Electronic differentiation competes with transition state sensitivity in palladium-catalyzed allylic substitutions
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Abstract
Electronic differentiations in Pd-catalyzed allylic substitutions are assessed computationally from transition structure models with electronically modified phospha-benzene-pyridine ligands. Although donor/acceptor substitutions at P and N ligand sites were expected to increase the site selectivity, i.e. the preference for "trans to P" attack at the allylic intermediate, acceptor/acceptor substitution yields the highest selectivity. Energetic and geometrical analyses of transition structures show that the sensitivity for electronic differentiation is crucial for this site selectivity. Early transition structures with acceptor substituted ligands give rise to more intensive Pd-allyl interactions, which transfer electronic P,N differentiation of the ligand more efficiently to the allyl termini and hence yield higher site selectivities.

Introduction
Palladium-catalyzed allylic substitutions allow very selective and mild allylations of C-,N- and O-nucleophiles. [1-13] The selectivity derives from steric and electronic properties of substrate and catalyst structures. "Side arm guidance" of nucleophiles with multifunctional phosphinoferrocenes [14-18] or "chiral pockets" in C₂-symmetric diphosphines based on 2-(diphenylphosphino)benzoic acid amides [19-22] were applied especially successfully. Chiral P,N-ligands (e.g. phosphinooxazolines, phox) [23-27] provide in addition to steric control the possibility for "electronic differentiation", originating from the trans-influence [28] of different donor atoms. Nucleophiles (e.g. dimethylmalonate) normally favour addition to the "trans to phosphorus" position at the Pd-η³-allylic intermediate (Scheme 1). [29-41] This "trans to P" rule is supported by X-ray and computational analyses of Pd-η³-allylic intermediates, which exhibit longer and hence weaker Pd-C⁰ bonds trans to P (i.e. the stronger π-acceptor vs. N) and hence are more susceptible to nucleophilic attack (Scheme 1). [29-41] This

Scheme 1: Electronic and steric differentiations provide the basis for the high selectivity of P,N-ligands in Pd-catalyzed allylic substitutions. Effects are studied with P,N-model ligands with para-substituted, coplanar phosphabenzene and pyridine moieties.
electronic differentiation contributes to the high selectivity in Pd-catalyzed asymmetric allylic substitutions[19] and provides also an explanation for α-memory effects. [42,43] Computational model systems for P,N-ligands, i.e. PH₃ and para-substituted pyridines, have shown that cis-trans differentiations, i.e. the electronic site selectivity, of nucleophilic additions to Pd-η¹-allylic intermediates is highest for electron poor pyridine ligands.[45]

To further explore origins of site selectivities based on electronic differentiations in Pd-catalyzed allylic substitutions, we here employ a more advanced model system with phosphabenzenes, [45-48] and pyridine moieties for the crucial step of Pd-catalyzed allylic substitutions. Both P- and N-coordination sites are tuned electronically with para-substituents to reveal energetic and geometrical effects on cis- vs. trans- additions of nucleophiles to the Pd-η¹-allylic intermediates (Scheme 1).

Results and Discussion
Electron donating or withdrawing groups (i.e. X, Y = HNMe, H, NO₂) in para-positions of phosphabenzenes (X) and pyridine (Y) units tune electronic characteristics of P,N-ligand models in Pd-catalyzed allylic substitutions (Scheme 1). The phosphabenzenes and pyridine moieties are linked via Caryl-Caryl bonds and a methylene bridge retains planarity and limits conformational flexibility. NHMe rather than higher substituted NMe₂ was employed as donor group, to retain lp-aryl conjugation. Ammonia serves as model nucleophile and attacks the Pd-η¹-allylic intermediate cis or trans to phosphorus. This cis vs. trans site selectivity is employed as measure for electronic differentiation induced by the ligand system (Scheme 2).

