On the Nature of the Intermediates and the Role of Chloride Ions in Pd-Catalyzed Allylic Alkylations: Added Insight from Density Functional Theory[†]

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Received: February 28, 2008; Revised Manuscript Received: May 27, 2008

The reactivity of intermediates in palladium-catalyzed allylic alkylation was investigated using DFT (B3LYP) calculations including a PB-SCRF solvation model. In the presence of both phosphine and chloride ligands, the allyl intermediate is in equilibrium between a cationic η^3-allylPd complex with two phosphine ligands, the corresponding neutral complex with one phosphine and one chloride ligand, and a neutral η^1-allylPd complex with one chloride and two phosphine ligands. The η^1-complex is unreactive toward nucleophiles. The cationic η^3-complex is the intermediate most frequently invoked in the title reaction, but in the presence of halides, the neutral, unsymmetrically substituted η^3-complex will be formed rapidly from anionic Pd(0) complexes in solution. Since the latter will prefer both leaving group ionization and reaction with nucleophiles in the position trans to phosphorus, it can rationalize the observed "memory effect" (a regioretention) in the title reaction, even in the absence of chiral ligands.

Introduction

Since its discovery more than two decades ago and with subsequent development, palladium-catalyzed allylic alkylation has become one of the most popular and versatile transformations in synthetic organic chemistry.[1] The generally accepted catalytic cycle (Figure 1) contains a number of steps where stereochemistry can be induced,[1f] but many experimental[2] and computational[3] studies have focused on the attack of the nucleophile on the cationic η^3-allylpalladium complex as the regio- and enantio-determining step.

Experimental and theoretical investigations by several groups have led to modifications and extensions of the proposed catalytic cycle.[4] For example, when an allylic leaving group (e.g., acetate or carbonate) can coordinate to palladium, the formation of a neutral η^1-allylpalladium species after the initial oxidative addition by the active Pd(0) species is possible,[5] albeit this complex is still in equilibrium with the traditional cationic η^3-allylpalladium species.[6] Many of these subtleties were discovered in experimental investigations of the stoichiometric reaction, and as a consequence, their relevance to the numerous catalytic reactions known for palladium is still not fully resolved. A discrepancy between observable intermediates and reactive intermediates is not an unfamiliar situation in catalysis, one prominent example being the induction of stereoselectivity in the rhodium(I)-catalyzed asymmetric hydrogenation, which was elegantly delineated by Halpern and co-workers.[7]

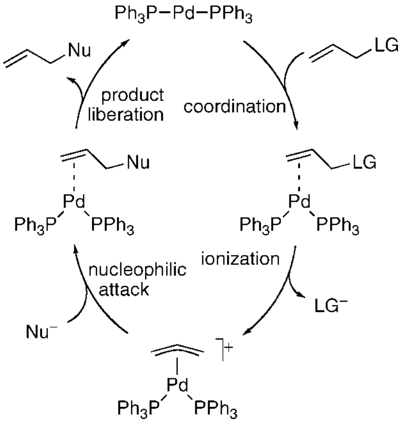

Figure 1. Proposed catalytic cycle for the Pd-catalyzed allylic alkylation. LG = leaving group (eg., acetate), Nu = nucleophile (eg., malonate).

In the presence of chloride ions, anionic chloride-ligated Pd(0) complexes of the general formula [PdL_2Cl] can form, as shown experimentally for L = PPh_3[8] and further verified theoretically by Shaik and co-workers in a recent computational study (DFT/B3LYP) covering a variety of phosphine ligands (L = PR_3; R = H, Me, vinyl, and Ph).[9] Such complexes are active in oxidative addition but tend to lose one ligand−palladium bond in the reaction.[9] Oxidative addition to an allylic substrate eventually leads to an η^3-allylpalladium complex which is an energy minimum on the potential energy surface both in the gas phase and when a continuum solvation model is employed. Our goal was to achieve an overall understanding of the catalytic reaction by addressing the reactivity of some of the proposed intermediates in the catalytic cycle for palladium-catalyzed allylic alkylation in the presence of chloride anions. In the present paper, high-level computational chemistry is applied in order to facilitate the inclusion of reactive intermediates, which are often not detectable during a catalytic process. For equilibria between anionic and neutral species, it is necessary to account for the effect of the solvent; for the transition state of the title

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[†] Part of the "Sason S. Shaik Festschrift".

