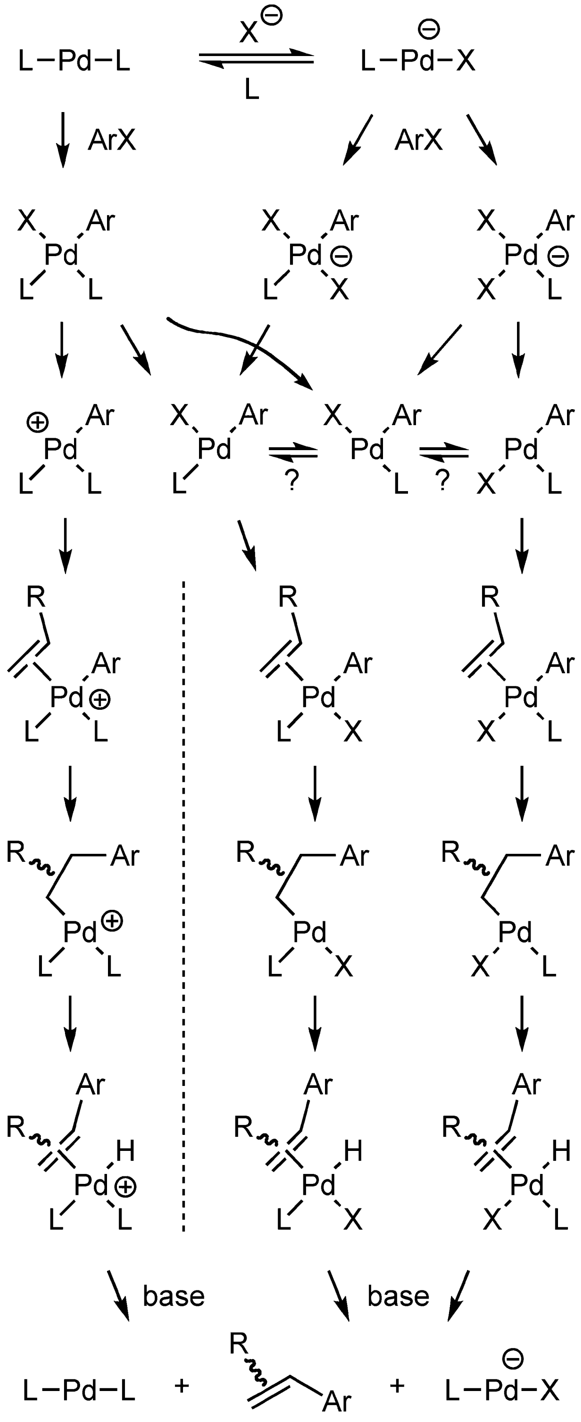
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1dt10558b



Scheme 2 Consensus mechanism for the cationic and neutral Heck reactions.

using a Poisson–Boltzmann self consistent reaction field (PB-SCRF)[16] with parameters suitable for dichloromethane (dielectricity constant: epsout = 8.9 and probe radius: radprb = 2.3385253). Ammonia was used as base, and formation of ammonium ion was assumed in the last step of the reaction cycle. Simplified activation strain analysis[17] was performed for the potential energy component of the total free energy only, as single point energy calculation of fragments from selected transition states and intermediates.

Results and discussion

This section opens with a discussion of the Free Energy Surfaces (FES) of the different Heck reactions. We first show the cationic mechanism, and thereafter the possible neutral mechanisms. We will then discuss situations where cationic and neutral mechanisms could be in competition, with monodentate ligands in the presence of excess halide. Finally, we try to rationalize the reactivities of each path based on the structure of the calculated transition states.