Table 1: Activation (Ea) and reaction energies (Er) reflecting electronic differentiations in transition structures (∆Ea) and Pd-ene products relative to Pd-allyl and NH₃ reactants (pb = phosphabenzenes; py = pyridine moieties) [a]

| pb-X | py-Y | Eac | ETS | Eprod | ∆Eprod |
|------|------|-----|-----|-------|--------|
| H    | HNMe | 8.55 | 0.03 | 7.81  | 0.55   |
| H    | cis  | 8.52 | 0.17 | 8.36  | 0.52   |
| H    | NO₂  | 4.47 | 0.27 | 2.48  | 0.54   |
| HNMe | HNMe | 10.47| -0.20| 10.33 | 0.65   |
| HNMe | cis  | 10.67| 0.03 | 10.98 | 0.60   |
| HNMe | NO₂  | 6.61 | 0.10 | 5.34  | 0.65   |
| NO₂  | HNMe | 6.34 | 0.08 | 5.05  | 0.53   |
| NO₂  | cis  | 6.26 | 0.23 | 2.26  | 0.43   |
| NO₂  | NO₂  | 2.52 | 0.33 | 0.22  | 0.54   |

[a] B3LYP/6-31G* (C, H, N, P, O), 6-31G (Pd) optimized structures. Energies include ZPE corrections scaled by 0.9806. [b] Negative ∆E TS with E TS < E prod. [c] exothermic reaction energy. The lowest activation energies (Ea Table 1) for ammonia addition to the Pd-η3-allylic intermediate are apparent for strong electron withdrawing para-substituted phosphabenzenes and pyridine units, i.e. X, Y = NO₂ (Figure 1 and Figure 2, ETS trans = 2.19, ETS cis = 2.52 kcal mol⁻¹, Table 1). The highest activation energies result from electron donating amino groups X, Y = NHMe (Figure 3 and Figure 4, ETS trans = 10.67, ETS cis = 10.47 kcal mol⁻¹, Table 1, Scheme 2). Such electronic tunings of the ligands strongly affect the reactivity and give rise to increased or decreased electrophilicity of Pd-allyl intermediates.

The reaction energies (Er) for ammonia addition to the Pd-η3-allylic intermediate show a similar preference: Pd-ene-adduct formation is favoured most for X, Y = NO₂ (Ertrans = 0.29, Er cis = 0.54 kcal mol⁻¹) and becomes most unfavourable (i.e. endothermic) for X, Y = NHMe (Ertrans = 10.98, Er cis = 10.33 kcal mol⁻¹, Table 1, Scheme 2). This points to a more π-donating character of the ene product relative to the allyl-cation reactant.

In agreement with the "trans to phosphorus" rule, [23-28] attack of ammonia is preferred for most X, Y combinations trans to P, due to the stronger π* / σ acidity at P in phosphabenzenes relative to N in pyridine (Table 1).[44] Surprisingly however, this electronic site selectivity, as it is measured from relative energies of the transition structures (∆Ea), is not largest for different X, Y donor-acceptor combinations (Figure 5, Figure 6, Figure 7 and Figure 8), but is highest for X and Y = NO₂ (∆Ea = 0.33 kcal mol⁻¹), Table 1). Likewise, the smallest electronic site "trans to P" selectivity is not found for X, Y donor-acceptor combinations, but for strong donating X and Y = NHMe. Here, the selectivity is so low, that it even inverts to "cis to P" (∆Ea = 0.20 kcal mol⁻¹, Table 1).
Transition structure for the energetically favored cis to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), /SDD (Pd)).

**Figure 1**
Transition structure for the energetically favored trans to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), /SDD (Pd)).

**Figure 2**
Transition structure for the energetically disfavored cis to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), /SDD (Pd)).

**Figure 3**
Transition structure for the energetically disfavored trans to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), /SDD (Pd)).

**Figure 4**
Transition structure for the energetically favored cis to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), /SDD (Pd)).

Bond distances are given in Å.
Figure 5
Transition structure for the energetically favored trans to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), SDD (Pd)). Bond distances are given in Å.

Figure 6
Transition structure for the energetically disfavored cis to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), SDD (Pd)). Bond distances are given in Å.

Figure 7
Transition structure for the energetically disfavored cis to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), SDD (Pd)). Bond distances are given in Å.

Figure 8
Transition structure for the energetically favored trans to phosphorus addition of ammonia at the Pd-η3-allylic intermediate (B3LYP/6-31G* (C, H, N, P, O), SDD (Pd)). Bond distances are given in Å.
For each phosphabenzene moiety with \( X = \text{H or NHMe or NO}_2 \), the "trans to P" site selectivity \( \Delta E_{\text{TS}} \) increases for pyridine substituents \( Y \) in the order \( \text{NHMe} < \text{H} < \text{NO}_2 \) (Table 1). Hence, there is apparently an additional effect, which controls the site selectivity \( \Delta E_{\text{TS}} \) besides the electronic donor vs. acceptor properties of different ligand atoms, i.e. P vs. N. Via this effect; electron withdrawing groups (e.g. \( \text{NO}_2 \)) give rise to the highest site-selectivities.

