Parameterization of Phosphine Ligands Reveals Mechanistic Pathways and Predicts Reaction Outcomes

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Phosphine-Metal Complexes are Ubiquitous in Catalysis

Phosphines are often evaluated and optimized empirically for a given reaction

Assess the relative e\textsuperscript{-} donating or withdrawing properties of ligand by measuring IR frequency of CO stretches

Measure size of phosphine ligands using cone angle: “apex angle of a cylindrical cone, centered 2.28 Å from the center of the P atom, which just touches the van der Waals radii of the outermost atoms of the model”

How are parameters interpreted in the context of reactivity?

Correlation of molecular parameters with experimental outcomes to probe origin of selectivity or reactivity
Parameterization of Phosphine Ligands

Define a set of parameters that reflect the steric and electronic properties of phosphines to model observed reaction outcomes

1. Perform conformational search for each ligand in silico to identify ground-state minimized conformations
2. Identify low-energy conformers with the smallest and largest cone angles
3. Compile computed and experimentally measured steric and electronic parameters for each conformer
4. Apply stepwise multivariate linear regression algorithms to generate models with training set and validate with external examples

Conformers with smallest and largest cone angles for PEt₃

Cone angle measured as apex angle of cone centered 2.28 Å from the center of the P atom (as originally defined by Tolman)

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Parameterization of Phosphine Ligands

Define a set of parameters that reflect the steric and electronic properties of phosphines to model observed reaction outcomes.

### Sterimol and cone angle steric parameters

- **Ligand length**
  - Sterimol

- **Minimal ($B_1$) and maximal ($B_5$) widths perpendicular to length**

- **Cone angle measured at Pd-P distance of 2.28 Å**
  - 2.28 Å

### NMR and IR steric and electronic parameters

#### Experimental NMR measurements
- $^{31}$P phosphine shift
- $^{31}$P phosphine shift
- $^1J_{P-Se}$ coupling

#### Computational infrared measurements
- P=O stretch
- P–C stretch
- P–C bend

**NMR measurements reflect thermal averaging of accessible conformers**

**IR values reflect directional measures of mass and charge (e.g., force constants, bond energy, bond length, symmetry)**
**Comparison of Selected Parameters**

Visualization of selected IR parameters and classic molecular parameters to assess for similarities

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**Similar trends for P-C and nickel carbonyl stretching frequencies for alkyl phosphines, but aryl phosphines have inverse relationship**

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**No correlation between P=O frequency and proton affinity for aryl phosphines, but inverse relationship for alkyl phosphines**
Modeling Selectivity of Ligand-Controlled Oxidative Addition in Suzuki Reaction

- Reaction developed by Fu and coworkers displays ligand-controlled selectivity for oxidative addition into chloride or triflate
  - Difference between two large electron-rich phosphines is not obvious

- Computational work suggested that different ligation states for Pd is responsible for observed selectivity
  - Chosen as interesting case study to model effects of phosphine on selectivity of oxidative addition

Construction of Phosphine Library

Select 26 representative phosphines for initial development and validation of models

- **Training set**
  - Trialkylphosphines: PEt₃, PrPr₃, PBn₃, PcHex₃, PcPent₃, PnBu₃, PfBu₃
  - Triarylphosphines: P(pOMePh)₃, PpTol₃, PmTol₃, PPh₃, P(pFPh)₃, P(oOMePh)₃, PoTol₃
  - Mixed phosphines: PMe₂Ph, PETPh₂, PMePh₂, PtBuPh₂, PtBu₂Ph, PcHex₂oTol, PcHex₂pNMe₂Ph

- **Validation set**

Training set used to generate models, which can then be used to predict ΔΔG‡ for phosphines in training set and validation set

\[ ΔΔG^\ddagger = -RT\ln\left(\frac{pdt_A}{pdt_B}\right) \]

**Buchwald phosphines**

- JohnPhos
- CyJohnPhos
- SPhos
- RuPhos
- XPhos
Development of Selectivity Models

1. **Reduce parameter set** for efficient modeling

2. Use stepwise linear regression analysis to **derive initial model**

3. **Optimize models** using statistical criteria

4. **Evaluate models** for mechanistic significance

Independently used two separate parameter sets derived from minimum and maximum cone angle conformers for modeling

**Example of initial crude model:**

![Graph showing ΔΔG+ predicted vs ΔΔG+ measured]

- **Equation:** $y = 0.74x + 0.70$
- **R²:** 0.45

*Statistical criteria dictating optimization:*

1. Number of terms
2. Goodness of fit ($R^2$)
3. Predictive ability (for validation set)

Initial simple models were refined by manually adding and removing terms and applying optimization criteria

**Five parameters in five terms, poor predictions**

$$
\Delta \Delta G^\ddagger = 0.06 - 0.63(31P-\text{Se}_J) - 0.56(\text{P-C}_\text{bend(\nu)}) + 0.35(\text{P-C}_\text{bend(\iota)}) + 0.57(\text{cone angle}) + 0.69(31P-\text{Se}_J \times \text{P-C}_\text{bend(\nu)})
$$
**Development of Selectivity Models**

Developed independent models based on parameters for minimum and maximum cone angle conformers.

### Minimum cone angle parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Training set</th>
<th>Validation set</th>
<th>External set</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta G^\ddagger$ predicted (kcal mol$^{-1}$)</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
<td><img src="image3" alt="Graph" /></td>
</tr>
</tbody>
</table>

- $y = 0.92x + 0.07$
- $R^2 = 0.64$

### Maximum cone angle parameters

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<td><img src="image4" alt="Graph" /></td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
</tbody>
</table>

- $y = 0.93x + 0.04$
- $R^2 = 0.90$

Models developed using only training and validation sets for maximum and minimum cone angles had essentially equal goodness of fit, so an external set of phosphines was added for evaluation.

