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The Mechanism of the Phosphine-Free Palladium-Catalyzed Hydroarylation of Alkynes

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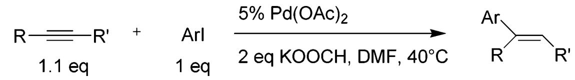
Abstract: The mechanism of the Pd-catalyzed hydroarylation and hydrovinylation reaction of alkynes has been studied by a combination of experimental and theoretical methods (B3LYP), with an emphasis on the phosphine-free version. The regioselectivity of the hydroarylation and hydrovinylation shows unexpected differences, which could be attributed mainly to the higher steric demand of the cyclohexenyl group as compared to the phenyl group. Hydroarylation of α,β-acetylenic carbonyl substrates yields a very unusual anti-Michael selectivity, which is shown to result from reaction of the nonconjugated double bond, leaving the conjugation intact. In all cases were the regioselectivities reproduced by the calculations.

Introduction

Over the past decades, palladium-catalyzed reactions have revolutionized synthetic organic chemistry.[1] With reactions such as the Suzuki-coupling[2] and the Heck reaction,[3] completely new tools to construct complex organic molecules have become available. Despite the fact that these methods were developed more than two decades ago, much of the mechanistic detail has not been elucidated to date. Experimental work on phosphine-ligated palladium species improved the understanding of these reactions substantially, although many details are still not fully understood.[4] A number of computational studies on different reaction steps of these reactions have improved the knowledge of the details of different steps in some of the catalytic cycles.[5]

Scheme 1. Typical Reaction Conditions for the Phosphine-Free Hydroarylation Reaction



The ligand-free palladium(0)-catalyzed hydroarylation reaction was developed by Cacchi and co-workers (Scheme 1).[6] It contains several challenges and a multitude of steps never described in detail in the literature. The reaction can be viewed as a reductive addition of an aryl iodide to a disubstituted acetylene, with formate acting as the reducing agent. It has been shown that the hydroarylation reaction is an effective protocol for producing trisubstituted alkenes and cyclic derivatives (with properly substituted alkynes) under mild ligand-free reaction conditions. Unfortunately, it has been proven difficult to control the regiochemical outcome of the reaction. Even on acetylenes substituted with a relatively non-bulky aryl on the one end, and a bulky *tert*-butyl group on the other, the addition may be nonregioselective under certain conditions. Quite surprisingly, complete regioselectivity has been observed when reacting a similar *tert*-butyl aryl acetylene, but with the aryl iodide substrate exchanged for a 4-phenyl cyclohexenyl triflate (Scheme 2).[7] In this paper, a rationalization for the observed regiochemical outcome is presented, as well as a full mechanistic investigation of all of the steps in the catalytic cycle of the hydroarylation reaction, by a combination of hybrid density functional (B3LYP) and experimental methods.

Results and Discussion

Using DFT methods, we have characterized the catalytic cycle of the title reaction, for each step investigating different compositions and geometries. The catalytic cycle consists of oxidative addition, migratory insertion, and reductive elimination as the major steps, but with many possible points on variation,

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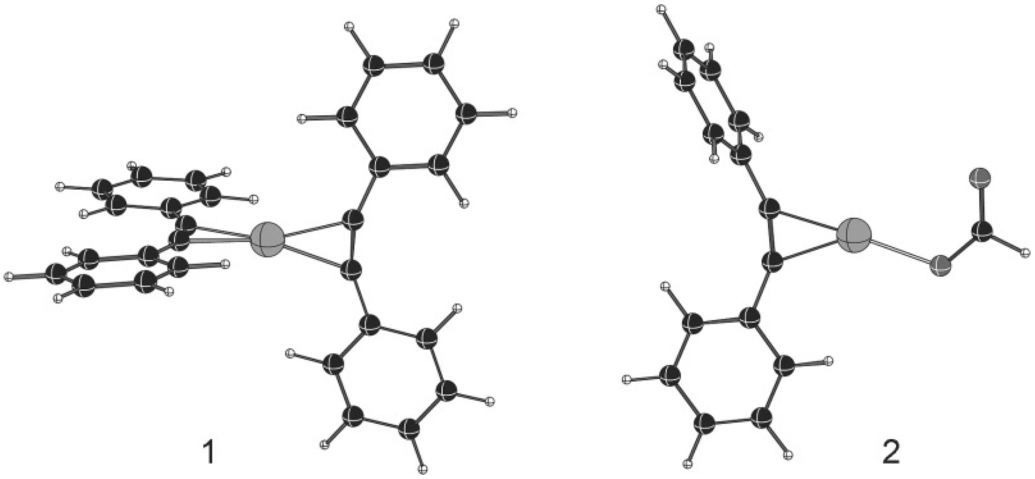
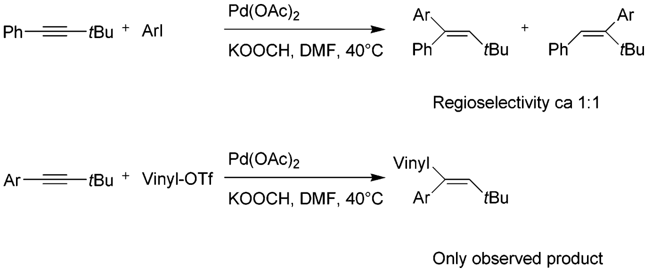


Figure 1. Proposed active species in the hydroarylation, under phosphine-free conditions.

Scheme 2. Regiochemical Outcome of the Hydroarylation and the Hydrovinylation



like the exact timing and mechanism of the formate hydride transfer and ligand exchange steps. We will go through the details of each step in order, starting with an analysis of the palladium(0) species present before oxidative addition.

