

Regioselectivity of Nucleophilic Attack on [Pd(allyl)(phosphine)(imine)] Complexes: A Theoretical Study

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Summary: Extended Hückel calculations help rationalize the observed regioselectivity of allylic alkylations catalyzed by Pd complexes containing either C_2 -symmetric or electronically asymmetric bidentate chiral ligands. Mixing of the empty high-lying π^* into the LUMO, made up mostly of the antibonding combination between the $d_{x^2-y^2}$ and the allyl nonbonding fragment orbitals, increases the electrophilicity of the carbon with the longest Pd–C bond as its weight in the LUMO increases.

Introduction

In the field of enantioselective catalysis, bidentate C_2 -symmetric ligands have proven extremely versatile.^{1–3} Their square-planar complexes are dissymmetric and have two *trans* sites which are electronically equivalent. The diastereoselective addition of prochiral substrates is thus governed by steric requirements of the ligand and the substrate. The resulting complex is asymmetric, and further reaction often proceeds to yield enantiomerically enriched products. More recently, chiral bidentate ligands with two different donors have attracted attention. Here a prochiral substrate is desymmetrized not only by steric factors but also through the electronic asymmetry induced by the bidentate ligand.^{4–7} A major breakthrough was achieved in palladium-catalyzed functionalization of allylic substrates,^{8–10} catalyzed by [Pd(phosphine)(imine)] complexes.^{11–18,20} For a symmetrical 1,3-disubstituted allyl coordinated in an η^3 mode, attack at C¹ or C³ yields the

opposite enantiomers. Therefore, the site of nucleophilic attack determines the chirality of the product, provided that the catalytically active complex shows a single reactive geometry. In the following, the carbon atoms C¹ and C³ are distinguished via the different donor atoms in *trans* positions and are called $C_{trans-P}$ and $C_{trans-N}$, respectively.

On the basis of *trans*-influence arguments, one would predict the $C_{trans-P}$ –Pd bond to be longer and thus this carbon atom should bear a greater negative charge as the σ -donation to palladium is less efficient. An incoming soft nucleophile would thus be expected to attack at $C_{trans-N}$. Similar reasoning was put forward by Williams and Frost on their related [Pd(allyl)(S \wedge N)] catalytic system.¹⁹ Recently, however, there has been evidence that a nucleophilic attack on coordinated allyls occurs at $C_{trans-P}$.^{13,15,20} However, under reaction conditions, the rotation of the allyl averages both sites with respect to the electronic asymmetry and thus precludes a correlation between the site of attack and the observed configuration of the product. This prompted us to undertake the present study.

Results and Discussion

Mechanistic considerations for the palladium-catalyzed allylic alkylation point toward an early transition state; therefore, the most electrophilic center of the coordinated allyl in the ground state reacts, leading to the major enantiomer of the product.^{20–22} Calculations on related systems reveal that the reaction is frontier orbital controlled rather than charge controlled, since the latter would yield a nucleophilic attack on the central carbon.²⁸

For our analysis, we simulate the {Pd(P \wedge N)} fragments with [Pd(PH₃)(NH₂)]⁺, the nitrogen nearly lying on the x axis and the phosphorus on the y axis. To confirm the validity of our model, we carried out calculations with [Pd(PH₃)(H₂C=NH)]²⁺ as well as the whole fragment [(ferrocenylphosphine–pyrazole)Pd]²⁺ described by Togni *et al.*²⁰ With all models, we obtained very similar results. Details of the calculation are listed in ref 32. An extended Hückel analysis^{23–26} of the fragment reveals hybridization of the metal orbitals $d_{x^2-y^2}$ with p_x and s with p_y . The phosphorus lone pair

