Ligand-coupling on hypervalent species: 
Transition metal chemistry without the metal

Literature Presentation
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Transition metal cross-couplings have transformed chemical synthesis

Transition metals have enabled elusive bond formations:

- Mn (Manganese)
- Fe (Iron)
- Ni (Nickel)
- Cu (Copper)
- Rh (Rhodium)
- Pd (Palladium)
- Ag (Silver)

2010 Nobel prize in chemistry

Fundamental processes:

- Oxidative addition
- Transmetalation
- Reductive elimination
Transition metal cross-couplings have transformed chemical synthesis

Transition metals have enabled elusive bond formations

... but can we mimic this reactivity with main group elements

Fundamental processes:

- Oxidative addition
- Transmetalation
- Reductive elimination
"Transition metal chemistry relies on d-orbital participation"

Oxidative addition

- Oxidation state increase of +2
- Increase in valence electrons
- Decrease in d-electrons

Reductive elimination

- Oxidation state decrease of –2
- Decrease in valence electrons
- Increase in d-electrons

“The difference between the common occurrence of oxidative addition in transition metal chemistry and the rare occurrence of this process in organic chemistry contributes to the distinction between the reactivity of transition metal complexes and (organic) molecules.”

“Reductive elimination is the reverse of oxidative addition.”

Organotransition Metal Chemistry – From Bonding to Catalysis
John F. Hartwig
Transition metal chemistry relies on d-orbital participation.

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Various groups: 1960s

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Various groups: 1960s

The curious case of triaryl sulfonium salts

Why are we observing aryl dimerization and what is the mechanism for its formation?

Trost: 1971

Single isomers obtained when using substituted aryls

Retention of stereochemistry

Evidence against benzyne

Evidence against radical

The curious case of triaryl sulfonium salts

$S_{N}Ar$

Sulfurane

Potential for ligand exchange means we can’t rule out $S_{N}Ar$ pathway

The curious case of triaryl sulfonium salts

$S_{N}Ar$

Sulfurane

Different lithiums provide different selectivities

8:1 selectivity

Direct evidence for reductive coupling at sulfur


Sheppard: 1971 Direct evidence for reductive coupling at sulfur

σ-sulfurane

70% yield

71% yield
Ligand-coupling and reductive elimination

Sulfurane coupling and reductive elimination show remarkable mechanistic similarities

Coupling mechanism was expanded beyond sulfur and termed “ligand-coupling” around 1985 by Shigeru Oae

“In organometallic chemistry, the terms “reductive elimination” and “oxidative addition” have been used to describe many chemical phenomena… most of these reactions can be understood in terms of ligand coupling.”

Ligand-coupling Reactions of Hypervalent Species
Shigeru Oae

Sulfurane coupling and reductive elimination show remarkable mechanistic similarities.

Coupling mechanism was expanded beyond sulfur and termed "ligand-coupling" around 1985 by Shigeru Oae.

"(Ligand-coupling reaction) is a new type of reaction and is different from widely used reductive elimination, and is unique and specific for hypervalent compounds in general."

Organo Main Group Chemistry
Kin-Ya Akiba
Ligand-coupling and reductive elimination

Sulfurane coupling

Sulfur

Sulfurane coupling

Bismuthorane coupling

Bismuth

Iodane coupling

Iodine

Iodane coupling

Additional Elements demonstrated to undergo ligand-coupling

Silicon

Tellurium

Arsenic

Tin

Ligand-coupling is distinct from reductive elimination

- Limited to main-group elements
- Requires hypervalency of central atom
- Concerted coupling process
- Allowed couplings are element and geometry dependent
Accessing hypervalent scaffolds

Hypervalent structures for ligand-coupling are accessed three ways:

1. **Stable compound**
   - Easy to handle
   - Harsh conditions to trigger ligand-coupling

2. **In situ addition to π bond**
   - Precursors typically bench stable
   - Organometallic reagents often required

3. **In situ addition to charged species or σ bond**
   - Established synthesis of precursors
   - Alkoxide addition leads to complications in coupling

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   ![Chemical structure](image1)

2. **In situ addition to charged species or σ bond**
   - Established synthesis of precursors
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   ![Chemical structure](image2)

Two synthetically useful strategies.
Hypervalency is the key to ligand-coupling

Hypervalent molecules: formal violation of the octet rule for bonding

3d orbitals are not involved in valence expansion

PPh$_5$
Pentaphenylphosphorane
“10 valence electrons”

SPh$_4$
Tetraphenylsulfurane
“10 valence electrons”

“Far too often have 3d orbitals been invoked as a kind of theoretical *deus ex machina* to account for facts apparently otherwise inexplicable”

Molecular Orbital Theory of Pentacoordinate Phosphorus
Roald Hoffmann

Hypervalency is the key to ligand-coupling

Hypervalent molecules: formal violation of the octet rule for bonding

$\text{PPh}_5$

Pentaphenylphosphorane

“10 valence electrons”

$\text{SPh}_4$

Tetrphenylsulfurane

“10 valence electrons”

