A Supramolecular Microenvironment Strategy for Transition Metal Catalysis

Kaphan, D. M.; Levin, M. D.; Bergman, R. G.; Raymond, K. N.; Toste, F. D. Science 2015, 350, 1235

Hannah Haley
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Enzymatic Catalysis

- Enzymes speed reactions and contribute to specificity by providing a specific environment within which reaction is favored.
- Reactions occur in the pocket of the enzyme called the active site.
- To catalyze a reaction, an enzyme active site must be complementary to a reaction transition state.
- Enzymes enhance reaction rate by lowering activation energy for transformation.

\[ E + S \leftrightarrow ES \leftrightarrow EP \leftrightarrow E + P \]

*ES and EP are transient complexes of enzyme with the substrate and with the product.*

- Chemists have applied concepts from biological catalysis to chemical synthesis.
- Supramolecular structures have been used in analogy to enzymes.
Supramolecular Catalysts in Organic Synthesis

- Supramolecular catalysts have been investigated extensively in the context of biomimetic transformations and cyclizations.

- Catalyst can effect selectivity and/or rate of reaction by stabilizing conformations, intermediates, and/or transition states.

Selectivity in tail-to-head terpene cyclization:

- Mild Bronsted acidity to activate substrate
- Hydrophobic cavity
- Known to complex cationic guests

- No reaction observed in absence of catalyst
- Eucalyptol had never before been observed from cascade reaction of acyclic terpenes

Zhang, Q.; Tiefenbacher, K. Nat. Chem. 2015, 7, 197
Supramolecular Catalysts in Organic Synthesis

Au(I) catalyzed hydroalkoxylation:

\[
\text{Me} = \bullet = \text{Me} \quad \text{Me} \quad \text{OH} \quad \overset{2.5 \text{ mol}\% \text{ PMe}_3\text{AuBr}}{\underset{\text{H}_2\text{O}, 23 \degree \text{C}, 18 \text{ h}}{\longrightarrow}} \quad \text{Me} \quad \text{Me} \quad \text{O} 
\]

Hypothesize yield is low due to limited ionization of Au(I) complex which is required for activity:

\[
\text{PMe}_3\text{AuBr} \iff \text{PMe}_3\text{Au}^+ + \text{Br}^- 
\]

- Highly anionic complex
- Known affinity for binding monocationic organometallic complexes
- Hypothesized to shift equilibrium towards ionized complex

8-fold rate enhancement for Au(I)-catalyzed hydroalkoxylation upon encapsulation

Represented the only example of increased reaction rate for transition metal complexes upon encapsulation

Transition Metal-Mediated Alkyl-Alkyl Coupling is Challenging

Reductive elimination to form sp$^3$-sp$^3$ bonds is slow resulting in side products and slow catalyst turnover

Targeted transformation:

\[
\text{Me}_3\text{P} \quad \begin{array}{c} \text{Au} \quad \text{I} \\ \text{Me} \quad \text{Me} \end{array} \xrightarrow{\text{reductive}} \text{Me} \quad \text{Me} \quad + \quad \text{Me}_3\text{P} \quad \text{Au} \quad \text{I} \]

Similar transformations are known, but they are slow and/or require significant heating:

Complexes are stable at room temp and only reductively eliminate at elevated temperatures:

\[
\begin{array}{c}
\text{Ph}_3\text{P} \quad \begin{array}{c} \text{Au} \quad \text{Me} \\ \text{Me} \quad \text{Et} \end{array} \\
70^\circ \text{C} \quad \rightarrow \\
\text{Me} \quad \text{Et} \quad + \quad \text{Ph}_3\text{P} \quad \text{Au} \quad \text{Me}
\end{array}
\]

\[
\left[ \begin{array}{c}
\text{Ph}_3\text{P} \quad \begin{array}{c} \text{Au} \\ \text{Me} \quad \text{Me} \end{array} \\
\text{PPh}_3
\end{array} \right] \quad \text{PF}_6 \quad 70^\circ \text{C} \quad \rightarrow \\
\text{Me} \quad \text{Me} \quad + \quad (\text{PPh}_3)_2\text{AuPF}_6
\]

Reductive elimination from complex is very slow:

\[
\begin{array}{c}
\text{Ph}_3\text{P} \quad \begin{array}{c} \text{Au} \quad \text{Cl} \\ \text{Me} \quad \text{Me} \end{array} \\
40^\circ \text{C} \quad \text{slow} \quad \rightarrow \\
\text{Me} \quad \text{Me} \quad + \quad \text{Ph}_3\text{P} \quad \text{Au} \quad \text{Cl}
\end{array}
\]