The FES of the cationic Heck reaction is depicted in Fig. 1. The calculated exergonicity is −114 kJ mol^{-1} for formation of the linear product stilbene from phenyl chloride and styrene, and −94 kJ mol^{-1} for formation of the branched product, α-phenyl styrene. Note that the absolute values depend on the choice of base and leaving group (here modeled by ammonia and chloride), but the relative values do not. We note that the linear product is significantly more stable, and therefore that formation of the branched product only can result from kinetic selectivity. This selectivity occurs in the carbopalladation step, which is effectively irreversible. For the system considered here, the two transition states are virtually isoenergetic, with the path leading to the branched product favored by only 1 kJ mol^{-1}. It is well known experimentally that favoring of the cationic path, by excluding coordinating anions and/or using bidentate ligands, will give significant amounts of branched product for substrates able to stabilize a cationic charge.[5,6] For styrene itself, the amounts of branched and linear products are almost equal,[6] in line with the current calculated results.

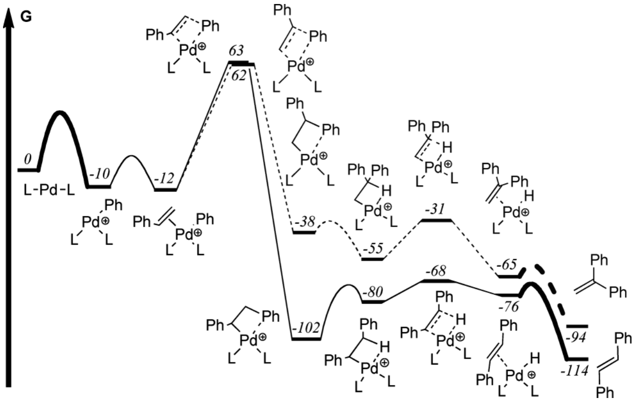


Fig. 1 The cationic Heck reaction, with free energies in kJ mol^{-1}.‡

The neutral Heck reaction is run in the presence of halide ions, as part of the starting palladium complex (frequently a Pd^{II} chloride complex), as leaving groups, or added specifically to the reaction mixture. It has been shown that oxidative addition can be substantially faster in the presence of halide ions,[18] and this effect has been rationalized in terms of oxidative addition to a linear complex with one halide and one phosphine bound to palladium.[19] We have therefore investigated the neutral Heck reaction starting from both anionic and neutral Pd^0 complexes (Scheme 2). The resulting free energy surface is depicted in Fig. 2.

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‡ Bold horizontal lines designate calculated stationary points, whereas curved lines indicate transition states that are ignored, either because they correspond to monotonous reactions on the PES (narrow lines), or because they are potential multistep reactions that have no influence on the selectivity (bold lines).

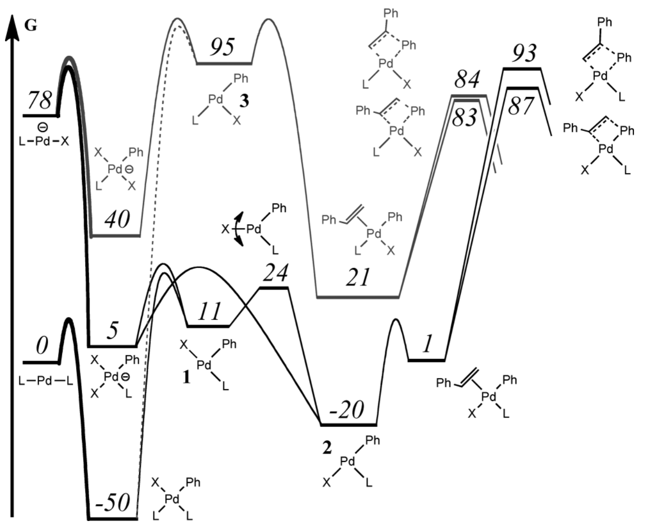

Fig. 2 Reaction paths leading to neutral carbopalladation, with free energies in kJ mol^{-1}.‡

The oxidative addition has been the subject of several studies,[19,20] and in particular Harvey and co-workers have recently investigated various aspects of this step in detail.[21] In here, we concentrate on the steps after oxidative addition, and the potential crossover between various paths.