$\text{sp}^2$ hybridized central atom
Hypervalency is the key to ligand-coupling

Hypervalent molecules: formal violation of the octet rule for bonding

3 center, 4 e⁻ bond

PPh₅
Pentaphenylyphosphorane

SPh₄
Tetraphenylsulfuran

Shorter equatorial bonds

Longer apical bonds

Apical bond described as distinct from equatorial bonds

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SPh$_4$ Tetr phenylsulfurane

Apical bond described as distinct from equatorial bonds... and polarized in comparison

Return to normal valency through extrusion of one pair of electrons provides ligand-coupling driving force in the forward direction

Hypervalent molecules have three reactivity pathways

Three pathways can occur to return to normal valency

**Self-decomposition**

Wittig reaction pathway

**Ligand-exchange**

$S_N2$-like outcome

**Ligand-coupling**

Reductive coupling
Hypervalent molecules have three reactivity pathways

Three pathways can occur to return to normal valency

Ligand-coupling

Reductive coupling
Hypervalent molecules have three reactivity pathways

Ligand-coupling can occur through four mechanistic pathways

**Ipso-ipso couplings**

- Homocoupling/Similar polarity: $\text{LC}_H$
  - Synchronous pathway
- Heterocoupling/Different polarity: $\text{LC}_N$
  - Asynchronous pathway

**Ipso-allyl couplings**

- $S_N2'$ type process: $\text{LC}_N$
  - Standard polarity
- Apical electrophile: $\text{LC}_E$
  - Unusual equatorial nucleophile
Hypervalent molecules have three reactivity pathways

- **Self-decomposition**
- **Ligand-exchange**
- **Ligand-coupling**

*Wittig reaction pathway*  
*SN$_2$-like outcome*  
*Reductive coupling*

Two pathways compete directly with each other

*How can we tune this reactivity?*
Geometry impacts the couplings available

These RE type arrows are deceptive at best and incorrect at worst

Geometry impacts the couplings available

Like transition metals, ligands position around the central atom plays a role in couplings

D3h

Geometry impacts the couplings available

Like transition metals, ligands orientation around the central atom plays a role in couplings.

distorted trigonal bipyramidal:  
$\text{S}$

Sulfur

Trigonal bipyramidal:  
$\text{P}$

Phosphorus

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\[ \text{Sulfur} \]

\[ \text{Phosphorus} \]

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The rules are more like guidelines anyways…

Presence of \( \pi \) orbitals allows for “forbidden” ligand-couplings to occur

- **Sulfur**
  - C4v
  - Orbital overlap
  - WH Allowed coupling: Apical-basal

- **Phosphorus**
  - D3h
  - Orbital overlap
  - WH Allowed coupling: Apical-apical

Equatorial-equatorial

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The rules are more like guidelines anyways…

Presence of $\pi$ orbitals allows for “forbidden” ligand-couplings to occur

WH forbidden coupling:
- Trans Apical-basal
- Apical-equatorial

WH allowed coupling:
- Apical-basal
- Equatorial-equatorial

Orbital overlap

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Geometry impacts the couplings available

Like transition metals, ligands orientation around the central atom plays a role in couplings.

Ligands on hypervalent species are not frozen in a single position

Ligands can “migrate” between positions on hypervalent species

Orientation for ligands can be manipulated through two rotation processes:

Berry pseudorotation and turnstile processes

Ligands on hypervalent species are not frozen in a single position

**Berry pseudorotation $\psi$:**

allows for apical and equatorial ligands to interconvert

Low barriers of <3 kcal/mol but goes through molecular geometry rearrangement

Does not actually involve rotational motion

Orientation for ligands can be manipulated through two rotation processes:

**Berry pseudorotation and turnstile processes**
Ligands on hypervalent species are not frozen in a single position

**Turnstile rotation:**

allows for apical and equatorial ligands to interconvert

Higher barriers (5-10 kcal/mol) and viewed as less likely to occur

Occurs through physical rotation of pentacoordinated molecule

Orientation for ligands can be manipulated through two rotation processes:

**Berry pseudorotation and turnstile processes**

Rotation has important considerations for coupling selectivity

Equatophilicity: more electron rich and π ligands favor equatorial positions

Apicophilicity: more electron-withdrawing groups favor apical positions

What is the most stable form of this phosphorane?
Rotation has important considerations for coupling selectivity.

What is the most stable form of this phosphorane?

What would we expect to be the ligand-coupling products?

Equatophilicity: more electron rich and π ligands favor equatorial positions

Apicophilicity: more electron-withdrawing groups favor apical positions

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Equatorial selectivity can be rationalized by ability to stabilize charge buildup over transition state


Coupling selectivity is governed by electronic effects

What would we expect to be the ligand-coupling products?

Equatorial selectivity can be rationalized by ability to stabilize charge buildup over transition state

Why do we not observe C-O coupling products?

