Overview

Supramolecular Chemistry and Molecular Flasks

Stoichiometric

Catalytic

Dual-Catalytic

Enantioselective
Organic Chemists Masters of the Covalent Bond

1828 by Friedrich Wöhler

Origin of Supramolecular Chemistry

Paul Ehrlich: Concept of the Receptor

Emil Fischer: Lock and Key Model

Alfred Werner: Coordination chemistry

Linus Pauling: Stabilization of Enzymatic TS

Supramolecular Chemistry Taming Intermolecular Bonds

Nobel Prize: 1987-development and use of molecules with structure-specific interactions of high selectivity

- Pedersen's Crown ether complex
- Lehn's cryptand
- Cram's host-guest complex
Types of Molecular Flasks

Covalently Synthesised Flasks

Flash Formed Through Hydrogen Bonding

Host cavity $\sim 5.6$−$8.8$ Å in diameter.


Coordination Flasks

1) MeMgl
2) (COCl)$_2$
3) Sat. NH$_4$Cl

Encapsulation Effects on Reactivity

Reaction course can be effected by a capsule in many ways
1. Preorganization of substrate by invoking proximity between reactive partners, thus increasing the effective concentration of substrates and making the RDS shift from bimolecular to intramolecular
2. The capsule stabilizes the transition state, lowering the activation barrier

The energy profile of a reaction can change upon encapsulation

Overview

Supramolecular Chemistry and Molecular Flasks

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Enantioselective
Early molecular flask

At high $\alpha$-CD concentration very high selectivities are observed.

The kinetic parameters for $k_o = 0$ and $k_p/k_{free} = 5.6 +/- 0.8$

**Table I**

<table>
<thead>
<tr>
<th>Cyclohexaamylose, $M \times 10^4$</th>
<th>Chloroanisol product ratio, $p:o$</th>
<th>% anisole bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.48</td>
<td>0</td>
</tr>
<tr>
<td>0.933</td>
<td>3.43</td>
<td>20</td>
</tr>
<tr>
<td>1.686</td>
<td>5.49</td>
<td>33</td>
</tr>
<tr>
<td>2.80</td>
<td>7.42</td>
<td>43</td>
</tr>
<tr>
<td>4.68</td>
<td>11.3</td>
<td>56</td>
</tr>
<tr>
<td>6.56</td>
<td>15.4</td>
<td>64</td>
</tr>
<tr>
<td>9.39</td>
<td>21.6</td>
<td>72</td>
</tr>
</tbody>
</table>

Hydrogen bonding softball for Diels-Alder


>200 fold rate increase
Product inhibition prevents turn over
Confined Spaces Allow Unique Regioselectivity

Origin of Unique Regioselectivity

TMEDA capped Pd crystal structure

force-field calculation.

Organocatalytic Vase Cavitand for Cyclization Reactions


Figure 2. Cavitand 1 represented in its folded vase-like conformation (left) and as its detailed Lewis structure (right).
Organocatalytic vase cavitand for cyclization reactions

Cyclization of Large Rings


Table 1. Yield Enhancements by Cavitand 1

<table>
<thead>
<tr>
<th>disocyanate</th>
<th>with 1</th>
<th>without 1</th>
<th>enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>83</td>
<td>17</td>
<td>4.9</td>
</tr>
<tr>
<td>3b</td>
<td>81</td>
<td>15</td>
<td>5.4</td>
</tr>
<tr>
<td>3c</td>
<td>81</td>
<td>15</td>
<td>5.4</td>
</tr>
<tr>
<td>3d</td>
<td>88</td>
<td>13</td>
<td>6.7</td>
</tr>
</tbody>
</table>

*Yields were calculated on the basis of $^1$H NMR integration using dimethyl sulfone as an internal standard. The concentration of substrate (3a−d) was 1.6 mM, and excess cavitand (6 mM) was used. In water/acetone.*
Usage of flasks for Photoexcited Electron Transfer

Aim:

hv

absorbance

E or e-

transfer

Proposed photochemical [2+2]:

Observed photochemical outcome

D₂O, 8.0 pD
100mM K₃PO₄
hv, UVA

+4kcal/mol

R⁺ + Br⁻

D₂O, 8.0 pD
100mM K₃PO₄
hv, UVA

J. Am. Chem. Soc. 2015, 137, 10128-10131
Overview

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Dual-Catalytic
Early Regioselective Catalytic Flask

- copolymerization of formaldehyde, glyoxal, and urea
- Exclusive selectivity for 1,4 triazole
- Prefer cationic substrates due to carbonyl coordination
- Catalyst can reach saturation at high concentrations of azide and alkyne
- Allows some catalytic turnover
- RDS is the product leaving the Cucurbituril
- Rate enhancement of $5.5 \times 10^4$ is observed

Catalytic Diels-Alder

Chemical Methods for Avoiding Product Inhibition

Table 2. Rate Constants for Free ($k_{\text{free}}$) and Encapsulated ($k_{\text{encaps}}$) Rearrangements (Measured at 50 °C in D$_2$O) and Their Acceleration Factors