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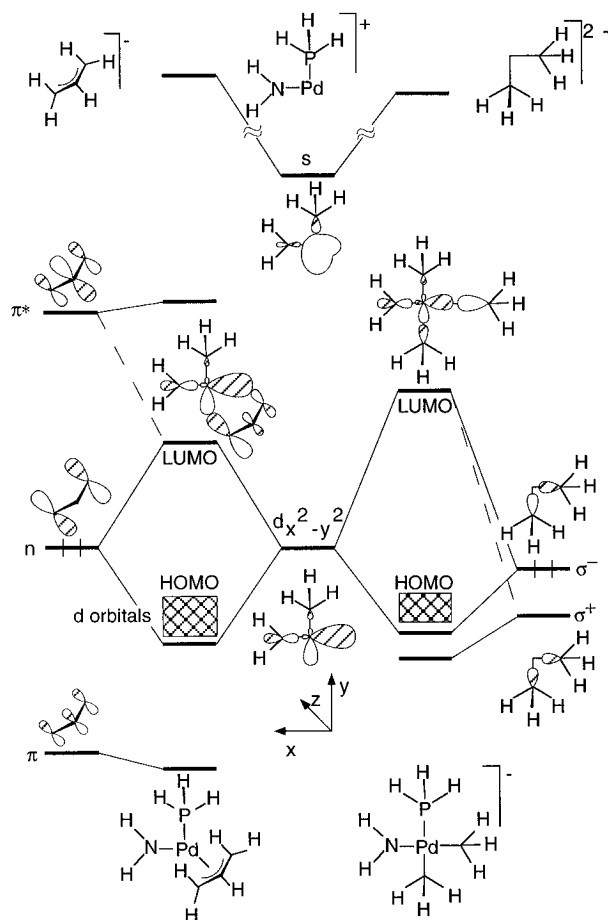


Figure 1. Simplified interaction diagram between $\{\text{Pd}(\text{NH}_2)\text{PH}_3\}^+$ and $(\text{C}_3\text{H}_5)^-$ (left) and $(\text{CH}_3)_2^{2-}$ (right).

contains a significant amount of s character, while the nitrogen lone pair is mostly p in character. This sets the ionization potential of the P-donor below that of the N-donor. As a consequence, the bonding combination of these lone pairs contains a greater weight on the phosphorus, while the nitrogen lone pair contributes more to the antibonding combination. As the metal orbitals mostly contribute to the antibonding combinations, the $d_{x^2-y^2}$ is polarized away from the nitrogen in this fragment molecular orbital (FMO), while the s orbital is polarized away from the phosphorus (Figure 1, center).

Before considering the coordination of an allyl to the palladium, let us focus on a system which bears simple σ -donors, e.g. $\text{cis-}[\text{Pd}(\text{CH}_3)_2(\text{PH}_3)(\text{NH}_2)]^-$. Both combinations of the methyl group lone pairs, σ^+ and σ^- , have a nonzero overlap with the above-mentioned hybridized metal orbitals, which results in mixing of these FMOs. The LUMO can be described with the help of perturbation theory as:²⁷

$$\text{LUMO} \propto d_{x^2-y^2} - (\sigma^-) - (\sigma^+)$$

Mixing in of the σ^+ level results in a greater coefficient of the sp hybrid at $C_{\text{trans-N}}$. Thus, for a frontier orbital controlled reaction,²⁸ an incoming nucleophile would preferentially attack $C_{\text{trans-N}}$, a mere reflection of the greater *trans* influence of P-donors vs N-donors.

The picture is quite different when an allyl moiety interacts with the *electronically asymmetric* $\{\text{Pd}(\text{P}^{\wedge}\text{N})\}$

Table 1. Electrophilicity Indexes

	ξ^{ele} (meV)	
	$C_{\text{trans-P}}$	$C_{\text{trans-N}}$
$\text{cis-}[\text{Pd}(\text{CH}_3)_2(\text{PH}_3)(\text{NH}_2)]^-$	-1305	-1919
$[\text{Pd}(\text{C}_3\text{H}_5)(\text{PH}_3)(\text{NH}_2)]$	-2557	-1563
$[\text{Pd}(\text{PhC}_3\text{H}_3\text{Ph})(\text{PH}_3)(\text{NH}_2)]$	-1583	-891
$[\text{Pd}(\text{C}_3\text{H}_5)(\text{SH}_2)(\text{NH}_2)]$	-2517 ^a	-1583
$[\text{Pd}(\text{C}_3\text{H}_5)(\text{NH}_2)(\text{NH}_2)]^-$	-1944 ^b	-1870

^a $C_{\text{trans-S}}$. ^b C with longest Pd-C bond.