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10.1021/jp801759z CCC: $40.75

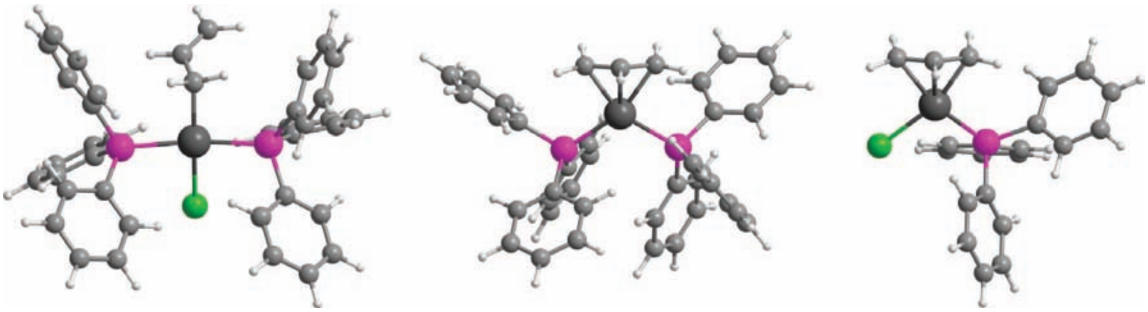

Figure 2. Structures of the optimized ground-state allyl complexes with PPh_3 as the ligand. Left: The η^1-allyl complex with one chloride and two phosphine ligands. Center: The cationic η^3-allyl complex with two phosphine ligands. Right: The neutral η^3-allyl complex with one phosphine and one chloride as ligands.

reaction, earlier work has shown that the structures are qualitatively different in the gas phase.[10] We have therefore chosen to employ a continuum model for the solvent. A recent investigation[11] has shown that even for a small species with high electron density like the chloride ion, reasonably accurate results are obtained using this type of model.

Examples of halide effects are abundant within the area of transition-metal-catalyzed organic transformations, and the subject has been reviewed thoroughly.[12] Halides can, for example, be used as additives to accelerate oxidative addition in cross-coupling reactions.[8,13] We have been especially interested in a particular halide effect, the so-called "memory effects",[14] which is a term used to characterize the transfer of structural features (most often regiochemistry and/or stereochemistry) from reactant to product despite a catalytic cycle with intermediates apparently lacking these features (as exemplified by the symmetrical allylpalladium complex in Figure 1). These phenomena have been observed independently by several research groups[14,15] and have been shown to appear in the presence of chloride anions either added as Bu_4NCl or originating from the precursor metal complex when using, for example, the $[(\eta^3\text{-}C_3H_5)Pd(\mu\text{-}Cl)]_2$ dimer along with added triphenylphosphine.[16]

Several different explanations of the memory effect have been put forward, including η^1-allyl complexes with Pd ligated by one chloride and two phosphines,[13] ion pairing between the leaving group (often acetate) and nucleophile,[17] and the existence of a trans-effect-directing nucleophilic attack to the allylic position trans to phosphorus in an η^3-allyl complex with Pd ligated by one chloride and one phosphine.[18]

The stability and reactivity of $[Pd(PPh_3)_2Cl]^-$ have been studied earlier[9] using geometries determined in vacuo, where intramolecular electrostatic interactions are expected to exaggerate stabilities and enforce close contacts of dipoles and ions. In the current study, we have considered ligand dissociation while using geometries obtained with a solvation model.[19] The stabilities and reactivities of η^1- and η^3-allylPd complexes have been investigated in detail, with an emphasis on rationalizing the observed regioretention in the presence of chloride ions.

