COORDINATIVE UNSATURATION IN TRANSITION METAL CATALYSIS

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what is it?

how to make it

refining definitions

case studies
what is coordinative unsaturation?

**Stable precatalysts**

- **Zeise's Dimer**
  - $[\text{Pt}(\eta^2-\text{C}_2\text{H}_4)(\mu-\text{Cl})\text{Cl}]_2$
  - 16 $e^-$/Pt

- **Wilkinson's Catalyst**
  - $\text{Rh(PPh}_3)_3\text{Cl}$
  - 18 $e^-$

- **Grubbs I**
  - $[\text{PCy}_3\text{Cl}_2\text{Ru}=\text{CHPh}]$
  - 16 $e^-$

- **NiCp$_2$**
  - 20 $e^-$ (rare)

**Active catalysts**

- **'Zeise's Monomer'**
  - $[\text{Pt}(\eta^2-\text{C}_2\text{H}_4)\text{Cl}]$
  - 14 $e^-$/Pt

- **Rh(PPh$_3$)$_2$Cl**
  - 14 $e^-$

- **Pd(PPh$_3$)$_4$**
  - 16 $e^-$
the importance of coordinative unsaturation in catalysis

• Greater substrate scope
• Increased reaction rates
• Lower temperatures

“A vacant coordination site is perhaps the single most important property of a homogeneous catalyst”

-James P. Collman,
then why isn’t everybody doing it?

ligand dissociation from a precatalyst to generate a highly unsaturated complex is often times very slow and/or thermodynamically unfavorable

generating unsaturated species in solution often leads to irreversible catalyst inactivation

There are considerable challenges associated with generating unsaturated catalysts, and these have often required creative solutions or serendipity to overcome
how to generate coordinative unsaturation: Ligand Dissociation

Bulky ligands promote formation of monoligated palladium

Strong donor ligands stabilize monoligated species

\[
\text{PPh}_3: \text{Less bulky, less donating} \quad \text{Pt-Bu}_3: \text{Bulkier, more donating}
\]

A ligand scavenger makes this process more efficient

how to generate coordinative unsaturation: Forced Ligand Dissociation

Photochemical dissociation of $H_2$ or CO can create very reactive intermediates, even at low temperatures

This principle has not been used in catalysis

Brown’s catalyst is activated by hydrogenation of the norbornadiene ligand to norbornane, which does not bind to the rhodium center

**how to generate coordinative unsaturation:**

***Reduction***

\[
\text{Ph}_3\text{P} \backslash \text{Pd} \wedge \text{OAc} \quad \text{slow} \quad \left[ \text{Ph}_3\text{P} \backslash \text{Pd} \wedge \text{OAc} \right]^- \quad \text{Ph}_3\text{P}^+ \wedge \text{OAc} \quad \text{H}_2\text{O} \quad \text{Ph}_3\text{P} = \text{O} \quad \text{Ph}_3\text{P} \wedge \text{Pd}
\]

**Pd(II)**

16 e⁻

**Pd(0)**

14 e⁻

Reduction of \((\text{R}_3\text{P})_2\text{Pd(OAc)}_2\) complexes occurs spontaneously by internal oxidation of a phosphine, but the resulting reduction product is not stable in the absence of an added ligand.

**Reduction via dialkylation**

\[
\text{Zr} \rlap{(\text{IV})} \quad 16 \text{ e}^- \quad \begin{array}{c} \text{Cl} \quad \text{Cl} \\ \end{array} \quad \text{2x BuMgBr} \quad \begin{array}{c} \quad \text{Zr} \\ \quad \text{Bu} \\ \quad \text{Bu} \\ \end{array} \quad \begin{array}{c} \quad \text{Zr} \\ \quad \text{H} \\ \quad \text{Bu} \\ \end{array} \quad \text{red. elim.} \quad \begin{array}{c} \quad \text{Zr} \\ \quad \text{Zr} \\ \end{array}
\]


‘Virtual’ Coordinative Unsaturation

Coordinative unsaturation: It’s not real!

Solvent molecules perform the same function

An example from main group chemistry:
using coordinative unsaturation as a focal point in viewing catalytic cycles

virtues

• often helps understanding of individual difference in catalytic activity based on ‘ancillary’ ligands

• key parameter in catalyst activation, catalyst deactivation, and substrate scope

caveats

• once you generate an unsaturated species, it still has to do the desired chemistry

• one species may behave as if it is coordinatively unsaturated, while a similar one with the same electron count will not

• not all active sites are created equal
olefin metathesis

cross coupling

Heck reaction

hydrogenation

iridium catalyzed allylic substitution
This reaction is inefficient in the presence of Grubbs I or Grubbs II catalysts.
Ligands dramatically affect the behavior of metathesis catalysts

ligands control metal’s affinity for substrate vs. phosphine

Rate of initiation is faster with PCy₃

Rate of propagation is $>10^4$ times faster with SIMes

Faster overall with SIMes

What has olefin metathesis taught us?