Oxidative addition of an aryl halide (here modeled by phenyl chloride) to anionic $ClPdPPh_3$ leads to two different anionic square planar complexes, where either the phosphine or a chloride is *trans* to the aryl moiety. Dissociation of one halide gives three neutral, T-shaped complexes (**1–3**). The low energy complexes **1** and **2** can interconvert *via* a Y-shaped TS, since the halide is positionally labile, being able to donate lone pairs into two neighboring sites simultaneously. Complex **3** is substantially higher in energy, with the two ligands with the strongest *trans* effect,[22] aryl and phosphine, *trans* to each other. Complex **1** is unproductive; association of the alkene substrate *trans* to the aryl group cannot lead to carbopalladation. Further reaction of **1** must proceed *via* isomerization to complex **2**. There is also a path connecting **1** to **3**, but this is very much higher in energy, and therefore not shown in Fig. 2. The T-shaped complexes **1** and **3** can also be obtained by oxidative addition to neutral $Pd(PPh_3)_2$ followed by dissociation of a phosphine ligand. In here, we will not further discuss the route to the T-shaped complexes, since it does not directly influence the selectivity, but instead refer to the detailed investigation of Harvey and co-workers.[21]

The neutral Heck reaction proceeds by association of the styrene substrate to the T-shaped complexes, followed by carbopalladation. The latter is the selectivity-determining step in the reaction. The subsequent intermediates and β-elimination transition states have been studied earlier,[10,11] and have always been found to be too low in energy to allow reversibility in the carbopalladation step. Only one alkene complex is shown from each T-shaped complex, but of course several forms are in rapid equilibrium with each other here. In particular, the alkene rotates around the axis connecting the centerpoint to the metal, with low barriers. For simplicity, alkenes are shown as being oriented in the coordination plane, but in reality they are skewed or even perpendicular, and thus not optimally oriented for insertion. However, due to the low barriers of rotation, we are in a Curtin–Hammett situation,[23] where the selectivity is determined solely by the relative energy of the carbopalladation transition states, not by the relative stabilities of intermediate conformations.

Interestingly, even though the T-shaped intermediates are very different in energy, the subsequent carbopalladation transition states have similar energies. In fact, the high energy intermediate **3** leads to the lowest energy barriers. A similar effect has been seen earlier in the Heck reaction,[11] and can be rationalized in terms of the shift in *trans* effect, from a strong aryl to an even stronger alkyl, during the course of the reaction.[24] However, in the current case, the energy of intermediate **3** is very high. We cannot easily calculate the barriers for dissociation and association leading to and from **3**, since these have a strong entropic component in the position of the TS, but Harvey and co-workers recently reasoned that such processes are diffusion controlled, and could therefore estimate the corresponding barriers to at least *ca.* 20 kJ mol^{-1}. These estimated barriers would be higher than the carbopalladation steps, and therefore prohibit involvement of intermediates of type **3**. We can also see that the path from **3** would predict a low selectivity for the linear product, whereas the path from **2** gives a high selectivity (6 kJ mol^{-1} corresponds to a ratio around 10 : 1 at ambient temperature). Experiments performed with monodentate ligands in the presence of halides generally give a strong preference for linear products,[5] in reasonable agreement with the path from **2** but in disagreement with the path from **3**, further supporting the conclusion that the neutral Heck reaction proceeds almost exclusively through intermediates of type **2**.

The β-elimination and subsequent product release are not shown in Fig. 2. In related systems where more than one β-elimination is possible, interesting selectivity shifts can arise from changes in the reaction conditions.[10] However, in the current case, these low energy steps cannot affect the branched/linear product distribution, and will therefore not be discussed further.