Results and Discussion

As a starting point for the catalytic cycle, we have chosen to investigate two di-ligated Pd(0) complexes, either the neutral $Pd(PPh_3)_2$ or the anionic $[Pd(PPh_3)Cl]^-$, both of which will be in equilibrium with $[Pd(PPh_3)_2Cl]^-$.[9] Previously, we have investigated and compared these complexes and their reactivity toward oxidative addition of phenyl iodide,[19] but here, we will instead focus on the reactivity toward allylic acetate. The allylic alkylation is a rather unusual chemical transformation in the sense that the two crucial steps in the catalytic cycle are mechanistically very similar (ionization and nucleophilic attack). Most synthetic applications involve formation of a new carbon−carbon bond, the reaction of a typical leaving group (e.g., acetate) being reversible,[20] whereas a typical carbon nucleophile (e.g., malonate) will add irreversibly to the allyl moiety. Selection of an appropriate model system is always a challenging task in computational chemistry, and one often has to make compromises between system size and level of theory. Without a solvent model, the reaction between a cationic η^3-allylpalladium complex and a carbanion occurs without a barrier, as shown previously.[10] Transition states can be located in vacuo when using neutral nucleophiles (e.g., ammonia), but the use of a carbanion and a solvent model seems to be a much more realistic model. In the current work, we have investigated the proposed catalytic cycle using a realistic leaving group (acetate) and nucleophile (sodium enolate of malonaldehyde) in combination with the full PPh_3 ligand.

Pd(II)−Allyl complexes. The first complexes considered were the classical cationic η^3-allylpalladium complexes, in which palladium is ligated by two phosphine ligands (Figure 2, center).

In the presence of chloride anions, there is a possibility for direct coordination to Pd while displacing one of the allylic termini to yield neutral $(\eta^1\text{-}C_3H_5)Pd(PPh_3)_2Cl$ complexes (Figure 2, left). As mentioned previously, these complexes have been proposed as possible intermediates in the palladium-catalyzed allylic alkylation in the presence of chloride ions.[9] A mechanism involving two consecutive S_N2' attacks can then explain the observed memory effects.[2a] Furthermore, a neutral η^3-allylpalladium complex ligated by one chloride and one phosphine, that is, having the formula $(\eta^3\text{-}C_3H_5)Pd(PPh_3)Cl$ and possibly originating from reaction between $[Pd(PPh_3)Cl]^-$ and the allylic precursor, has been considered (Figure 2, right). The difference in the trans-effect of the two ligands introduces electronic and geometrical differentiation of the two termini on the η^3-ligated allyl. This phenomenon has also been proposed as an explanation for the memory effect.[14,18]

The assessment of positions of equilibria with more than a single component on either side can sometimes be difficult in computational chemistry, especially if the comparison involves molecules of different charge, in which case an accurate method of accounting for solvation is absolutely crucial. With the computational methods applied in the current study (DFT/B3LYP, LACVP* basis set), we find all three isomers to have virtually identical energies (within 5 kJ/mol).[21] It is particularly interesting that the two neutral, chloride-ligated complexes have equal energies since this comparison includes only neutral species and therefore should be of good accuracy. The com-

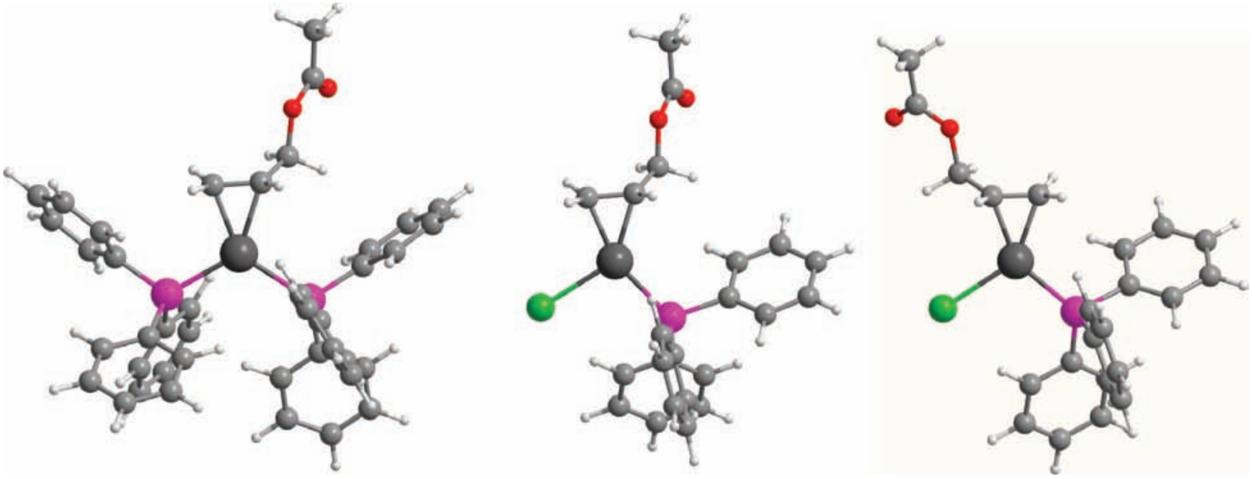

Figure 3. Structures of complexes derived from allyl acetate and either diphosphine-ligated palladium (left) or monophosphine- or monochloride-ligated palladium (center and right).

