Electronic Control of the Regiochemistry in the Heck Reaction

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Abstract: The migratory insertion of propene into the Pd−phenyl bond of a set of neutral palladium(II) complexes with N−N, P−O, and N−O chelating ligands has been investigated by using density functional methods. In contrast to cationic palladium(II)−diimine complexes, which favor 1,2-insertion, the more electron-rich neutral complexes lead to 2,1-insertion. Trans influences are substantial in the unsymmetrical ligand systems, primarily affecting the insertion barrier. Introducing steric effects leads toward improving 1,2-selectivity, due to destabilization of the 2,1-transition state. Electronic and steric influences can be systematically combined to control the regiochemistry in the Heck reaction.

Introduction

The versatility and flexibility of palladium catalysis in organic synthesis is underlined by a continuous and significant amount of research within the field. Among the key reactions forming C−C bonds, the Heck reaction has proven especially useful and has been thoroughly studied since its discovery in the late 1960s.[1,2] The Heck reaction provides a direct route to synthetically important arylated and vinylated olefins, from the corresponding alkene and aryl compounds, as exemplified by Scheme 1.

The scope and limitations of the Heck reaction have been reviewed in several recent articles.[3] Important mechanistic issues are still under investigation, such as the structure of reaction intermediates and the influence of electronic charge at the metal center.[3c−e] Also, despite considerable efforts, serious problems remain with regard to control of the regiochemistry in the addition to unsymmetrical alkenes. Some success in regiocontrol has been achieved by the use of alkenes attached to an auxiliary coordinating group.[4] This is also true for the use of special ligands and acrylate or styrene as substrates.[5,6] In most instances,

Scheme 1. Heck Carbon−Carbon Coupling Reaction
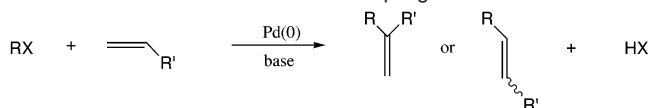
X=I, Br, Cl, OTf, COCl, N₂BF₄
R=aryl, vinyl

the regioselectivity is considered being dominated by steric effects.[7−9] However, electronic influences on the regiochemistry have also been proposed.[3c]

We have initiated theoretical studies concerning the influence of steric and electronic effects on the activity and the regiochemistry in the Heck reaction. In previous work we have been focusing on cationic palladium(II)−diimine systems.[10,11] Using propene as the inserting monomer we have found, in all instances, that the regiochemistry of the metal−alkyl addition leads to 1,2-insertion products and that the main influences on the selectivity stem from steric interactions. The observed selectivity agrees well with experimental results using substituted 1,10-phenanthroline ligands.[12] In the work presented here we compare the electronic influences on selectivity between cationic and neutral palladium catalysts. A number of symmetrical and unsymmetrical palladium complexes have been investigated, and it is concluded that electronic tuning of the catalytic center provides a powerful means of controlling selectivity. We have

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also shown that a systematic combination of electronic and steric effects can be employed to shift selectivity in the desired direction.

Computational Details

Geometries and energies of all intermediates and transition states were fully optimized using the gradient-corrected hybrid density functional method B3LYP[13] in the Gaussian98 program.[14] For Pd, the core electrons were replaced by a relativistic electron core potential (ECP) developed by Hay and Wadt.[15] We used a basis set of double-ζ valence quality provided in the literature.[15] For nonmetal atoms the double-ζ basis sets of Huzinaga and Dunning were assigned.[16] All relative energies were recalculated using a valence triple-ζ quality basis set at the B3LYP level. For all nonmetal atoms the 6-311G(d,p) basis set[17] was employed, and for Pd the primitive double-ζ basis set was recontracted to 4s4p3d and an f-function(1.472) was added. It should be noted that calculations are commonly more reliable in studying trends than providing absolute numbers for a specific reaction, although modern calculations have shown to afford remarkably accurate figures also in absolute terms for migratory insertions.[18]

Results and Discussion

In previous work we have focused on cationic phenylpalladium(II)−diimine systems.[10,11] Here, we have chosen to map and compare the potential energy surfaces of a cationic phenylpalladium(II)−diimine (**1**), a neutral phenylpalladium-(II)−amide−imine (**2**), a neutral phenylpalladium(II)−alkoxy-phosphine (**3,4**) and two neutral phenylpalladium(II)−alkoxy-imines (**5,6** and **7,8**). The structures of the active complexes are given in Figure 1. For catalysts with unsymmetrical ligands, two possible isomers provide starting points for migratory insertion.