Once again, coordinative unsaturation greatly affects catalyst efficiency.

We must refine our notion of coordinative unsaturation to include not only the reactivity of ‘vacant’ sites in general, but their relative reactivities towards substrate versus excess ligand.

NHCs do not act as π-acids, whereas phosphines act as weak π-acids. Coordination of a more strongly π-acidic ligand trans to an NHC is favored relative to the phosphine case.
olefin metathesis

cross coupling

Heck reaction

hydrogenation

iridium catalyzed allylic substitution
The Heck Reaction and Cross Coupling

Heck reaction

Cross coupling

oxidative addition

reductive elimination

rate limiting step

transmetallation
where the art started

<table>
<thead>
<tr>
<th>Precatalysts</th>
<th>Pd(PPh₃)₄</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pd(OAc)₂ + PPh₃</td>
</tr>
<tr>
<td></td>
<td>Pd(dba)₂ or Pd₂(dba)₃ + PPh₃</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Electrophiles</th>
<th>ArI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ArBr</td>
</tr>
<tr>
<td></td>
<td>ArOTf</td>
</tr>
</tbody>
</table>

| Temperatures       | Elevated temperatures often required          |

| Catalyst Loading   | 1 - 10 mol %                                  |

The active catalyst in homogeneous cross coupling reactions was usually $L_2Pd$, but ligand dissociation to this species isn’t always easy...
excesses of strong ligands lead to inert catalysts

\[ \text{I} \xrightarrow{\text{1 mol % Pd}_{2}(\text{dba})_{3}\cdot\text{CHCl}_{3}} \text{SnBu}_{3} \xrightarrow{\text{ligand, THF, 50 °C}} \text{I} \text{SnBu}_{3} \]

Strongly binding ligands inhibit the reaction by quenching coordination sites

A negative correlation exists between reaction rates and inhibition factors

This information led to the widespread use of (2-furyl)\(_2\)P and AsPh\(_3\) in cross coupling reactions – these seem to facilitate the formation of coordinatively unsaturated species in solution

<table>
<thead>
<tr>
<th>ligand</th>
<th>(k_{\text{rel-4}}) (P:Pd = 4)</th>
<th>(k_{\text{rel-2}}) (P:Pd = 2)</th>
<th>inhibition factor*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPh(_3)</td>
<td>1.0</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>(p-MeOC(_6)H(_4))(_3)P</td>
<td>&lt;0.7</td>
<td>7.2</td>
<td>&gt;100</td>
</tr>
<tr>
<td>(o-Tol)(_3)P</td>
<td>35.2</td>
<td>119</td>
<td>3.4</td>
</tr>
<tr>
<td>(2-furyl)(_3)P</td>
<td>105</td>
<td>391</td>
<td>3.7</td>
</tr>
<tr>
<td>AsPh(_3)</td>
<td>1100</td>
<td>1480**</td>
<td>1.3</td>
</tr>
</tbody>
</table>

reactions using P:Pd = 2 had >95% yield

*\(k_{\text{rel-2}} / k_{\text{rel-4}}\)

**Incomplete reaction because of catalyst decomp., 94% yield

Formation of $L_1$Pd type species makes previously impossible couplings routine


Formation of $L_1$Pd type species makes previously impossible couplings routine.
Sources of monoligated Pd: not all precatalysts are created equal

Some methods of generating L\textsubscript{1}Pd

- Better: [Pd(dba)$_2$] + Pt-Bu$_3$
- Good: [(t-Bu$_3$P)$_2$Pd]
- Best: [(t-Bu$_3$P)Pd(dba)]

[Chemical structures and reactions depicted with catalysts and products]

Monoligated Pd via dissociation of ‘innocent’ ligands

The activity of these monophosphine-diene complexes depends on their ability to release the diene, liberating $L_1$Pd.

Activity: $1 > 2 > 3$


The in situ formation of catalysts from palladium-dba complexes falls into this category.