Supramolecular Microenvironment Catalyst Promotes Reductive Elimination

Targeted transformation atypical for supramolecular catalysis

- Cation-stabilizing cavity

- Authors hypothesize that halide dissociation to form ionized cationic Au(III) species is required for efficient reductive elimination

- Propose that supramolecular species will selectively recognize and stabilize this intermediate, facilitating reductive while not altering metal center

- 4000-fold rate acceleration for reductive elimination with 10 mol% supramolecular catalyst

- Blocking cavity of catalyst with Et₄P⁺ eliminates rate acceleration observed with catalyst

- Substitution of PMe₃ with bulkier PPh₃ results in no rate acceleration, indicating complex does not fit in internal cavity of catalyst

Similar rates observed for reductive elimination from iodide, bromide, and chloride complexes

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**Optimization of Reductive Elimination**

- Hypothesized that using a phosphine of intermediate steric demand would disfavor formation of inactive bisphosphine complex while still allowing encapsulation

- 80,000-fold increase in observed rate for catalyzed reaction

- NMR indicates a unique encapsulated species identified as bisphosphine complex

- Encapsulated bisphosphine does not accelerate reductive elimination from (Me₃P)Au(Me₂)I

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For reference, rates of reductive elimination from the PMe₃ ligated complex:

- **kₗ = 4.7 x 10⁻⁶ Ms⁻¹ with catalyst**
- **kₗ = 9.5 x 10⁻¹⁰ Ms⁻¹ with catalyst blocked**
Investigating Mechanism of Catalyzed Reductive Elimination

Catalyst

- Linear relationship between rate of red elim and conc of catalyst shows 1st order dependence on catalyst

Halide

- Rate of red elim significantly attenuated with addition of exogenous iodide, consistent with halide dissociation preceding red elim

Gold

- Dependence on gold compound shows saturation behavior, indicative of a pre-equilibrium step before that involving the reactant

**Chemical Reaction:**

\[
\begin{align*}
\text{Me}_3\text{P}_2\text{Au} \quad &\xrightarrow{10 \text{ mol}\% \ 1} \quad \text{Me}_3\text{P} \cdot \text{Au} \cdot \text{I} + \text{Me} \cdots \text{Me} \\
\text{MeOH-d}_4 \quad &25 ^\circ \text{C} 
\end{align*}
\]
Investigating Mechanism of Catalyzed Reductive Elimination

**Proposed Michaelis-Menten-type mechanism:**

![Diagram showing a proposed mechanism for catalyzed reductive elimination, including pre-equilibrium halide dissociation, reversible encapsulation of cationic complex, and irreversible red elimination in catalyst cavity.]

**Relative rate acceleration for reductive elimination with supramolecular catalyst:**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>$k_{cat}$ (s$^{-1}$)</th>
<th>$\frac{k_{cat}}{k_{uncat}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{Me}_3\text{P}\text{AuI}$</td>
<td>$3.3 \times 10^{-2}$</td>
<td>$5.0 \times 10^5$</td>
</tr>
<tr>
<td>$\text{Et}_3\text{P}\text{AuI}$</td>
<td>$3.4$</td>
<td>$1.9 \times 10^7$</td>
</tr>
<tr>
<td>$\text{Me}_3\text{P}\text{PtI}$</td>
<td>$2.4 \times 10^{-2}$</td>
<td>$2.6 \times 10^4$</td>
</tr>
</tbody>
</table>

- Observed rate accelerations are of similar order of magnitude with those observed for many enzymatic processes
- Chymotrypsin accelerates amide bond hydrolysis with $10^7$-fold rate acceleration
Developing a Duel Catalytic Cross-Coupling

- Previous results demonstrate that catalytic amounts of the supramolecular complex accelerates one step of cross-coupling, reductive elimination, from a stoichiometric preformed alkyl-metal complex

- Extension of reactivity towards cross-coupling system catalytic in both supramolecular complex and catalyst would suggest broader generality and applicability of strategy

Supramolecular complex also catalyzes reductive elimination from stoichiometric platinum complex:

Envisioned duel catalytic process:
Developing a Duel Catalytic Cross-Coupling

Several challenges with the desired process had to be addressed

**Envisioned duel catalytic process:**

- Decomposition of standard supramolecular complex in presence of MeI required use of complex with reduced electron density
- Me₃SnI byproduct from transmetallation of SnMe₄ determined to be a strong guest for supramolecular catalyst
  - KF added to reaction to form Me₃SnF and prevent catalyst deactivation

**Optimized duel catalytic process:**

- Improved stability to Me-I
- MeOH-d₄/D₂O (8:2) at 45 °C
Developing a Duel Catalytic Cross-Coupling

Optimized duel catalytic process:

Efficient coupling only occurs with both Pt and supramolecular catalysts:

Conversion from SM only with both catalysts
Proposed Mechanism for Duel Catalytic Cross-Coupling