Coupling selectivity is governed by stereoelectronic effects

In symmetrical hypervalent structures, apical ligands share bond lengths and polarization

Appleton, T. G.; Clark, H. C.; Manzer, L. E. Coordination Chemistry Reviews 1973, 10, 335–422.
**Coupling selectivity is governed by stereoelectronic effects**

In symmetrical hypervalent structures, apical ligands share bond lengths and polarization. How does reactivity change when one apical ligand is differed?
Coupling selectivity is governed by stereoelectronic effects

Need to consider influence of apical ligands on each other (trans influence)

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Trans affect leads to undesired ligand exchange if dissociation outcompetes ligand coupling

Appleton, T. G.; Clark, H. C.; Manzer, L. E. Coordination Chemistry Reviews 1973, 10, 335–422.

**Ligand-coupling reactivity summary**

- Limited to main-group elements
- Requires hypervalency of central atom
- Concerted coupling process
- Allowed couplings are element and geometry dependent

- Driving force = return to normal valency
- “Concerted” process can be asynchronous, enabling WH forbidden couplings
- (Pseudo)rotation processes play a role in orientation of ligands
- Kinetic and thermodynamic trans affects lead to selective coupling of single apical ligand
- Both apical and equatorial partners need to be able to accept electron density over the reaction

Appleton, T. G.; Clark, H. C.; Manzer, L. E. Coordination Chemistry Reviews 1973, 10, 335–422.

Where does ligand-coupling find use?

Fundamental processes:

- Oxidative addition
- Transmetalation
- Reductive elimination

To understand the applications of ligand-coupling, we need to look at oxidative addition/transmetalation
Where does ligand-coupling find use?

To understand the applications of ligand-coupling, we need to look at oxidative addition/transmetalation.

**Fundamental processes:**

- Oxidative addition
- Transmetalation
- Reductive elimination

**Oxidative ligation aka S\textsubscript{N}2 or S\textsubscript{N}Ar**

**“Transmetalation”**

**Commentary on ligand coupling elements**

<table>
<thead>
<tr>
<th>Ligand coupling advantages</th>
<th>Ligand coupling Challenges</th>
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<tr>
<td>- Coupling selectivity easy to understand</td>
<td>- Limited coupling scopes</td>
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<tr>
<td>- Lewis basic groups tolerated</td>
<td>- Starting material synthesis</td>
</tr>
<tr>
<td>- Tunable process</td>
<td>- Stochiometric coupling</td>
</tr>
<tr>
<td>- Metal-free</td>
<td>- Metal-free</td>
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</tbody>
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**Ligand coupling advantages**
- High product yields
- Challenging unactivated sp² systems amenable
- Typically uses organometallics
- Starting material synthesis

**Ligand coupling Challenges**
- Starting material synthesis
- Ease of phosphorane formation
- Ligand exchange problematic
- Product formation can be low yielding

**Chemical Elements and Properties**
- **Sulfur (S)**: 18, 32, Unique reactivity, Most “metal” like, Starting material synthesis
- **Phosphorus (P)**: 15, 30, Expanded coupling possibilities, Underexplored, Side reactivities
- **Bismuth (Bi)**: 83, 208, Unique reactivity, Most “metal” like, Starting material synthesis
- **Iodine (I)**: 53, 126, Expanded coupling possibilities, Underexplored, Side reactivities

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Ligand-coupling in recent literature

Heterobiaryl synthesis: Qin – ACIE 2020

Phenol arylation: Bell – Nat. Chem. 2020

Di/Trifluoromethylation: McNally – Nature 2020

Ligand-coupling catalysis

Is catalysis possible through a ligand-coupling process?

Ligand-coupling catalysis

Is catalysis possible through a ligand-coupling process?

Josep Cornella: Max-Planck
Bismuth catalysis research area

Alex Radosevich: MIT
Phosphorus catalysis research area

Ligand-coupling catalysis

Ligand-coupling catalysis

**Phosphorus catalysis**

Mamoru Tobisu: Rikkyo University
Phosphorus catalysis research area

**Ligand-coupling catalysis**...

Ligand-coupling catalysis... or is it?

Mamoru Tobisu: Rikkyo University
Phosphorus catalysis research area

Ligand-coupling catalysis is complicated by alternate reaction pathways

Phosphorane intermediate

Ligand-coupling catalysis… or is it?

Ligand-coupling catalysis… or is it?

Phosphorane intermediate

DFT calculations: 6.9 kcal/mol barrier

ΔG\text{ub97XD/6-31+G(d,p)} with PCM(toluene)

Ligand-coupling catalysis... or is it?

ΔG_{ωB97XD/6-31+G(d,p)} with PCM(toluene)

Phosphorane intermediate

DFT calculations: 6.9 kcal/mol barrier

Ligand Coupling

Solv., rt

Toluene: 61% yield

MeCN: trace

34% yield

28% yield

Is this proof for ligand-coupling?
Ligand-coupling catalysis

Josep Cornella: Max-Planck
Bismuth catalysis research area

Alex Radosevich: MIT
Phosphorus catalysis research area

Mamoru Tobisu: Rikkyo University
Phosphorus catalysis research area

Ligand-coupling on hypervalent species: Transition metal chemistry without the metal

Questions?