1. Active Catalytic Palladium(0) Species. In the majority of the reactions catalyzed by homogeneous palladium described to date, palladium is ligated to phosphines to keep the active palladium(0) species from precipitating as palladium black. For the hydroarylation reaction, the observation that addition of phosphines did not improve the outcome of the reaction in some cases[6,8] or even can favor the reduction pathway (vide infra) when vinyl triflates are used as the vinyl components[7] led to a change of the protocol. Because the addition of phosphines brings several disadvantages, for example, tedious separation and oxygen sensitivity, the reaction is nowadays mostly performed under ligand-free conditions. As was just mentioned, ligand-free conditions are usually advantageous from a synthetic perspective, but from a theoretical viewpoint it makes the elucidation of the mechanism more challenging. With the phosphines left out, something else must be acting as a stabilizer of palladium(0) to keep active catalyst present in the solution phase. Under typical reaction conditions, there are several possibilities, which include the solvent DMF, the anions formate and iodide, or the substrates aryl iodide and alkyne. The d^{10} electronic configuration of palladium(0) indicates that the ligand should ideally be a strong π-acceptor. In an earlier study of the stability and reactivity of palladium alkyne complexes, it was found that these complexes are surprisingly stable, in some cases even more stable than the palladium phosphine analogues.[9] Two types of complexes were concluded to be the most probable active species, the first one being a neutral complex coordinated to two alkynes, which are strong π-accepting ligands. The second one considered is an anionic complex with one alkyne and one formate ligand because anionic complexes have been proposed as the active species in numerous studies.[9–12] With the theoretical tools employed herein (B3LYP + continuum solvation), we expect a fairly large but systematic error in the absolute solvation energies of anionic species.[13] We have therefore avoided a direct comparison of these two types of complexes, but instead characterized each reaction manifold fully.

In this investigation, we have chosen diphenyl acetylene as the model disubstituted alkyne, because this alkyne has been proven to function well as a substrate in the hydroarylation reaction.[8] The two palladium(0) species most likely to be present in high concentration are then $Pd(PhC{\equiv}CPh)_2$ (**1**) and $[Pd(PhC{\equiv}CPh)OOCH]^-$ (**2**) (Figure 1). The structure of $Pd(PhC{\equiv}CPh)_2$ is such that the two diphenyl acetylene ligands are situated in a perpendicular fashion. The C−C triple bond is prolonged from 1.21 Å in the free diphenyl acetylene to 1.26 Å, as a consequence of the electron backdonation from palladium. In $[Pd(PhC{\equiv}CPh)OOCH]^-$, where the triple bond does not have to compete for the electron density on Pd, the C−C triple bond is slightly longer, 1.27 Å. Both the neutral and the anionic complex are virtually linear across palladium.

2. Oxidative Addition. Oxidative addition of aryl iodides to palladium(0) complexes coordinated to two phosphines has recently been investigated by DFT calculations. Senn and Ziegler described addition to palladium(0) species ligated to a bidentate phosphine.[14] With incorporation of a solvent model in the transition state optimizations, the oxidative addition was shown to proceed via an S_NAr-type mechanism, in contrast to the three-

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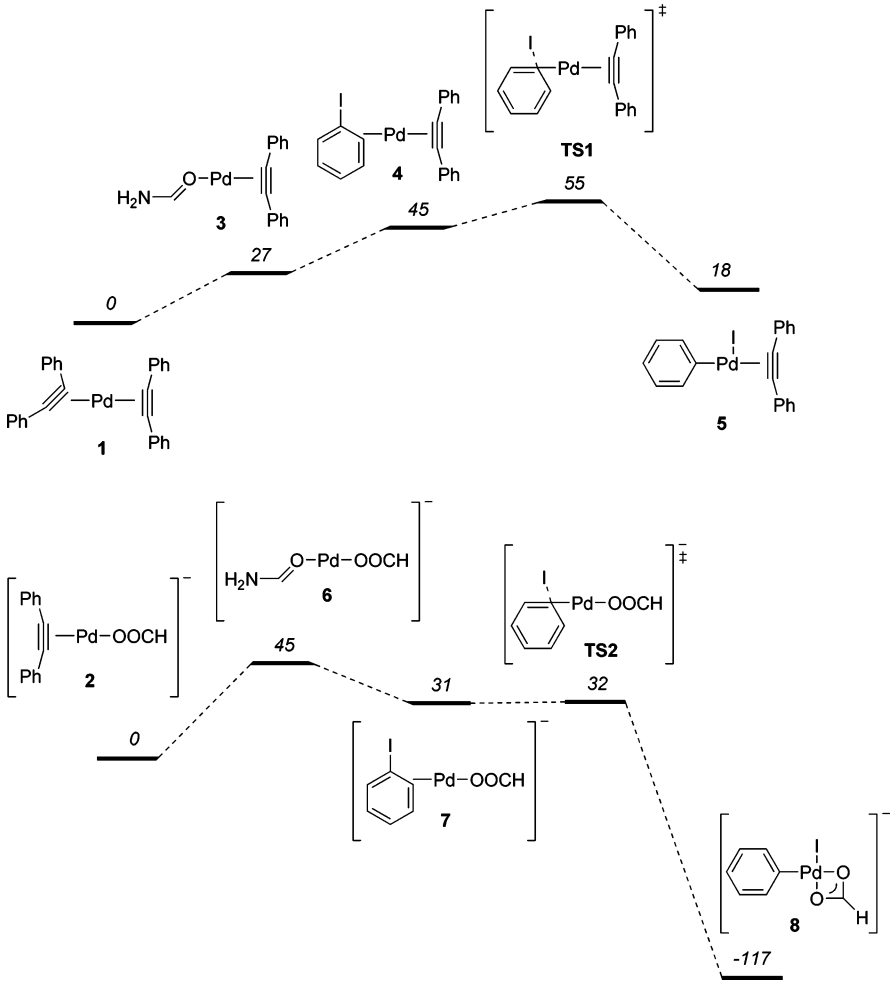

Figure 2. Reaction coordinates for the oxidative addition of phenyl iodide to a neutral and an anionic palladium(0) complex. Numbers in italics represent relative potential energies in kJ/mol.

centered oxidative addition mechanism found in the gas phase, frequently described in text books.[15] Two other groups have studied oxidative addition of phenyl iodide to anionic species of the type $[PdL_2X]^-$, in which the oxidative addition is preceded by decoordination of the anion.[11] Lately, investigations in our group have concluded that the reactive species in palladium-catalyzed oxidative addition of aryl iodide is most likely a low ligated one.[9,12] The reactivity toward oxidative addition of the lower coordinated species, Pd(HC≡CH)(PhI) and $[Pd(OOCH)(PhI)]^-$, was found to be substantially higher than that for the tricoordinate analogues, $Pd(HC{\equiv}CH)_2(PhI)$ and $[Pd(HC{\equiv}CH)(OOCH)(PhI)]^-$.