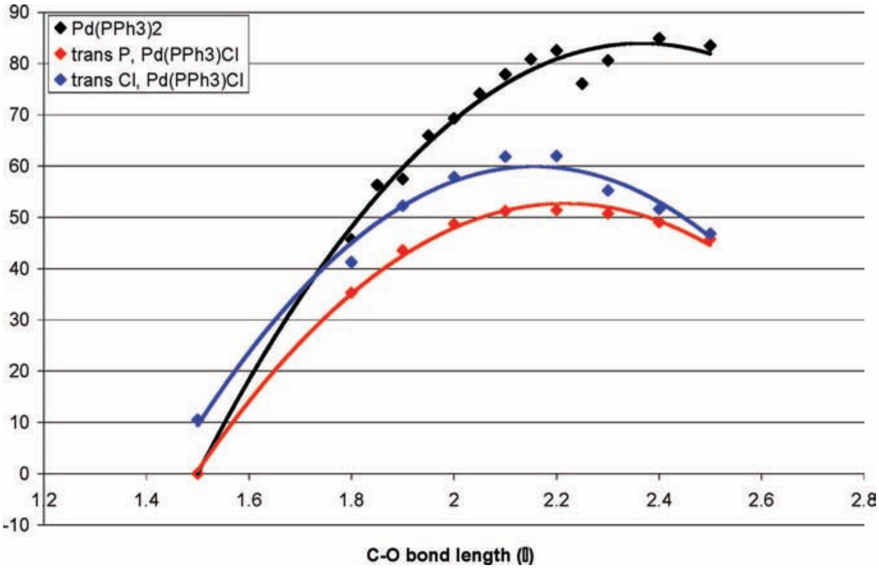

Figure 4. Energy as a function of C−O distance for acetate dissociation from the complexes depicted in Figure 3.

parison between complexes of different charge is usually regarded as being associated with a higher degree of uncertainty, in particular when the charge density is high. Previously, in an investigation of the free energy of solvation of small anions, the error was found to be 25 kJ/mol for solvation of chloride in THF,[10] which is larger than the observed energy differences in the current work. However, the computed free energy of solvation was always larger than the experimental values, which, in the comparison above, would disfavor the cationic η^3-allylpalladium complex (Figure 2, center).

Oxidative Addition. The first step in the catalytic cycle is oxidative addition, which, in the absence of chloride, is believed to proceed from a Pd(0)−olefin complex ligated by two PPh_3 molecules. With acetate as the leaving group, the Pd(0)−olefin complex has the expected trigonal geometry (Figure 3, left), with Pd−C bond lengths of 2.199 and 2.209 Å. The size and complexity of this system prevents a location of the TS, which instead forces us to perform a series of energy minimizations with a fixed C−O bond length to determine the energy profile for oxidative addition (Figure 4). This series of calculations indicated that the TS was very late and occurs at C−O distances of about 2.3Å.

With chloride present, the reactivity of a mixed complex with one chloride and one phosphine as ligands was investigated. These complexes are structurally quite similar to the usual cationic η^3-allylpalladium complexes ligated by two phosphines (or one diphosphine), but when a phosphine is replaced by a chloride, this induces electronic differentiation of the two allylic termini.[18] This difference is observable even in the ground state of the η^3-allylpalladium complexes (Figure 2, right), and in the transition state, this effect leads to a difference in energy for the two reaction pathways (Figure 4).

The Pd(0)−olefin complexes prefer a trigonal planar geometry with the olefin oriented in the coordination plane. Two such complexes are possible, with the acetate trans to either chloride (Figure 3, center) or phosphorus (Figure 3, right). In the minimized olefin structure, the conformation with the acetate trans to phosphorus is favored by 11 kJ/mol. This preference is constant for increasing C−O distances until the transition state is reached at around 2.1−2.2 Å, after which it rapidly decreases.