fragment. As the complex possesses C_1 symmetry, the three orbitals which make up the π system of the allyl, symbolized by π , n , and π^* , can interact with the hybridized $d_{x^2-y^2}$ and s orbitals of the $\{\text{Pd}(\text{P}^{\wedge}\text{N})\}$ fragment. The phases of the allyl orbitals are set so as to have a positive overlap with the hybridized $d_{x^2-y^2}$. The computed overlaps, for a realistic geometry^{15,20} with $\text{Pd}-C_{\text{trans-P}} = 2.26 \text{ \AA}$ and $\text{Pd}-C_{\text{trans-N}} = 2.14 \text{ \AA}$, are $S_{\pi-(d_{x^2-y^2})} < 0.005$ and $S_{\pi^*-(d_{x^2-y^2})} = 0.05$. The sign of the mixing coefficients is thus determined by the relative ordering of the interacting orbitals.²⁷ The LUMO for $[\text{Pd}(\text{C}_3\text{H}_5)(\text{PH}_3)(\text{NH}_2)]$ can be described as

$$\text{LUMO} \propto d_{x^2-y^2} - (n) + (\pi^*)$$

In contrast to the $[\text{Pd}(\text{CH}_3)_2(\text{PH}_3)(\text{NH}_2)]^-$ case, the mixing in of π^* yields greater atomic orbital coefficients for $C_{\text{trans-P}}$. The greater the atom contribution to the LUMO, the greater the electrophilicity for this atom. Since the coordinated allyl moiety is distorted, its π -system consists of a mixture of s and p AOs. We would thus have to compare four AO coefficients (s, p_x , p_y , and p_z) for each of the two carbons in the LUMO to determine which of the two centers is most electrophilic. Such a procedure has recently been implemented in the extended Hückel methodology by Dronskowski and Hoffmann.²⁹⁻³¹ In order to estimate the electrophilic character of a fragment, atom or bond, one seeks for the energy change in the molecule when additional charge is dumped into the LUMO. The higher the contribution of the atom or bond to the LUMO, the more its energy is lowered, and the more electrophilic it is. A partitioning scheme was introduced where the energetic contribution of individual atoms or bonds can be analyzed. The more negative this ξ^{ele} index, the more reactive the atom or bond. These indexes are collected in Table 1.

From these simple arguments, we predict that a soft nucleophile will attack $C_{\text{trans-P}}$. A simplified interaction diagram for $[\text{Pd}(\text{CH}_3)_2(\text{PH}_3)(\text{NH}_2)]^-$ and $[\text{Pd}(\text{C}_3\text{H}_5)(\text{PH}_3)(\text{NH}_2)]$ is presented in Figure 1. Replacing the allyl by a more realistic (*E,E*)-1,3-diphenylallyl does not change the qualitative arguments, although the energy gap between the allyl orbitals decreases, resulting in stronger mixing of the π^* into the LUMO (Table 1). Using similar arguments, for a chiral $S^{\wedge}\text{N}$ system^{19,33,34} mod-

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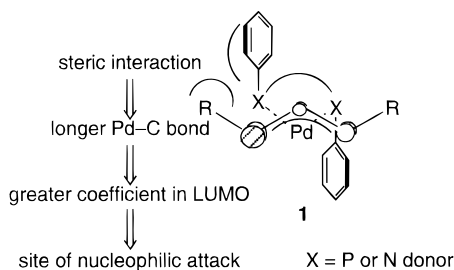
(32) All calculations were carried out with the CACAO program using default parameters for all atoms.²⁶ The geometries were taken from published X-ray structures; the imines were replaced by NH_2^- or alternatively by $\text{H}_2\text{C}=\text{NH}^-$ and the phenyl groups by hydrogens.^{15,20,42} Bond lengths (Å) and angles (deg) for $\text{P}^{\wedge}\text{N}$ systems: Pd-N, 2.13; Pd-P, 2.32; Pd- $C_{\text{trans-P}}$, 2.27; Pd- $C_{\text{trans-N}}$, 2.14; Pd-C, 2.17; C-H, 1.03; C-C, 1.40; N-H, 1.03; P-H, 1.40; P-Pd-N, 95.01; C-Pd-C, 67.77; N-Pd- $C_{\text{trans-P}}$, 94.79; N-Pd- $C_{\text{trans-N}}$, 105.17; dihedral angle between allyl and PPDN planes, 20.4; Ph-C, 1.48; Me-C, 1.51; C=C, 1.32; Pd- C_{olefin} , 2.19; substituents on olefin bent out by 20° from olefin plane. Bond lengths (Å) and angles (deg) for $S^{\wedge}\text{N}$ system: Pd-S, 2.29; S-H, 1.34; otherwise, structure identical with that of $\text{P}^{\wedge}\text{N}$ system. $\text{N}^{\wedge}\text{N}$ system: Pd-C, 2.16, 2.12, 2.08; Pd-N, 2.13, 2.11; N-Pd-N, 84.14; C-Pd-C, 68.46°.