**Table 2:** \( \text{H}_2\text{N-C}_\alpha \), \( \text{H}_2\text{N}^\oplus\text{-C}_\alpha \) and \( \text{Pd-C}_\alpha \) distances (Å) of transition states and Pd-ene product complexes (pb = phosphabenzene; py = pyridine)[a]

| Pb-X | py-Y  | Pd-C_\alpha | \( \text{H}_2\text{N-C}_\alpha \) | \( \text{H}_2\text{N}^\oplus\text{-C}_\alpha \) |
|------|-------|-------------|-----------------|-----------------|
| H    | HNMe | cis         | 2.754           | 1.930           | 1.594           |
|      |      | trans       | 2.834           | 1.906           | 1.604           |
| H    | H    | cis         | 2.728           | 1.968           | 1.588           |
|      |      | trans       | 2.815           | 1.947           | 1.598           |
| H    | NO2  | cis         | 2.696           | 2.010           | 1.583           |
|      |      | trans       | 2.797           | 1.989           | 1.592           |
| HNMe | HNMe | cis         | 2.767           | 1.898           | 1.598           |
|      |      | trans       | 2.850           | 1.866           | 1.611           |
| HNMe | H    | cis         | 2.745           | 1.932           | 1.593           |
|      |      | trans       | 2.840           | 1.902           | 1.603           |
| HNMe | NO2  | cis         | 2.718           | 1.969           | 1.588           |
|      |      | trans       | 2.824           | 1.940           | 1.598           |
| NO2  | HNMe | cis         | 2.733           | 1.970           | 1.587           |
|      |      | trans       | 2.805           | 1.957           | 1.596           |
| NO2  | H    | cis         | 2.703           | 2.012           | 1.582           |
|      |      | trans       | 2.787           | 1.997           | 1.590           |
| NO2  | NO2  | cis         | 2.674           | 2.051           | 1.578           |
|      |      | trans       | 2.765           | 2.040           | 1.586           |

[a] B3LYP/6-31G* (C, H, N, P, O), /SDD (Pd) optimized structures. Energies include ZPE corrections scaled by 0.9806.
These positions on the reaction coordinate indeed correspond to the site selectivity of the transition structures, i.e. $\Delta E_{a,TS}$: earlier transition structures have higher, later transition structures exhibit lower "trans to P" selectivities (Figure 10).

The distance between Pd and the allylic systems decreases from early (allyl cation like) to late (ene like) positions on the reaction coordinate. A closer, more intense Pd-C$_\alpha$ contact (e.g. 2.674 Å, Figure 2, Table 2) stronger delivers electronic differentiation of the ligand, and hence "trans to P" selectivity. Hence, higher electronic site selectivity closely corresponds to intense Pd-allyl interactions with short Pd-C$_\alpha$ distances (Figure 11).

Apparently, the positions on the reaction coordinate influence the site selectivity even stronger than the electronic differentiation between P and N ligand atoms: No substitution ($X = Y = H$) gives rise to even higher $\Delta E_{a,TS}$ than more pronounced electronic differentiations with $X$,
Y = NO₂ or NHMe (Figure 11), due to higher TS-sensitivity originating from closer Pd-allyl contact.

**Conclusion**

In Pd-catalyzed allylic substitutions, the electronic site selectivity, i.e. the preference for “trans to P” addition, is affected by the intrinsic electronic differentiation of the ligand atoms, e.g. P vs. N. However, the sensitivity for this electronic differentiation depends on the intensity of the Pd-allyl interaction. A close Pd-allyl distance in an early, allyl cation like transition structure delivers the electronic differentiation of the ligand system more efficiently to the allylic termini (C₆) than a more distant Pd-allyl (more ene like) unit of a late transition structure. Electron withdrawing (e.g. NO₂) substituents in the ligand system generate earlier transition structures with more intense Pd-allyl interactions and higher sensitivity for electronic differentiations. Hence, both intrinsic electronic differentiation in the ligand and high TS-sensitivity appear to be crucial for high site-selectivity in Pd-catalyzed allylic substitutions.

**Computational details**

All structures were fully optimized and characterized by frequency computations as minima or transition structures using Gaussian 03 [49] with standard basis sets [50,51] and thermochemical analysis were scaled by 0.9806.[56]

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