The regioselectivity in the Heck reaction is determined by the relative energy difference between the two possible insertion pathways, $\Delta\Delta E = \Delta E^*(2,1) - \Delta E^*(1,2)$. Figure 2 illustrates the investigated structures of propene insertion into the Pd−phenyl bond of the neutral phenylpalladium(II)−amide−imine catalyst.

Table 1 lists the energies associated with the insertion of propene into the Pd−phenyl bond. The activation barrier is calculated as the energy difference between the π-complex and the transition state. The selectivity is defined as the difference
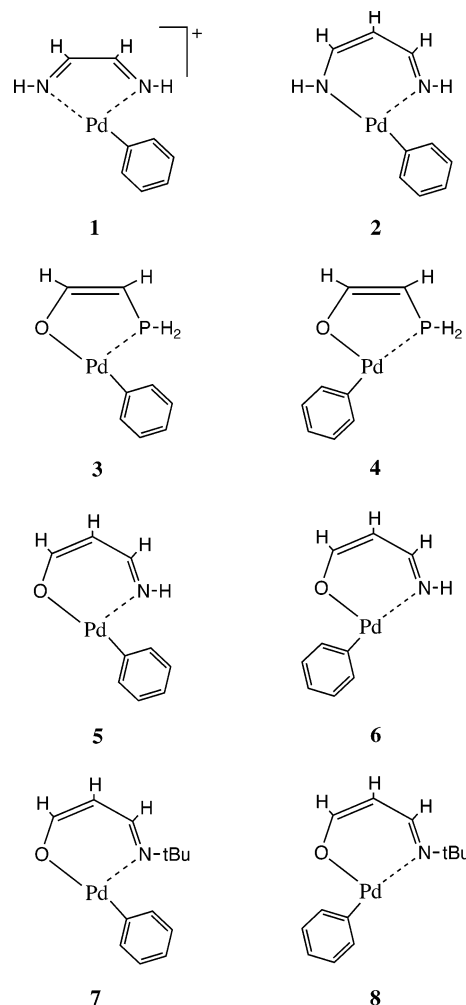
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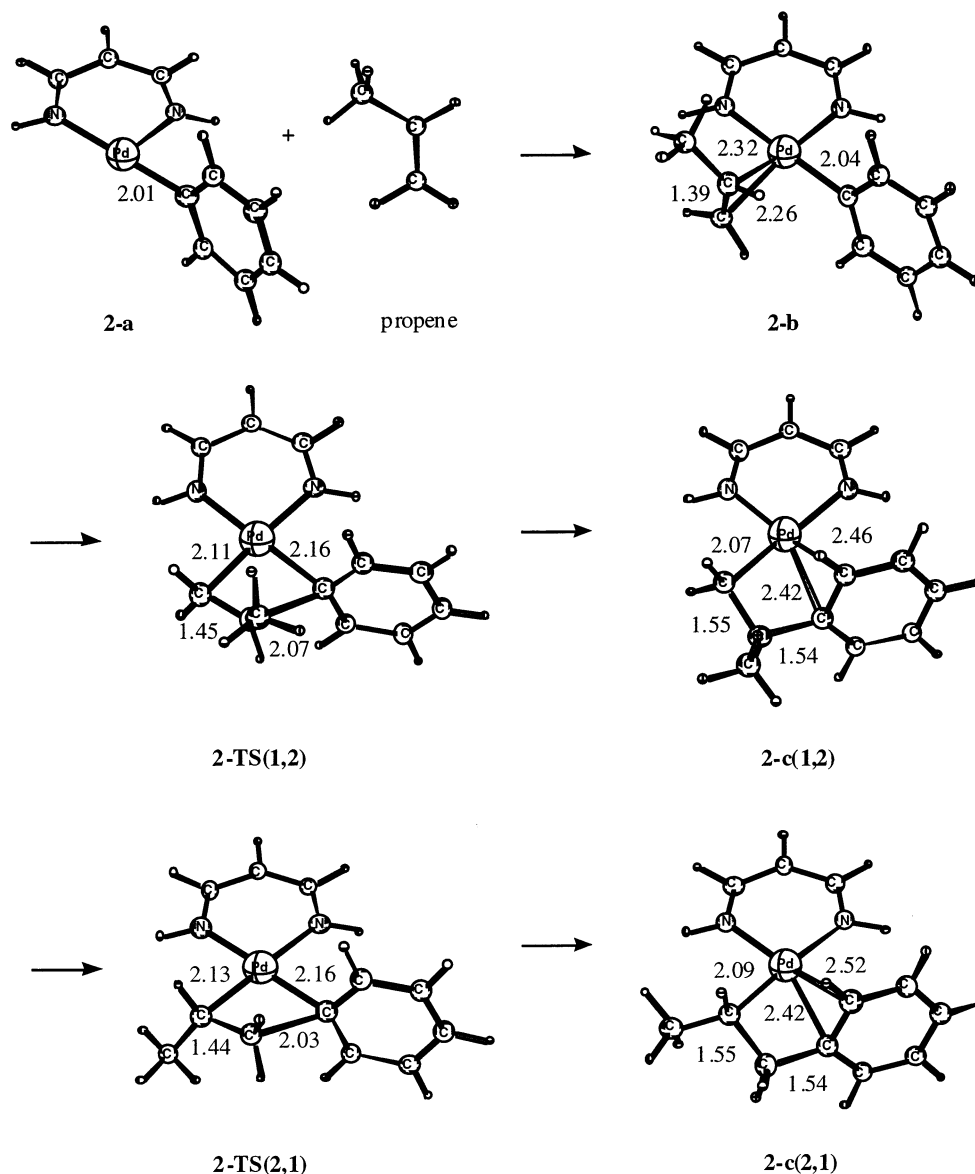
Figure 1. Active-catalyst structures of the investigated palladium complexes.