In general, it seems that this method leads to less active catalysts than reduction or reductive elimination – no ligand is truly innocent.
Monoligated Pd via reduction of Pd(OAc)$_2$ – a new take on an old method

Activation in water using Pd(OAc)$_2$ (0.01 mmol), L (0.03 mmol) and H$_2$O (0.04 mmol) in 1 mL dioxane at 80 °C

Monoligated Pd via reductive elimination from Pd(II) complexes


Monoligated Pd via reductive elimination of Pd(II) complexes


Recap of reductive elimination methods:

- **Homocoupling of organometallics**
  - Nolan 2003

- **Palladacycle reductive elimination via β-hydride elimination**
  - Nolan 2003

- **Palladacycle - external nucleophile reductive elimination**
  - Bedford 2001

- **Base induced palladacycle reductive elimination**
  - Buchwald 2008

- **Nucleophilic attack on η³-allyl**
  - This example: Nolan 2006
Why choice of ligand is crucial

To promote $L_1Pd$ type reactivity, a ligand must not only promote formation of $L_1Pd$ but stabilize the species to prevent catalyst deactivation

large trialkylphosphines are the ligands of choice

**Large size:**
- drives ligand dissociation equilibrium to the right
- offers steric protection from nucleation and precipitation of metallic palladium
- promotes reductive elimination of strained Pd(II) intermediates

**Strong basicity:**
- stabilizes the electron poor monophosphine complex
- promotes oxidative addition

![Chemical structures](image)


Additional weak interactions stabilize the $L_1Pd$ intermediate and provide sites of ‘virtual’ coordinative unsaturation

*An agostic interaction is present in ArPd(Pt-Bu$_3$)X intermediates, but (Pt-Bu$_3$)Pd has never been isolated*
Cross coupling summary

Generating highly unsaturated catalysts can lead to great increases in reaction rate and substrate scope

![Reaction Scheme]

Sterically bulky ligands can be used to bias an equilibrium in favor of dissociation, leading to a more reactive catalyst.

The precatalyst is very important – generally reductive elimination from stable Pd(II) species makes more active catalysts than does simple ligand dissociation.

Ligand choice is important – good ligands both facilitate the formation of monoligated Pd from the precatalyst and stabilize the active catalyst.

olefin metathesis

cross coupling

Heck reaction

hydrogenation

iridium catalyzed allylic substitution
Wilkinson’s (pre)catalyst reacts with $H_2$ to form a coordinatively saturated Rh(III) complex – ligand dissociation is required!

differences in rates of hydrogenation are accounted for by decrease in ability of more hindered olefins to bind to Rh

rates drop off to nearly 0 with tri- and tetrasubstituted olefins
Diene ligands are labile under the reaction conditions, allowing the formation of highly unsaturated species
virtual coordinative unsaturation and Crabtree’s catalyst

The highly unsaturated intermediates are prone to form clusters in the absence of ligands!

Non coordinating solvents are a must!

the effect of unsaturation in hydrogenation catalysis

<table>
<thead>
<tr>
<th>catalyst</th>
<th>Initial rates of hydrogenation in (mol product)</th>
<th>mol product (mol catalyst)(hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Ir(cod)(py)(PCy₃)]⁺PF₆⁻ (0 °C)</td>
<td>![image of cis-1,2-dimethylcyclohexene]</td>
<td>6400 4500 3800 4000</td>
</tr>
<tr>
<td>RhCl(PPh₃)₃ (25 °C) (0 °C)</td>
<td>![image of 1,3-cyclohexadiene]</td>
<td>650 700 13 0</td>
</tr>
<tr>
<td></td>
<td>![image of 2,3-dimethylcyclohexene]</td>
<td>60 70 0 0</td>
</tr>
</tbody>
</table>

nearly any olefin can be hydrogenated with Crabtree's catalyst, although tri- and tetr subsituted olefins require slow addition of catalyst

better anions, better catalysts

Even standard ‘non-coordinating’ anions such as PF$_6^-$ bind too strongly to the Ir center and extremely weakly coordinating anions such as BAr$^F_4$ and AlOR$^F$ are needed*


unsaturation allows directing effects through metal-substrate coordination

**cyclic substrates**

<table>
<thead>
<tr>
<th>R</th>
<th>Substrate</th>
<th>Rh⁺</th>
<th>Ir⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>N/A</td>
<td>2 mol %, 15 psi &gt;1000:1</td>
<td>N/A</td>
</tr>
<tr>
<td>Me</td>
<td>N/A</td>
<td>2 mol %, 15 psi &gt;1000:1</td>
<td>N/A</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>2 mol %, 15 psi 7:1</td>
<td>2 mol %, 15 psi 49:1</td>
<td>N/A</td>
</tr>
<tr>
<td>COMe</td>
<td>N/A</td>
<td>2 mol %, 15 psi 99:1</td>
<td>N/A</td>
</tr>
<tr>
<td>CH₂OH</td>
<td>10 mol %, 1000 psi 19:1</td>
<td>2 mol %, 15 psi 9:1</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>10 mol %, 1000 psi 64:1</td>
<td>2.5 mol %, 15 psi 52:1</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>2 mol %, 15 psi 7:1</td>
<td>2 mol %, 15 psi 32:1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**acyclic substrates**