When chloride is present, the nucleophilicity of the metal center is increased, thus resulting in a stronger bond to the alkene, which is manifested in a reduction of the Pd−C distances to about 2.15−2.16 Å. The results are in agreement with a recent experimental and theoretical investigation on the coordination of olefins to Pd(0) by Popp et al.,[22] where bonding is considered to occur between an electron-rich, nucleophilic Pd(0) and an electron-accepting olefin. Besides the obvious decrease in steric

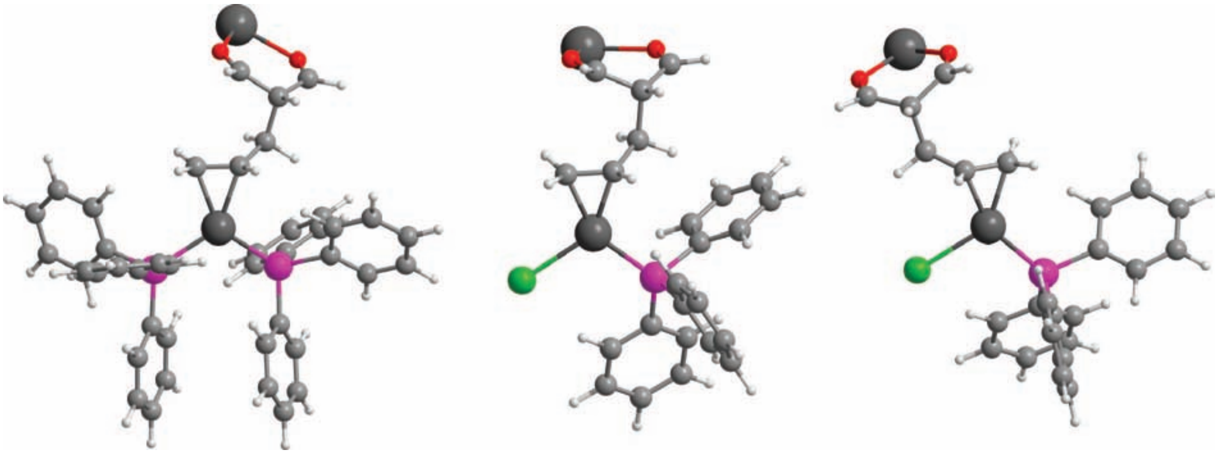

Figure 5. Structures of the complexes derived from attack of the sodium-chelated anion of malonaldehyde on either diphosphine-ligated palladium (left) or monophosphine- or monochloride-ligated palladium (center and right).

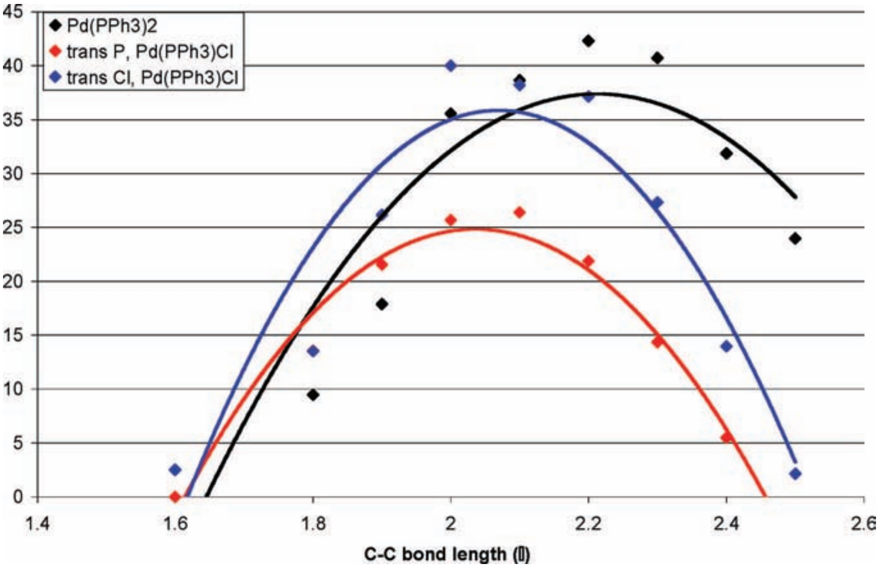

Figure 6. Nucleophilic addition of malonaldehyde to an allylpalladium complex where palladium is coordinated by two phosphines or one phosphine and one chloride. For the latter complex, both regioisomers were investigated, and the trans to phosphorus pathway was found to be favored. In both cases, the energy of the olefin−postcomplex was used as reference.

congestion around Pd, a chloride ligand can also increase the electron density on the metal center, thus making it a more capable electron donor.