Table 1. Activation Energy of π-Complex Isomerization, the Activation Energy of Insertion of Propene into the Pd−Ph Bond, and the Thermodynamic Driving Force of the Insertion Step [kcal/mol]

catalyst	$\Delta E_I^{*\ a}$	$\Delta E^*(2,1)^b$	$\Delta E^*(1,2)^c$	$\Delta\Delta E^d$	$\Delta E_D(2,1)^e$	$\Delta E_D(1,2)^f$
1	13.5	11.6	10.9	0.7	−10.7	−10.5
2	25.1	19.4	19.7	−0.3	−2.3	−3.5
3	25.0	22.6	24.0	−1.4	1.8	1.9
4	−	12.1	12.1	0.0	−13.9	−15.0
5	25.3	23.0	24.4	−1.4	3.3	3.2
6	−	14.6	14.9	−0.3	−9.6	−10.7
7	15.9	22.0	23.7	−1.7	−6.8	−3.5
8	−	15.3	13.1	2.2	−6.1	−12.6

^{a} ΔE_I^* is the barrier for π-complex isomerization, starting with the most stable π-complex. ^{b} $\Delta E^*(2,1)$ is the reaction activation energy, forming **TS(2,1)**. ^{c} $\Delta E^*(1,2)$ is the reaction activation energy, forming **TS(1,2)**. ^{d} $\Delta\Delta E = \Delta E^*(2,1) - \Delta E^*(1,2)$. ^{e} $\Delta E_D(2,1)$ is the thermodynamic driving force of the insertion step, passing through TS(2,1). ^{f} $\Delta E_D(1,2)$ is the thermodynamic driving force of the insertion step, passing through TS(1,2).

in the barrier between the two possible insertion pathways, i.e., 1,2- and 2,1-insertion. The barriers for isomerization of related π-complexes are given with respect to the most stable of the two structures.

Reaction Barrier. The reaction barrier correlates nicely with the thermodynamic driving force of the insertion step, as illustrated in Figure 3 for 1,2-insertions. Complex **7** deviates somewhat from the linear trend due to a relatively high insertion

Figure 2. **2-a** is the active catalyst; **2-b** is the resting state where propene is π-coordinated to the metal; **2-TS** is the transition-state structure for a given insertion pathway; **2-c** is the intermediary insertion product, stabilized by π-aryl−Pd interaction.
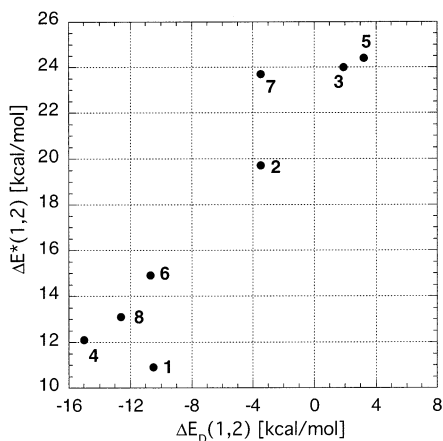