The situation becomes more complex if both cationic and neutral pathways must be considered simultaneously. This is the case when, for example, the phosphine ligand is present in excess, but the amount of halide is limited, as is the case in many common recipes for the Heck reaction.[2,5] This could occur when the pre-catalyst is a palladium halide but the aryl substrate is a triflate. As shown in Scheme 2, the neutral square planar oxidative addition product can enter either the neutral Heck pathways by dissociation of a phosphine ligand, or the cationic pathway by dissociation of an anionic leaving group. Comparison of two pathways with different charge is non-trivial, and highly dependent on the solvation model used in the calculations, but the continuum solvation model has been found to give a fair representation of the relative energies.[25] Still, care needs to be exercised when evaluating such comparisons. Selected parts of the FES for the mixed system are shown in Fig. 3. As can be seen, the current calculations indicate that the cationic mechanism should be able to compete with the neutral mechanism even under conditions where halide ions are present. However, the difference in activation barrier is not very high, and could easily be shifted by a number of factors. For example, the current study models all halides by the chloride ion, whereas many experimental protocols utilize bromides or iodides that would be expected to bind more strongly to palladium, and thereby favor the neutral mechanism. The same would happen in

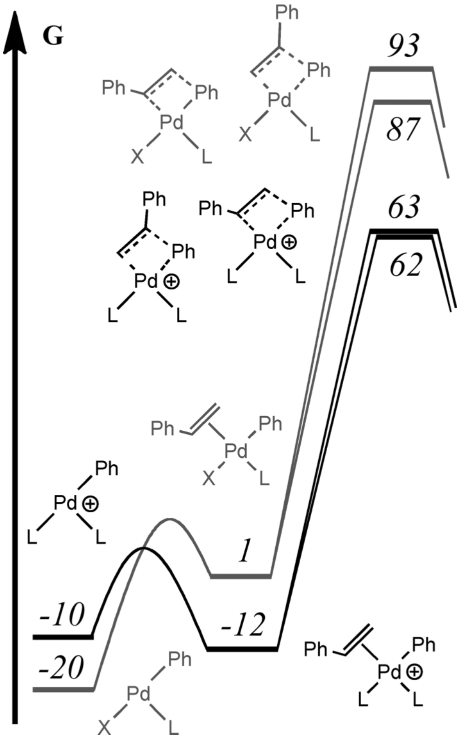

Fig. 3 Competition between cationic and neutral pathways, with free energies in kJ mol^{-1}.‡

less polar solvents, or when a more sterically demanding phosphine is employed. The opposite effect, an additional favoring of the cationic mechanism, would be expected in more polar solvents, or when employing bidentate ligands.

Observed effects in the transition states involved in the migratory insertion step

In the systems investigated here, the regioselectivity is settled in the migratory insertion, as this step is effectively irreversible. Thus, we will analyze geometries, energies, and interactions like *trans* effects and steric hindrance in the transition states for this step in detail.

In general, *trans* influence is attributed to ground states properties, *e.g.* bond lengths, and *trans* effects attributed to activation energies concerning transition states. As we investigate the transition states geometries in terms of bond lengths, we will use the term *trans* influence when we talk about the geometry, and *trans* effect when we refer to the activation energy.

The cationic reaction

The transition states leading to the two product types are virtually isoergic (Fig. 1). Thus, small influences in the order of a few kJ mol^{-1} can be expected to shift the preference significantly. The factors controlling the energy difference can be clearly seen by analyzing the different contributions to the free energy for the two competing transition states in Fig. 4. Looking at only the potential energy, TS (b) leading to the branched product is favored by *ca.* 8 kJ mol^{-1}. There is no significant difference in solvation, but the vibrational contribution adds another 6 kJ mol^{-1} to the energy difference; TS (a) leading to the linear product is stiffer. However, the dispersion contribution stabilizes TS (a) by 13 kJ mol^{-1} relative to TS (b), thanks to the favorable interactions between the styrene moiety and the ligand.