Despite several attempts, we were not able to obtain transition states resulting from nucleophilic attack on the η^1-allylpalladium complexes without dissociation of ligands from the coordination sphere of the metal. This lack of reactivity toward nucleophiles is in good agreement with a recent computational study involving the PH_3 model ligand where the η^1-allyl complex was found to react with an NH_3 nucleophile through a “traditional” η^3-allyl TS resulting from decoordination of the second phosphine ligand.[23] The observation that the η^1-allylpalladium complexes possess nucleophilic not electrophilic character has been advanced earlier[24] and forms the basis for several catalytic protocols developed by Szabo and co-workers.[25]

Nucleophilic Addition. The oxidative addition results in the formation of an allylpalladium intermediate, which, in turn, can be intercepted by a nucleophile. As a model for the nucleophile, we have chosen the sodium-chelated anion of malonaldehyde. The complexes of the product olefins are shown in Figure 5.

For the malonaldehyde model, nucleophile formation of the bond trans to phosphorus was the most facile reaction pathway, and also here, the calculations indicated a difference of about 10 kJ/mol between the two possibilities (Figure 6).

Cationic or Neutral? When compared to the cationic diphospine-ligated pathway, the major difference when chloride is present lies in the coordination of the olefin prior to oxidative addition. The olefin can easily be accommodated in the coordination sphere of the metal in the presence of only one phosphine and a small chloride ligand, which in combination with the increased electron density on Pd can significantly accelerate the oxidative addition. Since the oxidative addition is the first step in the catalytic cycle, the acceleration of this step in the presence of chloride has important consequences for the overall selectivity under catalytic conditions. During a catalytic reaction, the neutral η^1-allyl complexes, which we propose to consider as an allylpalladium reservoir, that is, unreactive toward nucleophiles, will not be present in significant amounts. When there is no chloride present, the reaction will proceed through the cationic η^3-allylpalladium diphosphine complex. In the presence of chloride, the preference is for the neutral η^3-allylpalladium complex with one chloride and one phosphine ligand due to a more favorable first step in the catalytic cycle (i.e., oxidative addition). A direct energy

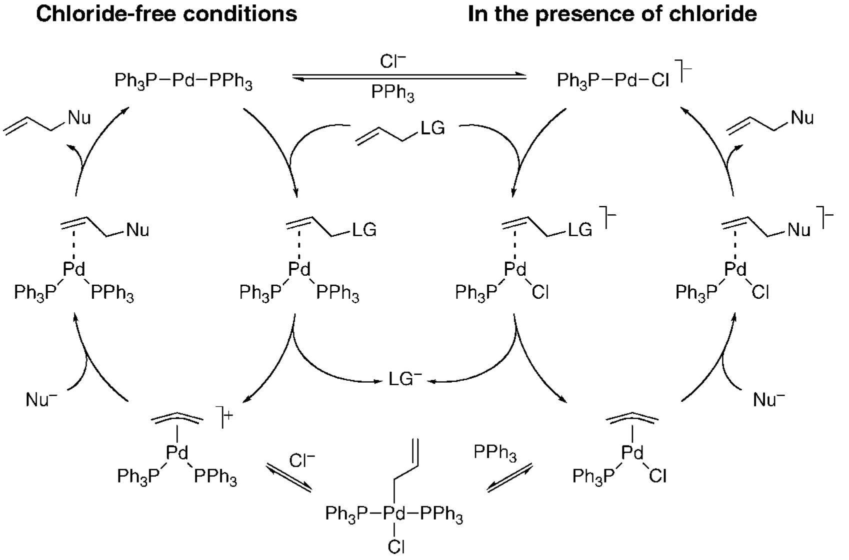

Figure 7. Competing catalytic cycles for the allylic alkylation in the presence of chloride anions.

comparison of the differences in reactivity between the cationic (diphosphine) and neutral (mixed phosphine/chloride) η^3- allylpalladium is difficult since it involves a comparison between charged and neutral species. However, when including the oxidative addition step, there is a clear preference for the pathway originating from the facile coordination of the allylic substrate to the anionic Pd(PPh$_3$)Cl species.