Figure 3. Insertion barrier correlates linearly with the driving force of the insertion step.

barrier, caused by steric interaction destabilizing the transition state.[11] Complex **1** is cationic and gives a lower insertion barrier

compared to the neutral complexes. This effect has been correlated with the HOMO stability of the active complex.[11] A general observation is that active complexes **3**, **5**, and **7** have considerably larger insertion barriers than their isomeric counterparts **4**, **6**, and **8**, respectively.

Trans influences are primarily responsible for this interesting trend. Comparing the energy of the π-complex **3-b** with that of **4-b**, and that of **5-b** with that of **6-b**, gives an idea of the strength of the trans influence.[19] Structure **3-b** is more stable than **4-b** by 9.4 kcal/mol, and **5-b** is more stable than **6-b** by 8.7 kcal/mol. Clearly it is energetically preferable for the π-coordinating propene to be cis to oxygen. The intermediary products, e.g., **3-c(1,2)** and **4-c(1,2)**, are structurally related to the complexes **3-b** and **4-b**, respectively. In the intermediary product, a π-interaction is present where the aryl group interacts with the metal, while a σ-interaction is due to the newly formed Pd−

(19) **7-b** and **8-b** are kept out of the discussion at this point since the steric bulk of the *t*-Bu group influences the relative energies considerably. Steric influences will be discussed below.
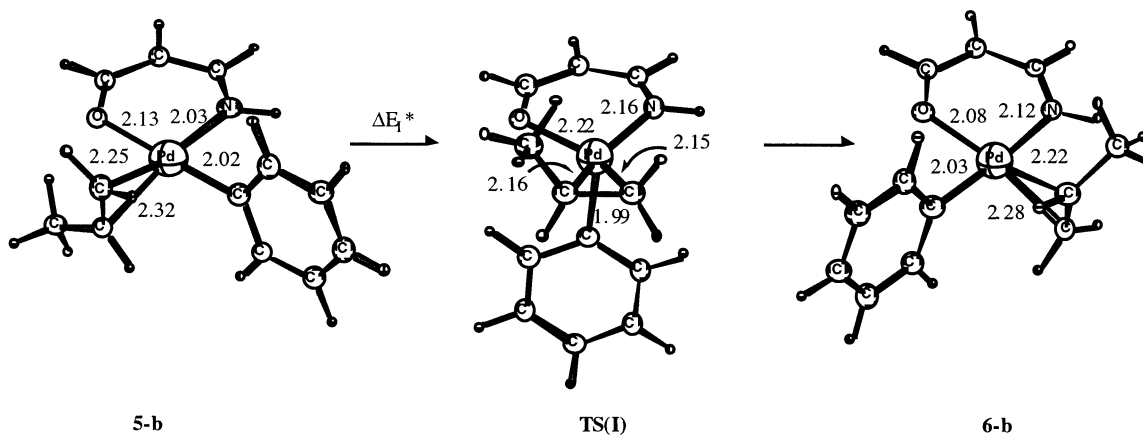
Figure 4. Resting state π-complexes isomerize through rotation. Here **5-b** isomerizes into **6-b** over the transition state **TS(I)**.

alkyl bond (see Figure 2). As a result of the insertion, the coordination sites of these two components are switched, compared to the π-complex. Indeed, **4-c(1,2)** is more stable than **3-(1,2)** by 7.6 kcal/mol, and **6-c(1,2)** is more stable than **5-c(1,2)** by 5.2 kcal/mol. Starting the insertion reaction from the more stable π-complex will thus result in a relatively unstable intermediary product and vice versa, explaining the high insertion barriers of **3-a**, **5-a**, and **7-a**, and the lower barriers of **4-a**, **6-a**, and **8-a**. Similar effects have been noted for neutral nickel(II)−salicyladiminato complexes[20] and also for cationic Pd complexes with substituted diimine ligands.[11] It should be noted that although the energy $\Delta E_D > 0$ for **3-a** and **5-a**, the overall driving force is exothermic for the respective insertion.[21]