Ligand exchange at $Pd(PhC{\equiv}CPh)_2$ to dicoordinate complex with a diphenyl acetylene and phenyl iodide Pd(PhC≡CPh)(PhI) is an endothermic reaction by 45 kJ/mol. A possible intermediate in the formation of the prereactive complex is the solvent complex formed by exchange of one of the diphenyl acetylenes by an explicit solvent molecule (formamide has been employed as a model for DMF throughout this investigation). Structurally the prereactive complex **4** is very similar to the previously reported complex Pd(HC≡CH)(PhI),[9] with the phenyl iodide coordinating with the $C_{ipso}C_{ortho}$ double bond to palladium trans to the diphenyl acetylene ligand. The oxidative addition at the prereactive complex Pd(PhC≡CPh)(PhI) takes place via a barrier of 10 kJ/mol (**TS1**). The C−I bond is elongated from 2.20 Å in the prereactive complex to 2.44 Å in the transition state. The product of this reaction is the tricoordinate palladium(II) complex (**5**). Most probably a solvent molecule will fill the free coordination site, to give a complex with the typical square planar structure of d^8-metal complexes.

Another possibility for oxidative addition has also been considered, exchange of the neutral ligand at $[Pd(PhC{\equiv}CPh)OOCH]^-$ to the dicoordinate anionic prereactive complex $[Pd(PhI)OOCH]^-$, possibly via the solvent complex $[Pd(formamide)OOCH]^-$. Formation of the prereactive complex was calculated to be endothermic by 31 kJ/mol. The prereactive complex and the oxidative addition to this species was described in an earlier study,[12] where the oxidative addition was shown to take place basically without any barrier (<1 kJ/mol), which reflects the higher nucleophilicity of the anionic palladium(0) species as compared to the neutral analogue. The immediate product complex is an anionic palladium(II) complex coordinating to phenyl, iodide, and formate in which the formate is coordinating in a bidentate fashion **8**. The exothermicity of the oxidative addition step was calculated to be 117 kJ/mol from the separated reactants and products, respectively. Reaction

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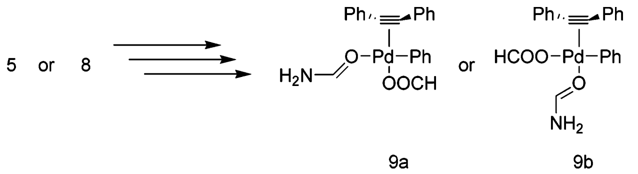


Figure 3. Ligand exchange to the migratory insertion prereactive complex.

coordinates of the oxidative addition reactions are illustrated in Figure 2. As we have shown earlier, the anionic and neutral palladium(0) complexes do not differ significantly in calculated energy.[9] However, the computational comparison depends upon a solvation model using empirically parametrized cavity radii, which to our knowledge has not been validated for comparison of transition metal complexes with differing charge. Thus, the expected uncertainty is larger than the calculated energy difference between the two paths. We will therefore, throughout this work, refrain from direct comparisons between the calculated reaction paths and limit ourselves to the observation that the reaction barrier is lower for the anionic path, in good agreement with the experimental observation that anions increase the rate of oxidative addition to palladium.[10]

3. Ligand Exchange. Before the migratory insertion can take place, a complex with the alkyne in a cis-position to the phenyl must be formed. One of the two coordination sites that do not coordinate the aryl group and the alkyne is likely to coordinate to a formate, because it is present in large excess. To the fourth site of the square planar palladium(II) intermediate, most probably a solvent molecule is coordinated, in this study represented by a formamide. Because the alkyne must be coordinated cis to the aryl, two isomeric complexes should be considered, **9a** and **9b** (Figure 3), which have calculated relative energies of nearly identical magnitude. The coordination mode of the diphenyl acetylene is such that the triple bond is out of the plane.

4. Carbopalladation − Regioselectivity of the Carbopalladation of Alkynes. With the alkyne in a position cis to the aryl group on palladium, a migratory insertion is set to take place. It is in this step that the new carbon−carbon bond is formed and thus also the regiochemical outcome of the reaction is determined. Below follows first a description of the step for the model system, followed by experimental results for different substrates, and finally theoretical results, which rationalize the experimental observations.

4.1. Carbopalladation of PhC≡CPh. Two transition states **TS3a** and **TS3b** for the migratory insertion of PhC≡CPh into the palladium phenyl bond were located, differing only in the relative position of the spectator ligands (formamide and formate). The two transition states were found to be isoenergetic and structurally very similar, and because they are essentially identical in the interesting parts, only the one from the prereactive complex with the formate situated trans to the phenyl will be described. From the structure of the transition state, it appears to be asynchronous. In the transition state, the alkyne has rotated so that it is aligned with its C−C triple bond almost parallel to the Pd−C_{Phenyl} bond. Only a slight elongation of 0.02 to 1.27 Å of the triple bond is observed (1.25 Å in the prereactive complex as compared to 1.35 Å for the resulting double bond in complex **10a**). The Pd−C_{Vinyl} bond, which is formed in this step, is close to being fully formed, with a distance of 2.05 Å (2.00 Å in the resulting vinyl complex). The Pd−C_{Phenyl} bond is, on the other hand, very reactant-like with a bond distance that is basically identical to the one in the prereactive complex, 1.99 and 2.00 Å in **9a** and **TS3a**, respectively. Also, the forming C−C bond is very far from the one in the resulting complex, 2.27 Å in **TS3a** as compared to 1.50 Å in the vinyl complex **10a**. The overall barrier for the carbopalladation step, from the prereactive complex **9a**, was calculated to 86 kJ/mol. The reaction is illustrated in Figure 4.