A catalytic cycle in accordance with all computed energies and reactivities is shown in Figure 7.

Most synthetic reactions are run with only catalytic amounts of palladium and phosphine (usually two PPh$_3$ per Pd), which is formed in situ either from Pd(dba)$_2$ + 2 PPh$_3$ or from [(η^3-allyl)Pd(μ-Cl)]$_2$ + 4 PPh$_3$. When chloride ions are present in the reaction mixture, the higher reactivity of the anionic [Pd(PPh$_3$)Cl]$^-$ in the initial oxidative addition compared to that of the neutral Pd(PPh$_3$)$_2$, followed by a nucleophilic attack (which is faster than ligand exchange), means that the major part of the product will arise from small amounts of the unsymmetrical [Pd(PPh$_3$)Cl(η^3-allyl)]. The electronic difference between the phosphine ligand and chloride in the unsymmetrical η^3-allylpalladium complex can rationalize the observed "memory effects".[14,15] This scenario is outlined in Figure 8. Under catalytic reaction conditions, there is a large excess of allyl acetate, and the initial oxidative addition will be the selectivity-determining step in the catalytic cycle. If this step is accelerated when chloride is ligating palladium, the major part of the product will arise from the pathway shown on the right-hand side. Notice how the position of the carbon atom bearing the leaving group (OAc, marked with a star in Figure 8) is kept trans to phosphorus, and this is also the favored place of attack by the nucleophile. In the "cationic" path, all information is lost in the symmetrical η^3-allylpalladium complex.

Conclusion

The palladium-catalyzed allylic alkylation was investigated using DFT/B3LYP with acetate and malonaldehyde as the leaving group and nucleophile, respectively. The relative energies of the intermediate allyl complexes were determined, along with their reactivity in oxidative addition and nucleophilic addition processes. Two different catalytic cycles were proposed with the presence of chloride ions determining which one is operative. When chloride is present, the increased reactivity of monophosphine- or monochloride-ligated Pd(0) species toward oxidative addition readily explains the "memory effects" observed in experiments as arising from nucleophilic addition trans to phosphorus in an neutral, unsymmetrical η^3-allylpalladium complex.

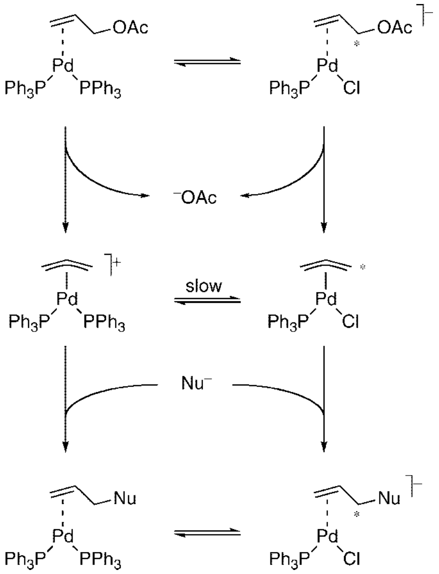

Figure 8. The two pathways involving η^3-allylpalladium complexes in Pd-catalyzed allylic alkylation. The overall selectivity-determining step under catalytic conditions is coordination of the olefin and subsequent oxidative addition, which is significantly faster when chloride is coordinating to palladium.

Computational Methods

All structures were minimized using density functional theory (DFT) with the hybrid density functional B3LYP,[26] which has become the method of choice for studying reactions involving metal complexes. The calculations were performed in Jaguar v. 6.5[27] using the LACVP* basis set. The LACVP* basis set uses the Hay–Wadt small-core ECP and basis set for palladium, and 6-31G* for all light atoms. All calculations were carried out using the PB-SCRF solvation model in Jaguar,[27,29] employing parameters suitable for dichloromethane (dielectric constant of 9.08 and probe radius of 2.33237 Å). In this model, the solvent is described as a continuum, where the molecule is put into a reaction field consisting of surface charges on a solventaccessible surface constructed using a hypothetical spherical solvent probe molecule with the indicated radius.[30] The wave function and the reaction field charges were solved iteratively until self-consistency was reached. Global minima and transition states were converged on gradients.

Supporting Information Available: Cartesian coordinates and solution phase energies for all structures discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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JP801759Z