At this point it becomes relevant to discuss whether a π-complex such as, for example, **5-b** can isomerize into **6-b** and then proceed to insert via the lower barrier (see Table 1). This possibility has been noted for a neutral nickel(II)−salicylaldiminato complex polymerizing ethylene.[20] A first indication of the plausibility of such a reaction comes from simply comparing the stabilities of the transition states. The energies of **5-TS(2,1)** and **6-TS(2,1)** are similar, with the former being only 0.3 kcal/mol more stable. **4-TS(2,1)** is more stable than **3-TS(2,1)** by 1.1 kcal/mol, and **8-TS(1,2)** is more stable than **7-TS(2,1)** by 2.1 kcal/mol. It is therefore not evident which reaction path the most stable π-complex will take. In an effort to clarify this point, the isomerization path was investigated in greater detail. Three isomerization mechanisms were tested for **1-b** and **2-b**, using ethene as coordinating olefin: (a) a dissociative mechanism where ethene first left the metal complex and then re-coordinated to the metal after the phenyl group had flipped; (b) a direct isomerization, which can be viewed as a rotation of the ligand; (c) an associative exchange mechanism, where a second olefin coordinated to the metal center. For both the cationic species **1-b** and the neutral complex **2-b**, the lowest barrier of isomerization was found for path (b). The barrier for this type of reorganization, starting at the most stable π-complex, is given for the relevant ligands in Table 1 as ΔE_I^* (see also Figures 4 and 5).

In all instances except **7-b**, the barrier for isomerization is higher than the insertion barrier. This means that the formation
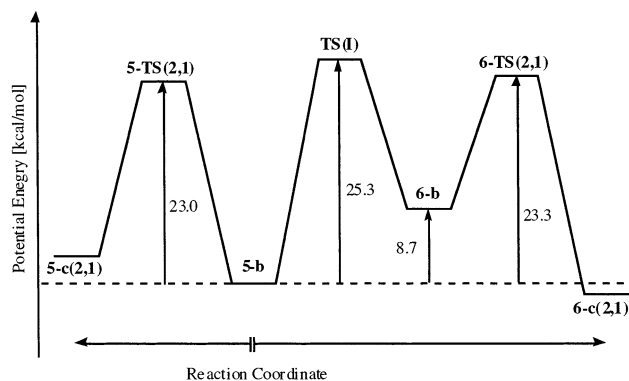

Figure 5. **5-b**, the most stable π-complex, will go on to insert propene, rather than isomerizing to **6-b**, prohibited by the reaction barrier for isomerization. See also ref 21.

of the more stable of the two isomeric π-complexes will determine the insertion path.

Regiochemistry. One of the central issues at hand is the question of selectivity. For the sterically undemanding ligands presented here,[19] electronic factors are mainly responsible for effects on the regioselectivity.[11] From Table 1 it is seen that choosing a cationic or a neutral active complex will lead to 1,2- or 2,1-insertion of propene, respectively. This is in agreement with experimental observations for Heck reactions employing various substituted α-olefins (e.g., C_2H_3Y; $Y = -OC_4H_9$, $-CH_2OH$, $-C_4H_9$).[3c,22] Also, for the addition of styrene to arylpalladium complexes with dppe and dppp[23] ligands, it was found that decreased cationic character of the metal center increased the relative amount of 2,1-product.[5]

The selectivity trend can be explained by a Markovnikov-type addition scheme.[24] In the case of a cationic metal center, the dominant character of the transition state involves propene acting as a Lewis base reacting with the electrophilic palladium atom. The more stable carbocation is formed, and hence the electrophile ends up on the least substituted carbon. For a neutral complex, the transition state has anti-Markovnikov character, with the nucleophilic attack of the phenyl on the least substituted alkene carbon being favored.