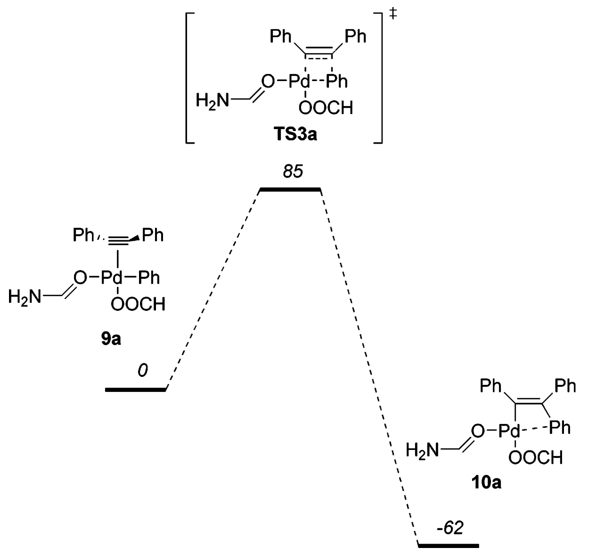


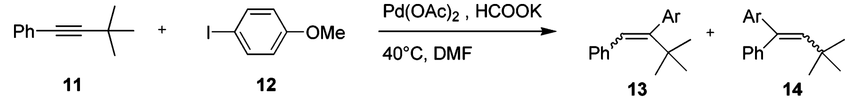
Figure 4. Migratory insertion of PhC≡CPh into the Pd−C_{Phenyl} bond.

4.2. Regiochemistry − Experimental. The outcome of the hydroarylation reaction was investigated by reacting phenyl-*t*-Bu-acetylene with 4-iodo-anisole under standard hydroarylation conditions. The overall yield of the reaction was 76%, and the two regioisomers were observed in the ratio outlined in Scheme 3.

The low observed selectivity when one of the substituents on the acetylene is ^{t}Bu is quite surprising. In a previous study of the hydrovinylation reaction, the similar *p*-acetamidphenyl-^{t}Bu-acetylene (**15**) was reacted with 4-phenylcyclohexenyl-triflate (**16**) under the same reaction conditions as above.[7] This yielded product **17** exclusively in 94% yield (Scheme 4).

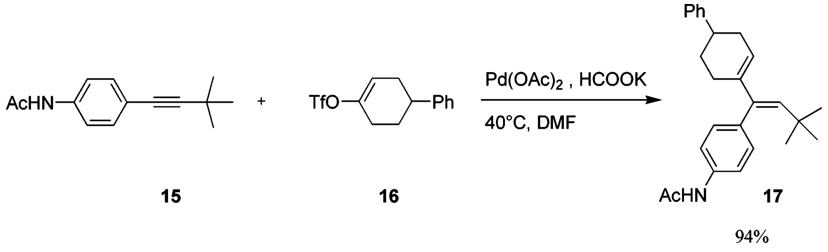
There are two major differences in the two reactions described above. The first is the change from aryl to vinyl, and the second is the change of leaving group from iodide to triflate. The *para*-substituents on the aryl group of the alkyne have previously been shown to only have a minor influence on the regiochemical

Scheme 3. Product Distribution of the Hydroarylation of Phenyl-^{t}Bu-acetylene

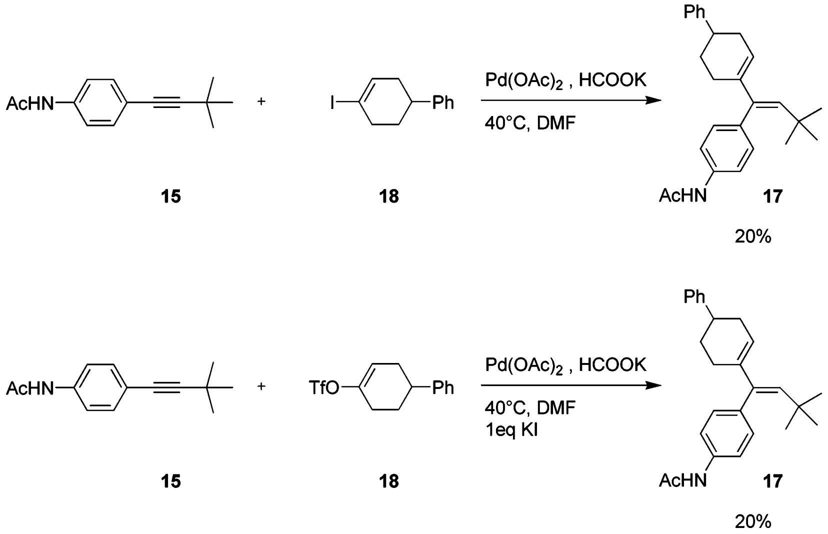


Ratio (**13** : **14**) = 1: 1.1

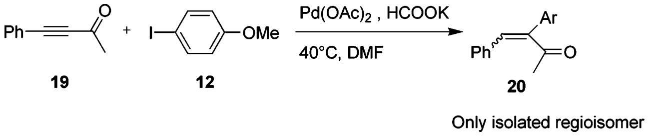
Scheme 4. Product Distribution in the Hydrovinylation Reaction



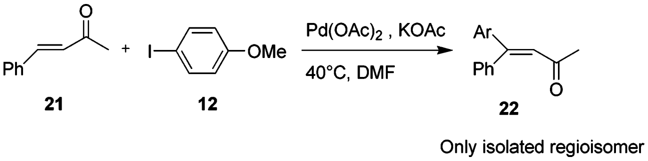
Scheme 5. Product Distribution of the Hydrovinylation Reaction in the Presence of Iodide



Scheme 6. Observed Regiochemical Outcome of Hydroarylation of **19**[6]



Scheme 7. Observed Regiochemical Outcome of the Heck Reaction of **21**[6]



outcome.[7] To find out which change in the substrate is responsible for the change in reactivity, two more reactions were conducted. In the first, the vinyl triflate was replaced with the corresponding vinyl iodide **18**, and in the second iodide ion was added as the potassium salt. As Scheme 5 shows, the regio- and stereochemistry is unchanged, and the only hydrovinylation product observed is **17**. The only difference is the yield, which is reduced from 94% to 20%. This is due to reduction of the vinyl electrophile to 4-phenyl-cyclohexene, a frequently observed side reaction under hydroarylation/vinylation reaction conditions. Why the presence of iodide induces reduction of the vinyl−X species is not clear and is not further commented herein. Still, only one regioisomer is observed in the hydrovinylation reaction.