<table>
<thead>
<tr>
<th>R</th>
<th>R’</th>
<th>Rh⁺</th>
<th>Ir⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Ph</td>
<td>2 mol %, 15 psi 32:1</td>
<td>N/A</td>
</tr>
<tr>
<td>Ph</td>
<td>CO₂Me</td>
<td>0.5 mol %, 15 psi 99:1</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17.5 mol %, 640 psi 10:1</td>
<td>2.5 mol %, 15 psi 3:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mol %, 15 psi 19:1</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mol %, 15 psi 99:1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Rh⁺ = [Rh(nbd)(dppb)]⁺BF₄⁻  Ir⁺ = [Ir(cod)(py)(PC₅₃)]⁺PF₆⁻

hydrogenation summary

highly unsaturated hydrogenation catalysts exhibit a larger substrate scope as well as a tendency to deactivate.

the activity of cationic, unsaturated hydrogenation catalysts is remarkably dependent on both the nature of the counterion and the solvent – strong coordination from either deactivates the catalyst.

due to the open coordination site, the catalyst can complex the substrate, opening the door to directing effects.
cross coupling

Heck reaction

hydrogenation

iridium catalyzed allylic substitution

olefin metathesis
iodium catalyzed asymmetric allylic alkylation

Yet another case of ligand inhibition

Standard conditions with 2:1 P:Ir gives sluggish reactions and narrow scope

Substrate has to compete with ligand for a binding site on Ir!

\[ \text{substrate-ligand exchange equilibrium} \]
The tempting solution doesn’t work

Solving this problem isn’t as easy as just lowering the P:Ir ratio!
**Evolution of the solution**

**Problem: ligand deficient systems do not undergo activation readily**

Hartwig: perform cyclometallation in the presence of excess ligand, then add a ligand scavenger

Alexakis: Use sterically bulky ligands to promote activation through strain relief

Helmchen: Use a stronger base and make both the excess ligand and the scavenger cheap

Another problem

Unsaturated catalysts can deactivate by retro-cyclometallation
Continuing the evolution

**Problem:** Preactivated catalysts can still decyclometallate and dimerize to release excess ligand

Hartwig: Use a single-component, preactivated catalyst with a weak ancillary ligand (ethylene) to fill the remaining coordination site

Helmchen: Use a single-component, preactivated Ir(III) precatalyst that is activated by nucleophilic attack on the $\eta^3$-allyl ligand

Summary of iridium catalyzed allylic substitution

The \([\text{IrCl(cod)(L)}]\) precatalyst is coordinatively saturated at 16 electrons, but the complex strongly prefers an 18 electron configuration after cyclometallation.

Ligand deficient systems can undergo disproportionation to coordinatively saturated species.

The most efficient methods for keeping catalytically active complexes in the cycle involved preventing this disproportionation from occurring, thus preventing the release of free ligand into solution.
**Key points**

Generating highly unsaturated catalysts can have profound effects on reaction rates and substrate scope.

![Chemical structure](image)

Ligand dissociation is the ‘standard’ way of making an unsaturated catalyst, but other methods, such as reduction often give rise to more active systems.

![Chemical structure](image)

Ligand choice is important – good ligands both facilitate the formation of unsaturated species from the precatalyst and stabilize the active catalyst.
**General**


**Ligand Parameters**


**General Directing Effects**


**Light Induced Ligand Dissociation**


**Olefin Metathesis**


**Cross Coupling**

**Reviews**


**Mechanism**


**Ligands – Pr-Bu\textsubscript{3}**


**Ligands – AsPh\textsubscript{3}**


**Ligands – Dialkyl Biarylphosphines**


**3-Coordinate Oxidative Addition Products**


**Methods: Reduction of Pd(II) Catalyst Precursors**


**Methods: Precatalysts employing innocent ligands (including dba)**


Andreu, M. G.; Zapf, A.; Beller, M.: Molecularly defined palladium(0) monophosphine complexes as catalysts for efficient cross-coupling of aryl chlorides and phenylboronic acid. *Chemical Communications* 2000, 2475-2476.


**Hydrogenation**


Rhodium


Iridium Catalyzed Allylic Substitution