We can analyze the potential energy difference in more detail by applying activation strain analysis[17] on the two transition states and the common pre-insertion complex. For this analysis, we calculate the separated fragment energies in the geometries found in the intermediate and transition states at the B3LYP/LACVP* level. At this level, distorting the styrene into the geometry found in the pre-reactive complex carries a penalty of 9 kJ mol^{-1}, whereas the distortion of the cationic T-shaped Pd-complex costs 43 kJ mol^{-1}. The calculated interaction potential energy is 76 kJ mol^{-1}. Going to the TS leading to the linear product, (a) in Fig. 4, with the separated reactants as a reference point, the styrene suffers 58 kJ mol^{-1} and the Pd complex 125 kJ mol^{-1} in distortion energy, with an interaction energy of 134 kJ mol^{-1}. Going instead through TS (b) leading to the branched product, all energies are

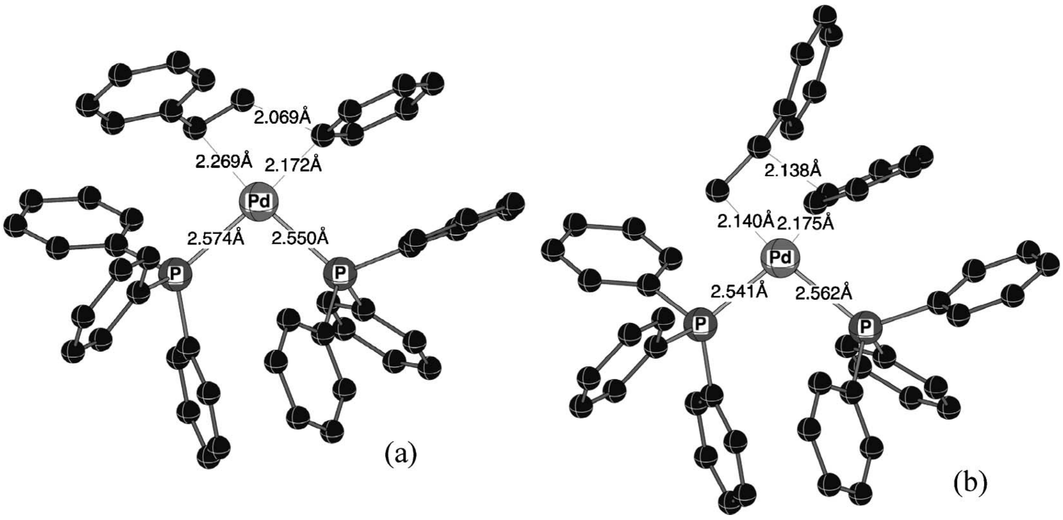

Fig. 4 The two transition states in the cationic Heck reaction.

larger; an additional 69 and 142 kJ mol^{-1} for styrene and the Pd complex, respectively, and an interaction energy of 167 kJ mol^{-1}. Thus, the distortion is more serious for adding an aryl group at the already substituted carbon and forming an anion in an unstabilized terminal position, but this effect is fully compensated by the efficient stabilizing interaction with Pd.

An examination of the transition state geometries show important *trans*-influences (Fig. 4). In the pre-insertion intermediate, the Pd–P bond *trans* to the phenyl group is very long, 2.61 Å, whereas the Pd–P bond *trans* to the coordinated styrene substrate is only 2.40 Å. The long bond shrinks when going to the transition state. This is in accordance with the decreasing *trans* influence of the migrating phenyl group as it is transferred to the alkene, going from a formally anionic ligand to a neutral substituent. The effect is most noticeable in the transition state leading to the branched product, (b), where the bond length is decreased to 2.54 Å.

Looking at the forming Pd–C bonds, we can see that the benzylic position in the linear TS (a) has little need of stabilization and therefore shows a long forming bond to Pd, whereas the unstabilized terminal carbon in the branched TS (b) gives rise to a much shorter forming Pd–C bond. Thus, the electron donation from the substrate to Pd in forming the new Pd–C bond is more pronounced in the branched TS. This is in line with experimental Hammett studies showing that the branched product formation is initiated by electrophilic attack of Pd on the substrate, resulting in significant buildup of positive charge on the benzylic carbon in TS (b).[6]

The neutral reaction

The neutral Heck reaction is quite different from the cationic version. Firstly, the lack of positive charge means that palladium is substantially less electrophilic. Secondly, the ligands are strongly differentiated, both in terms of *trans* influence and steric properties. Finally, with two different ligands, the number of possible paths is doubled. The best conformations of the four different types of transition states in the neutral Heck reaction are depicted in Fig. 5.