Another interesting observation made previously regarding regiochemical outcome of hydroarylation of alkynes is that α,*β*-acetylenic carbonyls tend to yield the α-addition product and not the more intuitive Michael-addition product (Scheme 6).[6] On the contrary, in the Heck reaction the corresponding alkenes react in the expected manner, yielding the *β*-substituted product (Scheme 7).

4.3. Rationale for the Regiochemistry. 4.3.1. Difference in Regioselectivity between Aryl and Vinyl. A series of transition states for the carbopalladation step of ^{t}BuC≡CPh were characterized by DFT. Both cis/trans isomers with respect to the spectator ligands formate and formamide were studied. For the hydroarylation, phenyl was used as the migrating group, and in the hydrovinylation case 2-butenyl was used as a model for 4-phenyl-cyclohexenyl to include the steric effects induced by the protons present in proximity to the reactive center. The relative energies of the transition states are presented in Figure 5 (only the results of the lowest energy isomers of the respective transition states are reported).

As shown in Figure 5, an excellent agreement was found between the theoretical and the experimental results. In the transition states, the forming carbon−carbon bonds are relatively long, over 2 Å. A consequence of such long distances is that sterics are likely to play a different role than in complexes where the bond distance is closer to what it is in the product. When comparing the geometries of the transition states in Figure 6, three of them appear to have similar steric interactions, **TS4**, **TS5**, and **TS7**. The one that differs is **TS6**, in which introduction of a methyl group in the α-position to the nucleophilic carbon adds substantial steric strain between the methyl group and the *tert*-butyl group of the alkyne.

To further support the hypothesis that the introduction of the α-protons of the 2-butenyl is the cause of the difference in regiochemical outcome, two additional systems were investigated. In the first, the 2-butenyl group was replaced by

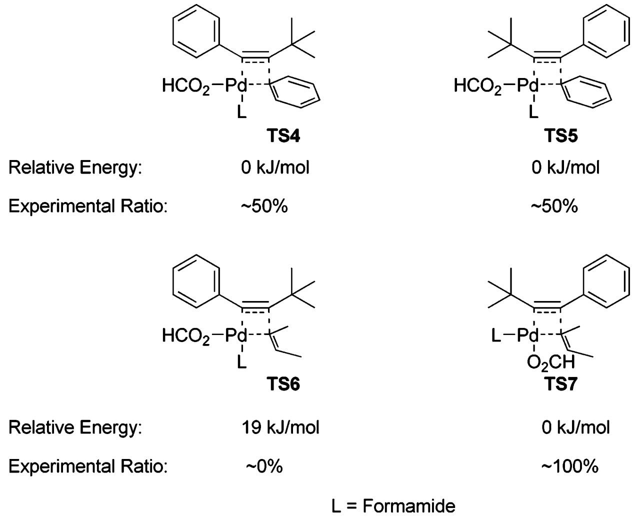


Figure 5. (Top) Relative energies and experimentally observed regioisomer for the migratory insertion of ^{t}BuC≡CPh into a Pd−Aryl bond. (Bottom) Relative energies and experimentally observed regioisomer for the migratory insertion of ^{t}BuC≡CPh into a Pd−2-butenyl bond.

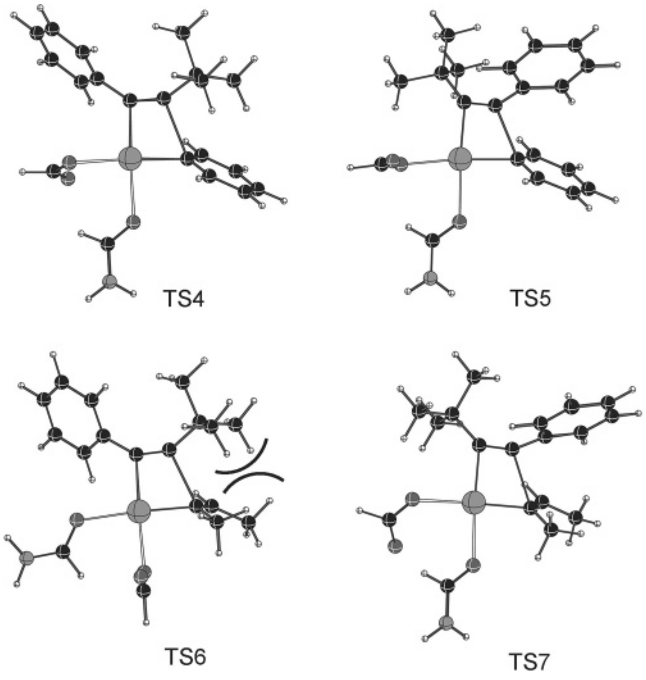


Figure 6. Calculated geometries of hydroarylation and hydrovinylation transition states.

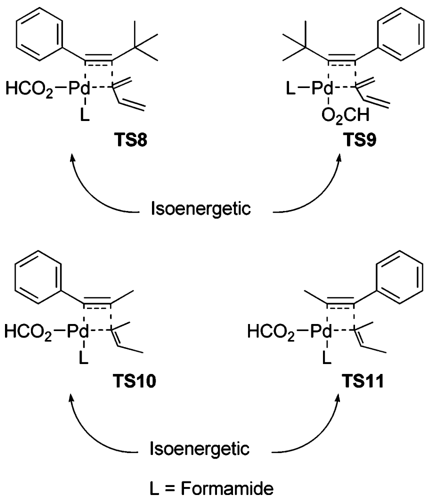


Figure 7. Relative energies of regioisomeric transition states.