**Model for maximum cone angle parameters:**

$$
\Delta G^\ddagger = 0.12 - 0.76(P-C_{\text{bend(\nu)}}) + 0.57(P-C_{\text{bend(\i)}}) + 0.79^{(31P_{\text{shift}} \times P-C_{\text{bend(\nu)}})} - 1.49^{(31P_{\text{Se shift}} \times P-C_{\text{bend(\nu)}})} + 0.35^{(31P_{\text{Se shift}} \times P-C_{\text{bend(\i)}})} + 0.85^{(31P_{\text{Se shift}} \times \text{cone angle})}
$$
Mechanistic Experiments Consistent with Importance of Palladium Ligation State

Because the selectivity model complex and hard to evaluate mechanistically, additional mechanistic experiments were performed.

Key question: Is L₂Pd or LPd intermediate responsible for oxidative addition and how does this effect regioselectivity?

- Work by Amatore and Hartwig suggest small phosphines such as PPh₃ (131° cone angle) react through L₂Pd complexes and larger phosphines such as PoTol₃ (147° cone angle) react as LPd complex.
- Sought to probe the effect of ligand concentration on site selectivity of oxidative addition.

**PET₃ (small, 122°)**
- Selective for addition at -OTf at all ratios
  - Consistent with L₂Pd

**PtBu₃ (large, 153°)**
- Selective for addition at -Cl at all ratios
  - Consistent with LPd
Mechanistic Experiments Consistent with Importance of Palladium Ligation State

Because the selectivity model complex and hard to evaluate mechanistically, additional mechanistic experiments were performed

Key question: Is \( \text{L}_2\text{Pd} \) or \( \text{LPd} \) intermediate responsible for oxidative addition and how does this effect regioselectivity?

- Increasing selectivity for oxidative addition at -\( \text{OTf} \) with increasing ligand:Pd ratios
  - Consistent with \( \text{L}_2\text{Pd} \) leading to addition at -\( \text{OTf} \)
- Selective for addition at -\( \text{OTf} \) at all ratios
  - Consistent with “\( \text{L}_2\text{Pd-like} \)” coordination
Cyclic Voltammetry Measurements for All Ligands Indicate \( \text{L}_2\text{Pd} \) Resting State

Cyclic voltammetry can be used to indicate the ligation state of palladium

\textit{Oxidation potentials for all ligands are consistent with an \( \text{L}_2\text{Pd} \) complex (\( \text{L}_2\text{Pd(dba)} \))}

\begin{itemize}
  \item Propose that the relative concentrations of LPd and \( \text{L}_2\text{Pd} \) are responsible for reaction selectivity
  \item For large and small phosphines, one ligation state is favored, while state dependent on [phosphine] for intermediate sizes
\end{itemize}
Phosphines divided into two groups for further modeling, those with angles larger and smaller than PPh₃.

**Cone angle larger than PPh₃ (131°)**

\[ \Delta \Delta G^\ddagger = -0.103(^{31}\text{P-Se}_{\text{shift}}) + 7.136 \]

- Phosphine selenide shift alone models selectivity.
- This value represents relative deshielding of phosphorous atom when bound to another atom.
- Proposed to correspond to equilibrium of LPd and L₂Pd species.

![Graph](image-url)

The graph shows a linear relationship between \( \Delta \Delta G^\ddagger \) and \( ^{31}\text{P-Se}_{\text{shift}} \) with the equation \( y = -0.103x + 7.136 \) and a correlation coefficient \( R^2 = 0.86 \). The data points are color-coded for different sets: black squares for the training set, red crosses for the validation set, and blue circles for the external set.
Phosphines Divided by Cone Angle for Modeling

Phosphines divided into two groups for further modeling, those with angles larger and smaller than PPh3

Cone angle smaller than PPh3 (131°) and biaryl Buchwald-type ligands

\[ \Delta \Delta G^\ddagger = 0.56 - 0.24(31P-Se_{shift}) - 0.32(31P-Se_{J}) + 0.14(P-Pd complex) + 0.20(31P-Se_{shift} \times \text{cone angle}) \]

- Most predictive model uses minimum cone parameters
- Term with largest contribution is P-Se coupling
Phosphines divided into two groups for further modeling, those with angles larger and smaller than PPh$_3$.

Cone angle smaller than PPh$_3$ (131°) and biaryl Buchwald-type ligands

$\Delta\Delta G^\ddagger = 0.56 - 0.24(^{31}P$-Se$_{\text{shift}}) - 0.32(^{31}P$-Se$_{\nu}) + 0.14(P$-C$_{\text{bend}}(\nu)) + 0.20(^{31}P$-Se$_{\text{shift}} \times$ cone angle)

- Term with largest contribution is P-Se coupling
- P-Se correlated inversely to phosphine nucleophilicity
- Higher nucleophilicity, i.e. lower P-Se coupling (714 vs 730 Hz for P(pOMePh)$_3$ vs PPh$_3$) gives better selectivity for triflate (3.5 vs 2.6 kcal/mol)
- Larger cone angle also correlates to increased selectivity
  - 4.2 kcal/mol for SPhos (202°) vs 3.3 kcal/mol for CyJohnPhos (184°)