Of the transition states in Fig. 5, (c) and (d) are not expected to contribute to product formation in the current case, since the path leading to these two transition states is too high in energy (Fig. 2), even though the transition states themselves are low in energy. However, this is not expected to be general for all types of ligands; in an earlier case, it was noted that the preferred path included the high energy intermediate,[11] a Halpern-type selectivity.[26] Thus, we will discuss the structure–reactivity relationship in all four transition states, since all could influence product selectivities in other types of systems.

The lowest barrier is found for case (c), where the migrating aryl group is *trans* to the ligand with the strongest *trans* effect,

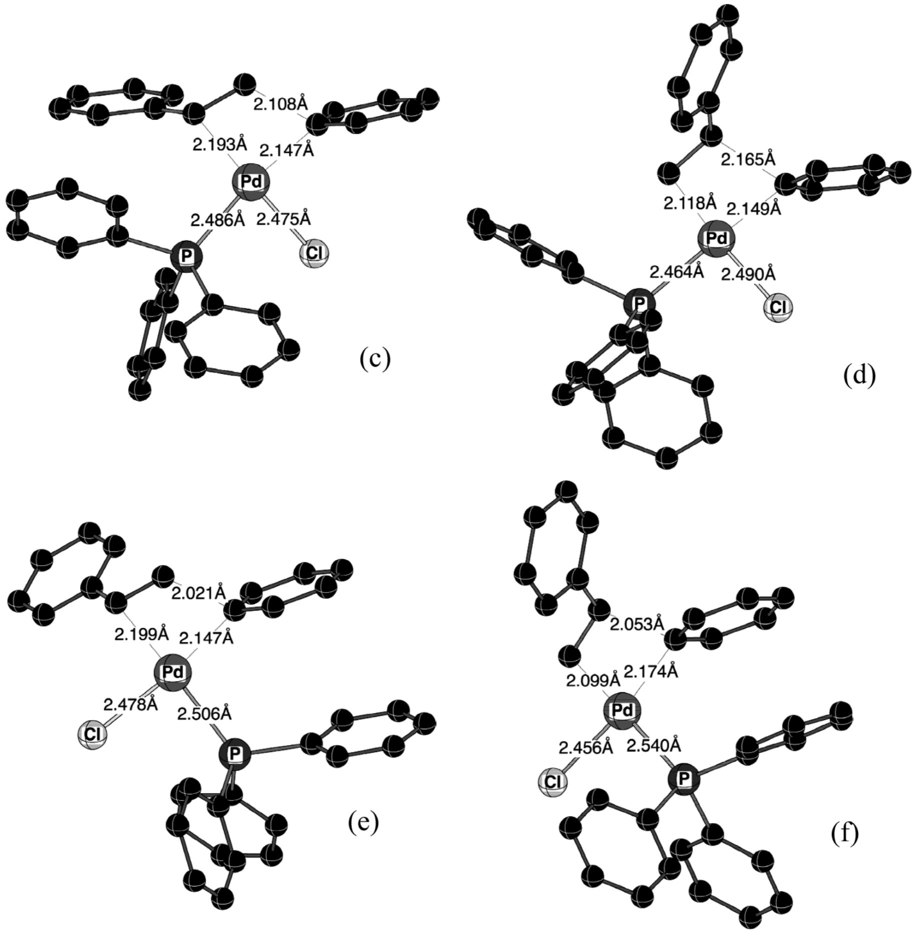

Fig. 5 The four carbopalladation transition states in the neutral Heck reaction.

the phosphine. This can be rationalized in terms of much higher reactivity of the aryl group that is *trans* to the ligand with the strongest *trans* effect.[11,24] The balance between reactivity and accessibility is fine in the Heck reaction; for the neutral reaction investigated here, the accessibility seems to be too low to allow involvement of TS (c) and (d), whereas for cationic Heck with PN-ligands, the path *via* the high energy intermediate is accessible and indeed preferred.[11]