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(21) Forming the product π-complex 1-phenylpropene with the palladium hydride is exothermic by 6.5 kcal/mol for **3-b** and by 4.0 kcal/mol for **5-b**. Forming the π-complex of 2-phenylpropene with the palladium hydride is exothermic by 3.2 kcal/mol for **3-b** and by 0.5 kcal/mol for **5-b**.
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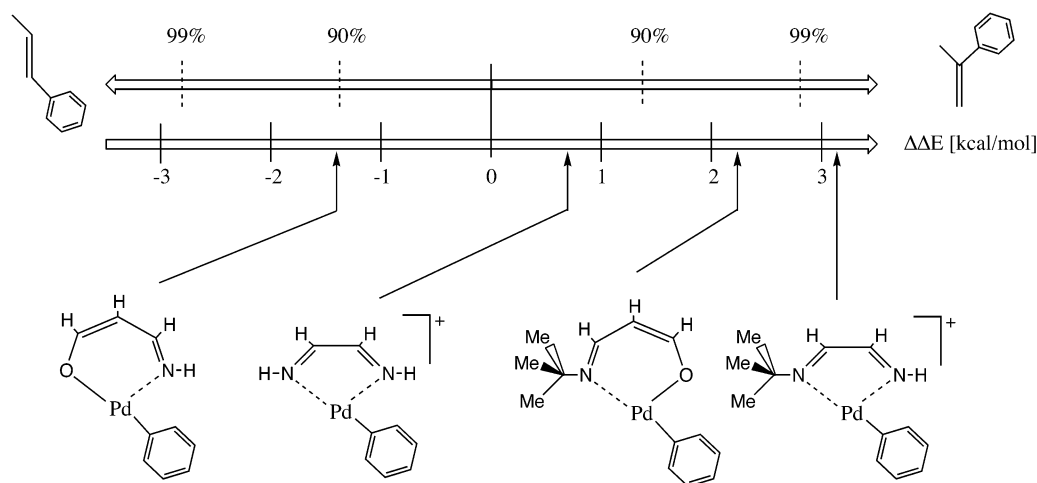
Figure 6. Illustration of electronic and steric factors affecting the regioselectivity of propene insertion in the Pd-phenyl bond. $\Delta\Delta E = \Delta E^*(2,1) - \Delta E^*(1,2)$, i.e., $\Delta\Delta E < 0$ leads to 2,1-insertion and $\Delta\Delta E > 0$ leads to 1,2-insertion.

Table 2. Selectivity of Active Complexes **1-a** and **2-a**, Reacting with Propene, 2-Methyl Propene, and Methyl Vinyl Ether

monomer	$\Delta\Delta E(1)^a$	$\Delta\Delta E(2)^b$
CH_2CHCH_3	0.7	−0.3
$CH_2C(CH_3)_2$	0.1	−1.9
CH_2CHOCH_3	6.6	1.4

^{a} $\Delta\Delta E(1) = \Delta E(2,1) - \Delta E(1,2)$ for active catalyst **1-a**. ^{b} $\Delta\Delta E(2) = \Delta E(2,1) - \Delta E(1,2)$ for active catalyst **2-a**.

The selectivity for a few additional alkenes was calculated, and the trend with respect to Markovnikov addition was noted. Alongside propene, 2-methyl propene and methyl vinyl ether were used as inserting monomers for the active complexes **1-a** and **2-a**. An increasing effect in terms of Markovnikov selectivity is expected in the order of the presented monomers, since stabilization of positive charge at the substituted carbon increases. The results with respect to regioselectivity are shown in Table 2.

Keeping focus on the change in selectivity as we go from a cationic to a neutral palladium complex, results show a shift toward 2,1-insertion of +1.0 kcal/mol for propene, +2.0 kcal/mol for 2-methylpropene, and +5.4 kcal/mol for methyl vinyl ether. This trend correlates with the expectations of Markovnikov addition.[24]

Another important result, evident from Table 1, is that unsymmetrical ligands display different selectivity, depending on the π-complex isomer. Starting the insertion from **3-b** gives better 2,1-selectivity compared to **4-b**. The same is seen for **5-b** compared to **6-b**. This effect can be interpreted in terms of the anti-Markovnikov character of the transition states proposed for the neutral catalysts. Within this context, a stronger nucleophile would be expected to give an improved selectivity. The electronic charge of the phenyl carbon performing the attack on propene serves as an indicator of the nucleophilicity of the group. This electronic charge was evaluated using Mulliken population analysis for the active catalysts. We find that increased negative charge at the phenyl carbon correlates with an increased 2,1-selectivity, comparing **3-a** with **4-a**, **5-a** with **6-a**, and **7-a** with **8-a**.[25] The phenyl group is an electron-

accepting group. In structures **3-a**, **5-a,** and **7-a**, the phenyl group is positioned trans to a σ-donating alkoxy functionality. In structures **4-a**, **6-a**, and **8-a** the phenyl is located trans to imine and phosphine functionalities that also have π-accepting properties. Hence, there appears to be a correlation between electron-donating groups positioned trans to the phenyl ring and the amount of 2,1-selectivity in the insertion reaction.