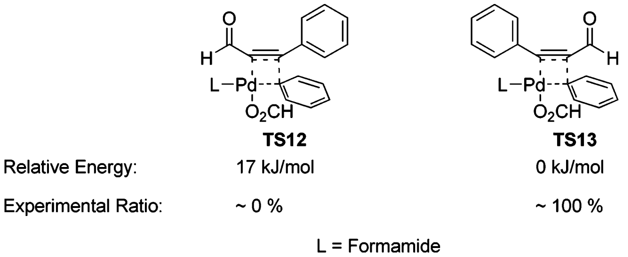


Figure 8. Relative energies and experimentally observed regioisomer for the migratory insertion of PhC≡CCHO into a Pd−Aryl bond (L = formate or formamide).

2-butadienyl, a vinylic moiety with steric properties similar to a phenyl. The two regioisomeric transitions states (**TS8** and **TS9**) were found to be close to isoenergetic (Figure 7). In the second system, the ^{t}Bu of the alkyne was replaced by a methyl group, while the 2-butenyl was retained intact. Also, for this system the two regioisomeric transition states (**TS10** and **TS11**) were found to be close to isoenergetic. These results strongly support the view that the sp^3-hybridized carbon substituent on the vinyl group supplies the steric bulk that enables the substrate to differentiate between the ^{t}Bu and Ph substituents and provides a good regioselectivity in the reaction.

4.3.2. α-Insertion versus *β*-Insertion. To model the carbopalladation of α,*β*-acetylenic carbonyls by a Pd−Aryl bond, the model alkyne 3-phenyl-pronynal was used. Because two conformations of the carbonyl group are possible, s-cis and s-trans, transition states for both conformations were localized. The results for the s-cis case are shown in Figure 8; the s-trans structures were slightly higher in energy, but gave an almost identical energy difference between the two insertion modes, 15 instead of 17 kJ/mol. As for the system described above, the spectator ligands (formate and formamide) have two possible cis/trans coordination modes, and both isomeric transition states were characterized in every case. In Figure 8, the relative potential energies of the lowest energy forms of the α- and *β*-insertion transition states are shown.

Also for this transformation an excellent agreement between theory and experiments was found, but the rationalization seems to be less straight forward. In most nucleophilic addition reactions to α,*β*-unsaturated carbonyl compounds, one would expect *β*-addition, which is the case in the cuprate additions to the same type of alkynes. Yet, in the hydroarylation the α-addition product is observed experimentally, and also the calculations herein show a clear preference for addition to the α-carbon. While α,*β*-acetylenic carbonyl gives α-addition product, the α,*β*-unsaturated alkene analogue (*E*-benzylideneacetone) reacts mainly at the *β*-carbon in these reactions,[6] indicating some fundamental difference between the alkyne and alkene substrates. In Figure 9, the calculated geometries of one transition state leading to the α- and the *β*-addition products, respectively, are shown. One striking feature is that the reacting *π*-bond of the alkyne is orthogonal to one that is in conjugation with the carbonyl moiety and the *β*-phenyl group. Because the

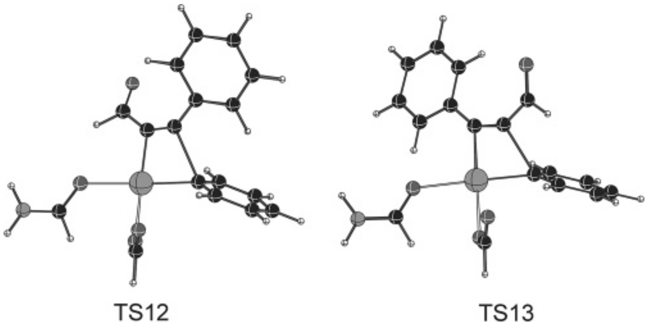


Figure 9. Geometries of transition states for carbopalladation of PhC≡CCHO.

Table 1. Coefficients of π*-Orbitals

molecule	orbital	coefficient α-carbon	coefficient β-carbon
trans-cinnamic aldehyde **23**	π^*	0.6869	−0.7267
3-phenyl-propynal **24**	$\pi^*_{\text{conjugated}}$	0.6804	−0.7329
	$\pi^*_{\text{nonconjugated}}$	0.7137	−0.7004

reacting π-bond is not in conjugation with the carbonyl, it is necessary to investigate further the properties of this nonconjugated π-bond.

NBO analyses of *trans*-cinnamic aldehyde (**23**) and 3-phenyl-propynal (**24**), with their respective geometries optimized in planar C_s symmetry, were performed.[16] From these calculations, the coefficients of the p-orbitals that combine to form the π*-orbitals were extracted (Table 1). For the conjugated π*-orbitals, the coefficient is substantially larger on the β-carbon on both **23** and **24**, and thus nucleophilic addition is expected to occur on the β-carbon. This is in accordance with the experimental findings for the Heck reaction of α,β-unsaturated carbonyls,[3b,6] as well as with the observed regiochemistry for cuprate additions.[17] The picture changes completely when looking on the nonconjugated π*-orbital of 4-phenyl-propynal, where the coefficient is actually larger on the α-carbon. The difference is less than for the conjugated π*-orbital, so from an orbital interaction point of view a lower regioselectivity can be expected than for addition to the conjugated π-bond. In a recent investigation of the regioselectivity of the Heck reaction, a dependence of the orbital coefficients as well as of the electrostatic interaction between the reacting atoms was found for the regiochemical outcome of the reaction.[18] The natural charges from the NBO analysis of 3-phenyl-propynal gave values of −0.10 and +0.06 for the α- and β-carbons, respectively. Such partial charges would favor the β-addition product. To summarize, for the alkene substrate **24**, the frontier orbital and charge contributions give a consistent picture in agreement with experiment, whereas for alkyne substrates like **23**, the frontier orbital and charge control arguments are conflicting and inconclusive, and the selectivity seems in fact to be controlled by steric interactions.