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eled by $[\text{Pd}(\text{C}_3\text{H}_5)(\text{SH}_2)(\text{NH}_2)]$, we predict that $C_{\text{trans-S}}$ will be attacked preferentially (Table 1).

For a C_2 -symmetric bidentate ligand, steric interactions between the ligand and the allyl may force one terminal allyl carbon away from palladium (see **1**).



Again here, the π^* interaction with $d_{x^2-y^2}$ is turned on as the symmetry is lowered, and the nucleophile attacks the carbon which has the longest Pd-C bond. Although the differences are not as pronounced as with *electronically asymmetric* ligands, the electrophilicity index nicely reflects the trend (Table 1). This observation has been reported in several instances, for both chiral bidentate $\text{P}^{\wedge}\text{P}$ and $\text{N}^{\wedge}\text{N}$ donors.³⁵⁻³⁸

After nucleophilic attack on a coordinated allyl, an olefin-bond complex results. If the allylic alkylation was to proceed via a late-transition-state mechanism, the transition state would resemble an olefin-bond complex, which we simulate with $[\text{Pd}(\text{PH}_3)(\text{NH}_2)((E)\text{-methylstyrene})]^-$. The atomic orbital coefficients of (E) -methylstyrene³⁹ for both the HOMO and the LUMO are given in **2a** and **2b**, respectively. Due to the good energy

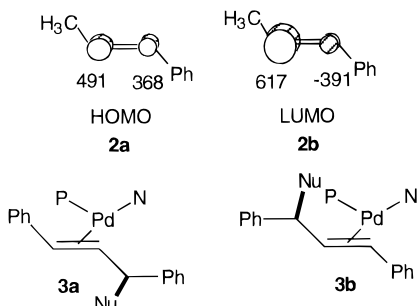


Figure 2. Schematic reaction profile for an allylic alkylation involving an early transition state (top) and a late transition state (bottom).

match between the now filled $d_{x^2-y^2}$ in $\text{Pd}(0)$ and **2b**, this interaction dominates and we therefore predict **3b** to be preferred over **3a**, as the overlap between the two FMOs is maximized.⁴⁰ Although the preference is small, for a late-transition-state mechanism, the nucleophile may preferentially attack $C_{\text{trans-N}}$ as it results in a **3b**-like structure. One should keep in mind, however, that steric interactions, absent from our model, may well outweigh this small electronic preference (<0.05 eV), as suggested by Brown *et al.*, who postulate a nucleophilic

Conclusion

Extended Hückel calculations help rationalize the observed regioselectivity of allylic alkylations for palladium systems containing C_2 -symmetric as well as *electronically asymmetric* bidentate chiral ligands. Mixing of the empty high-lying π^* into the LUMO, made up mostly of the antibonding combination between the $d_{x^2-y^2}$ and the nonbonding allyl FMOs, increases the electrophilicity of the carbon with the longest Pd-C bond as its weight in the LUMO increases, independent of the conformation (exo or endo), of the coordinated allyl. As both these conformations interconvert rapidly under true catalysis conditions, we conclude that the nucleophile preferentially attacks the $C_{\text{trans-P}}$ of the exo conformation, yielding the observed enantiomer. This is in contrast with Faller's remarkable $[\text{CpMo}(\text{NO})(\text{CO})(\text{allyl})]$ complex, where the site of attack depends on the conformation of the allyl.⁴¹ We are currently investigating both theoretical and synthetic aspects of the effect of *electronic asymmetry* on various enantioselective catalytic processes.

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