In previous work on cationic palladium(II)−diimine catalysts we found that the steric bulk of *t*-Bu at the coordinating nitrogens influenced the selectivity of propene insertion into the Pd−phenyl bond.[11] With the *t*-Bu group trans to the phenyl ring, the 1,2-selectivity was considerably increased, due to destabilization of TS(2,1) through interaction between methyl groups on propene and *t*-Bu. When *t*-Bu was placed cis to the phenyl, the steric bulk of *t*-Bu deflected the ring, leading to a somewhat decreased 1,2-selectivity, due to a relative destabilization of TS(1,2). Similar steric interactions can been introduced into neutral palladium(II) complexes with unsymmetrical ligands. The structures **7** and **8** represent such a system. Taking into account results for the cationic complexes, we predict **7-a** to be somewhat more selective in favor of 2,1-insertion compared to **5-a**. Furthermore, we expect **8-a** to have reversed selectivity compared to **6-a**. As can be seen from Table 1, both of these predictions turn out to be true. The steric effect on the stability of the transition states and hence directly on selectivity is very similar for the *t*-Bu-substituted cationic palladium(II)−diimine system as for the neutral palladium(II)−alkoxy−imine system.

There is an interesting secondary effect on the selectivity caused by the *t*-Bu group, comparing **7-b** to the related **5-b** complex. For **5-b**, the barrier for isomerization to **6-b** is predicted to be high enough to prevent the isomerization from occurring. Propene thus inserts into the Pd−phenyl bond in **5-b** (see Figure 5), forming 2,1-insertion products. For **7-b** the barrier for isomerization to **8-b** is comparatively low, $\Delta E_I^* = 15.9$ kcal/mol (see Table 1). As a consequence, the isomerization **7-b** → **8-b** will precede the insertion of propene. Furthermore, steric interaction will disfavor transition state **8-TS(2,1)**, leading to the 1,2-insertion products being formed.[26] This relative lowering of the isomerization barrier compared to **5-b** is mainly due to destabilization of the π-complex structures, caused by the

(25) The charge at the phenyl carbon bonding to Pd was calculated using Mulliken population analysis; **3-a** = −0.22, **4-a** = −0.18; **5-a** = −0.22, **6-a** = −0.14; **7-a** = −0.26, **8-a** = −0.14 (electrons).

(26) The reaction barrier **7-b** → **7-TS(2,1)** is 22.0 kcal/mol and the reaction barrier **7-b** → **8-TS(1,2)** is 19.9 kcal/mol.

presence of the *t*-Bu group.[27] Experiments comparing the product outcome of catalysts similar to **5** and **7** would no doubt prove revealing.

Conclusions

In this work we have investigated the energetics of propene insertion into the Pd−phenyl bond for a series of neutral palladium(II) complexes with N−N, P−O, and N−O chelating ligands. Comparisons have been made between the neutral complexes as well as with previous results from cationic palladium−diimine systems. Most notably, there is a general shift in selectivity from 1,2-insertion for the cationic case to 2,1-insertion for the neutral complexes. This is rationalized by a Markovnikov-type addition scheme. For a cationic system, the transition state is dominated by the alkene addition to the electron-poor metal center, forming a bond between the least substituted carbon and the metal. In the more electron-rich neutral systems, a nucleophilic attack of the phenyl on propene is more important to the transition-state formation, leading to an anti-Markovnikov-type addition of propene to the metal. The steric effect on transition-state stability, and hence directly on selectivity, has been tested using bulky *t*-Bu substituents in the ligand backbone, and is parallel for the cationic palladium(II)−diimine system and for the neutral palladium(II)−alkoxy−imine system. Most importantly, steric interaction between the methyl groups on *t*-Bu and propene lead to destabilization of the 2,1-transition state, thereby improving 1,2-selectivity. While the steric effects in general work toward improving 1,2-selectivity, the electronic effects can be used to favor 1,2- or 2,1-selectivity, using cationic or neutral palladium complexes. Figure 6 shows how combining these effects in a systematic way enables tailoring of catalyst selectivity.

Supporting Information Available: Cartesian coordinates of all presented structures as well as the calculated energies (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The π-complexation energy, $\Delta E\pi$, is 25.2 kcal/mol for **5-b** and 18.8 kcal/mol for **7-b**.