5. Palladium Hydride Formation. Before product liberation, a palladium hydride species needs to be formed. One could also envision a mechanism that involves direct hydride transfer from a formate to the vinyl carbon, but no such transition state could be localized. Gradual decrease of the $C_{\text{vinyl}}-H_{\text{formate}}$ distance in a *cis*-formate-vinyl palladium complex leads to a large increase in energy, yet no complete transfer of the hydride. Instead, a β-hydride elimination mechanism where a hydride is transferred from the formate moiety to palladium was characterized. The starting point was the complex formed in the carbopalladation step, in which the formate is situated in a trans-position to the vinyl **10a**. A transition state was located in which the hydride is transferred to the cis-position relative to the vinyl **TS14**. The geometry of the transition state is such that the formate species is in the plane of the square planar complex, where the hydride is transferring to the site previously coordinating the migrated phenyl group. The barrier was calculated to 71 kJ/mol (94 kJ/mol relative to the most stable formate complex **10b**). Another possibility is hydride formation from the complex in which the formate is situated in a cis-position relative to the vinyl. From here, a different type of transition state was located, **TS15**, one where the formate rotates to form a complex with the formate coordinating with the hydrogen atom to palladium. The barrier for this reaction was calculated to be 99 kJ/mol, and formation of the complex **25** was found to be endothermic by 85 kJ relative to **10b**. Dissociation of CO_2 to yield the palladium hydride complex takes place virtually without any barrier (0.1 kJ/mol). The reactions are outlined in Figure 10.

Both of the transformations described for palladium hydride formation yielded the *cis*-vinyl-hydride palladium species. No transition state for the formation of the *trans*-vinyl-hydride palladium complex could be located. Because the trans-influence of both the vinyl group and the hydride is of substantial magnitude, palladium species with these substituents positioned trans to each other are likely to be highly unstable. To investigate the stabilities of *cis*- and *trans*-vinyl-hydride palladium species, their relative potential energies were investigated for a model system (Figure 11). The results showed that indeed the trans-isomer **28** was much disfavored relative to the cis analogue **27**, by as much as 91 kJ/mol. It is thus concluded that the formation of the hydride does not depend on the formate position in the prereactive complex. The hydride will always end up in the position needed for further reaction, that is, cis to the vinyl moiety.

6. Reductive Elimination − Product Formation. Once the cis palladium hydride vinyl complex (**26a**/**b**) is formed, the final product is obtained through a reductive elimination. A transition state was located (Figure 12), similar to the type described by Diefenbach et al. for the reverse oxidative insertion reaction in the gas phase.[19] From the structure, it is obvious that it is a concerted-type transition state. The forming C−H bond distance was found to be 1.62 Å, a value very close to the ones in the earlier study. The barrier (**TS17**) for the reaction was found to be relatively low, 40 kJ/mol relative to **26b**, and the reaction step can be expected to proceed rapidly. Finally, a palladium(0) alkene complex **29** is formed, and the exothermicity for the transformation of **26b** to **29** was calculated to 96 kJ/mol.

Using a model complex with two formamide molecules coordinated to palladium, no reductive elimination transition state could be located. A gradual decrease of the C−H distance

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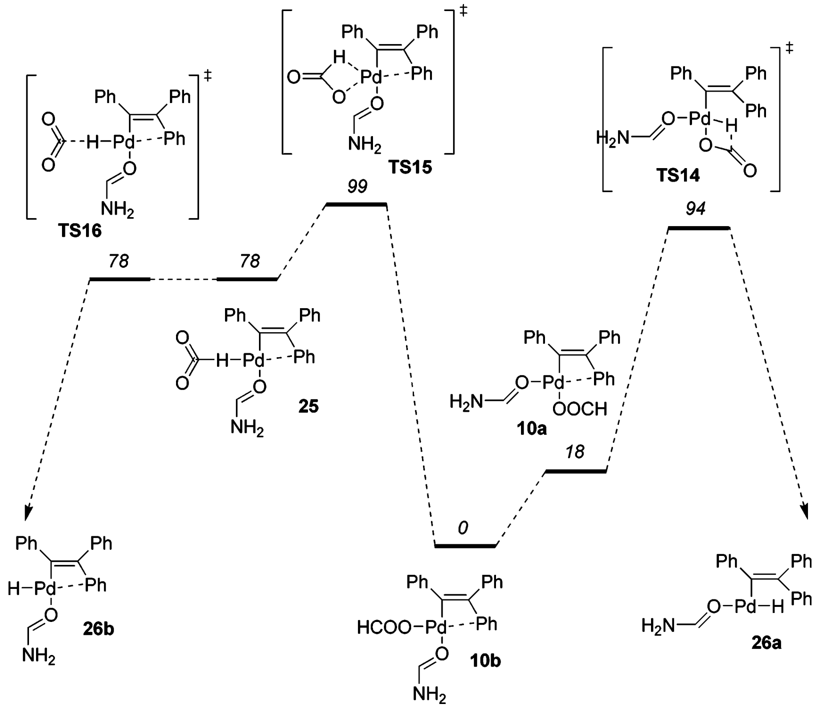

Figure 10. Reaction profile for palladium hydride formation.

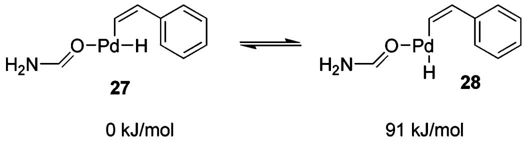

Figure 11. Relative potential energies of cis and trans isomers of a vinyl hydride palladium(II) complex.