Deconvoluting the energy difference for (c) and (d), the two transition states are virtually isoergic, and also have similar potential energies. Again, TS (c) leading to the linear product is a bit stiffer, giving a vibrational penalty. It is also slightly less well solvated. However, both of these effects are counteracted by the dispersion correction; again, the styrene moiety is well stabilized by interactions with the ligand. The activation strain analysis gives values very similar to the cationic case; styrene is more strongly distorted when going through TS (c) leading to the branched product, but this strain is compensated by the stronger interaction with the Pd center. The detailed values can be found in the ESI.†

The two accessible transition states, (e) and (f), differ by 6 kJ mol^{-1}, giving rise to a preference for the linear product in the neutral Heck reaction, in good agreement with experimental observations.[5] In this case, the driving force is weaker, since only a weakly *trans*-influencing chloride is *trans* to the migrating aryl group. In addition, the phosphine ligand provides resistance to formation of a *trans* Pd–C bond, in particular for the unstabilized alkyl position, less seriously for the more stable benzylic position. The relative *trans* influence of these two carbons is also seen in the length of the Pd–P bond, 2.51 Å in (e) and 2.54 Å in (f). From the same perspective, we can compare the two branched transition states, (d) and (f). We can see that when the phosphine is *trans* to the forming Pd–C bond, case (f), both this bond and the forming C–C bond is significantly shorter than in case (d), indicating that TS (f) is "later", again showing the resistance of the strongly *trans*-influencing phosphine ligand to the formation of the Pd–C bond. The same effect can be seen when comparing the two linear transition states (c) and (e), although the difference here is slightly less pronounced.

Comparing the energy contributions for transition states (e) and (f), we see a strong potential energy difference of 14 kJ mol^{-1}, due to formation of a localized alkyl anion *trans* to the phosphine in TS (f). As before, the stiffness and solvation penalizes TS (e) more than TS (f), reducing the free energy difference to the final value of 6 kJ mol^{-1}. However, in this case, there is no difference in the dispersion correction, the styrene cannot get any stabilization from the chloride ligand. The activation strain of the styrene moiety in TS (d) is larger than that in TS (f), but so is the interaction energy, indicating that TS (f) is the "later" of the two transition states. As before, this can be attributed to the resistance of the phosphine to formation of a localized carbanion in the *trans* position.

Conclusions

In this study, we have used computational calculations to investigate the regio-selectivity for addition of phenyl to styrene in the well-known Heck reaction. Two mechanistic pathways were investigated, the cationic and the neutral Heck reaction. In both cases, the migratory insertion step was found to be irreversible and therefore the regioselectivity determining step. In the neutral reaction, the styrene can associate either *trans* to the halide or to the phosphine. The former path would lead to low selectivity, but is strongly disfavored by severe *trans* effects in the T-shaped intermediate and therefore unlikely to contribute to the final selectivity. The latter path goes *via* the favored T-shaped intermediate, and gives a preference for the linear product, in agreement with experimental observations.[5] For the halide free cationic reaction, the two paths are very close in energy, and therefore a branched/linear mixture is expected, again in agreement with experimental observations.[6]

The cationic path would be expected to be competitive with the neutral path even in the presence of small amounts of halide, but the difference in activation barrier is small, and subject to computational uncertainty, in particular for the relative solvation energy of the cationic and neutral intermediate. A strong dielectric solvent, small or bidentate phosphine ligands, and weakly coordinating counterion would all be expected to favor the cationic path, whereas solvents of lower polarity, bulky monodentate ligands, or strongly associated halide ions should be able to switch the reaction to the linear preference found in the neutral path.

Acknowledgements

We are grateful to AstraZeneca for generous support, and to Tobias Rein, Per Ryberg, and Sten Nilsson Lill for helpful discussions.

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