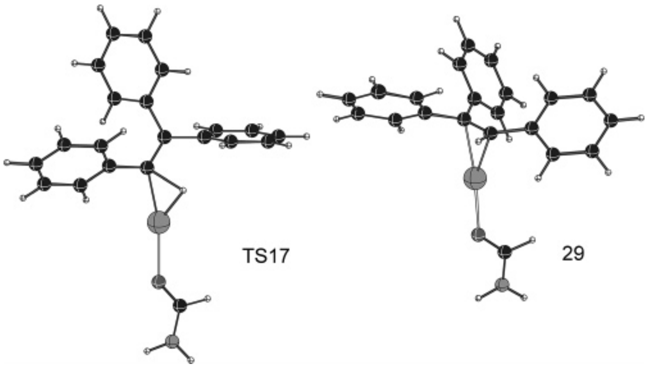

Figure 12. (Left) Geometry of the reductive elimination transition state of the product alkene. (Right) Final palladium(0) alkene complex.

always led to decoordination of one of the formamide ligands. This is likely to be due to the palladium(0)-like structure of the transition state, where a linear dicoordinate structure is expected to be favored.

7. Reductive Path. It has sometimes been observed that instead of formation of the hydroarylation product the aryl is reduced. This is most likely to occur from an intermediate like **9a**, before the *cis*-alkyne-aryl palladium species is formed. A transition state (**TS18**) from **9a** was located. Resulting from this step is a palladium(II) hydride complex **30** where the carbon dioxide is weakly coordinating toward the hydride, similar to the previously described complex **22**. Because the dissociation of CO_2 at **22** has a low barrier and **22** and **30** are structurally very similar, also the dissociation of CO_2 at **30** is assumed to proceed rapidly once **30** is formed. The activation energy for the hydride formation (**TS18**) is 102 kJ/mol, which is higher than the barrier for the migratory insertion and is thus less likely to occur under the reaction conditions described. Caution should be taken, because changing the properties of the reactants or the reaction conditions might very well lead to reduction of the aryl rather than the desired hydroarylation product.

Conclusions

The catalytic cycle for the phosphine-free palladium-catalyzed hydroarylation of alkynes has been characterized by DFT methods. The active catalyst is believed to be Pd^0 ligated by one alkyne and one additional ligand, which can be either another alkyne or a formate. This species can in principle add oxidatively to the electrophilic substrate (e.g., PhI), but we find that oxidative addition is strongly facilitated by loss of one ligand before oxidative addition. This path is also strongly favored by entropy, and we therefore believe it to be of general high importance for oxidative addition reactions.

The favored oxidative addition leads to a tri-coordinate Pd^{II} species, which rapidly adds one additional ligand from solution. Subsequent migratory insertion sets the product regiochemistry. This step has been validated by close reproduction of experimental selectivities in three model reactions, and the differences in regiochemical outcome have been rationalized.

Looking at the electrophilic partner, it is found that aryl groups are insensitive to steric bulk under the conditions that were used, and therefore give a mixture of products, whereas substituted vinyl groups strongly avoid steric hindrance and give substitution at the less hindered position.

The surprising α-substitution observed for carbonyl-substituted alkynes is completely reproduced by the calculations. It is found that the addition occurs to the nonconjugated double bond in the alkyne, leaving untouched the double bond which is conjugated to the carbonyl, and therefore is determined mostly by steric effects.

The migratory insertion is followed by reaction with formate, expelling carbon dioxide and leaving hydride on palladium. Two different mechanisms were located for this process, one which delivers the hydride to the site occupied by the formate, and one which delivers it to the neighboring site. With these two processes available, the hydride can always be delivered to a position cis to the vinyl group, and this position is also very strongly favored, because both the hydride and the vinyl are strong σ-donors, and therefore avoid being trans to each other. The subsequent reductive elimination occurs with a very low barrier, closing the catalytic cycle.

Experimental Section

All reagents, solvents, and catalysts commercially available were used as received without further purification. Aryl-*t*-butyl-acetylenes were synthesized as described in ref 20. Vinyl triflate **16** was prepared according to the procedure given in ref 21. Vinyl iodide **18** was synthesized from the corresponding vinyl triflate according to ref 22. Reaction products were purified on axially compressed columns, packed with SiO_2 25−40 μm (Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/ethyl acetate mixtures. ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded with a Bruker Avance 400 spectrometer. IR spectra were recorded with a Jasco FT/IR 430 spectrometer.

General Procedure for Hydroarylation/Hydrovinylation of Alkynes. To a stirred solution of **18** (0.139 g, 0.49 mmol) and **15** (0.126 g, 0.59 mmol) in DMF (1.5 mL) were added HCOOK (0.082 g, 0.98 mmol) and $Pd(OAc)_2$ (5.5 mg, 0.024 mmol) under argon. The mixture was stirred at 40 °C. The consumption of starting material **18** was monitored by HPLC. The reaction was quenched when no more **18** remained in the mixture, and subsequently worked up by addition of EtOAc and washing with brine. The organic layer was separated and dried over Na_2SO_4 evaporated under vacuum, and the residue was purified by chromatography on silica gel eluting with a *n*-hexane/AcOEt 70/30 (v/v) mixture to afford 0.037 g of **17** (20% yield), whose IR and NMR spectra are identical to those reported in the literature.[7]

Computational Details

To include both steric interactions as well as the correct electronics, we have included the complete ligand and substrate in all calculations, to avoid artifacts from calculations on small model systems. All calculations were performed with the Jaguar 4.2 program package[23] using the hybrid functional B3LYP.[24] The basis set used was LACVP*, which applies the 6-31G* basis set for all light elements and the Hay−Wadt ECP and basis set for palladium and iodine.[25] To simulate solvent, the Poisson−Boltzmann self-consistent reaction field (PB-SCRF) incorporated in Jaguar 4.2 was used.[26] PB-SCRF is a continuum solvation model, where the molecule is put into a reaction field consisting of surface charges on a solvent accessible surface constructed using a hypothetical spherical solvent probe molecule with the indicated radius.[27] The wavefunction and the reaction field charges are solved iteratively until self-consistency is reached. The parameters for the solvent simulated have been set to 38, probe radius = 2.47982 for DMF.

Transition states were located either by the simple quasi-Newton transition state search starting from a structure resembling that of the transition state, or by a quadratic synchronous transit search. Input geometries for the transition state searches were mostly located by a gradual change of the distances of the bonds forming or breaking.

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Supporting Information Available: Cartesian coordinates and absolute energies of calculated geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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