<table>
<thead>
<tr>
<th>compound</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$k_{\text{free}}$ ($\times10^{-5}$ s$^{-1}$)</th>
<th>$k_{\text{encaps}}$ ($\times10^{-5}$ s$^{-1}$)</th>
<th>acceleration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Br</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>3.49</td>
<td>16.3</td>
<td>5</td>
</tr>
<tr>
<td>2-Br</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>7.61</td>
<td>198</td>
<td>26</td>
</tr>
<tr>
<td>3-Br</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>3.17</td>
<td>446</td>
<td>141</td>
</tr>
<tr>
<td>4-OTs</td>
<td>H</td>
<td>H</td>
<td>Et</td>
<td>1.50</td>
<td>135</td>
<td>90</td>
</tr>
<tr>
<td>5-OTs</td>
<td>H</td>
<td>n-Pr</td>
<td>H</td>
<td>4.04</td>
<td>604</td>
<td>150</td>
</tr>
<tr>
<td>6-OTs</td>
<td>H</td>
<td>H</td>
<td>n-Pr</td>
<td>1.69</td>
<td>74.2</td>
<td>44</td>
</tr>
<tr>
<td>7-OTs</td>
<td>H</td>
<td>i-Pr</td>
<td>H</td>
<td>0.37</td>
<td>316</td>
<td>854</td>
</tr>
<tr>
<td>8-OTs</td>
<td>H</td>
<td>n-Bu</td>
<td>H</td>
<td>3.97</td>
<td>222</td>
<td>56</td>
</tr>
<tr>
<td>9-OTs</td>
<td>H</td>
<td>TMS</td>
<td>H</td>
<td>0.033</td>
<td>1.17</td>
<td>35</td>
</tr>
<tr>
<td>10-Br</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>6.3</td>
<td>331</td>
<td>53</td>
</tr>
</tbody>
</table>

$\Delta H^\ddagger$ and $\Delta S^\ddagger$ values are provided in parentheses.
Chemical Methods for Avoiding Product Inhibition

Figure 15. Overall proposed mechanism of iminium hydrolysis.

Kinetic Regioselectivity

Kinetic Regioselectivity

Overview

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Stoichiometric

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Enantioselective

Dual-Catalytic
Remote Chiral Transfer into Molecular Flasks


[Chemical structures and reaction scheme with enantiomer excess values provided]
Remote Chiral Transfer into Molecular Flasks

Table 1. Enantiomeric excess (%) of [2 + 2] and [2 + 4] cycloadditions of aromatics with maleimide 3 within chiral cage 1b.

<table>
<thead>
<tr>
<th>Aromatic guest</th>
<th>[2 + 2]</th>
<th>[2 + 4]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>2b (Me)</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>26</td>
</tr>
</tbody>
</table>

[4+2] crystal
[2+2] crystal

Providing a Second Coordination Sphere

Providing a Second Coordination Spheres


\[
\text{H}_2/\text{CO} \quad \text{[Rh(acac)(CO)]}_2 \quad \text{capsule}
\]

\[
\begin{array}{c}
\text{H} \\
\text{Cl} \\
\text{Me} \\
\text{MeO} \\
\text{OMe}
\end{array}
\]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>( k )</th>
<th>ee (%)</th>
<th>conv (%)</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha)C4(BArF) (_3)</td>
<td>99.1</td>
<td>74 (R)</td>
<td>14</td>
<td>797</td>
</tr>
<tr>
<td>( \alpha)Zn-TPP (_3)</td>
<td>99.1</td>
<td>9 (R)</td>
<td>7</td>
<td>363</td>
</tr>
<tr>
<td>( \alpha)C4(BArF) (_3)</td>
<td>91.1</td>
<td>61 (R)</td>
<td>31</td>
<td>1564</td>
</tr>
<tr>
<td>( \alpha)Zn-TPP (_3)</td>
<td>91.9</td>
<td>12 (R)</td>
<td>10</td>
<td>482</td>
</tr>
<tr>
<td>( \alpha)C4(BArF) (_3)</td>
<td>91.9</td>
<td>69 (R)</td>
<td>22</td>
<td>1125</td>
</tr>
<tr>
<td>( \alpha)Zn-TPP (_3)</td>
<td>97.3</td>
<td>7</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>( \alpha)C4(BArF) (_3)</td>
<td>99.1</td>
<td>&lt;1</td>
<td>4</td>
<td>180</td>
</tr>
<tr>
<td>( \alpha)Zn-TPP (_3)</td>
<td>99.1</td>
<td>&lt;1</td>
<td>7</td>
<td>340</td>
</tr>
<tr>
<td>( \alpha)C4(BArF) (_3)</td>
<td>99.1</td>
<td>&lt;1</td>
<td>4</td>
<td>180</td>
</tr>
<tr>
<td>( \alpha)Zn-TPP (_3)</td>
<td>99.1</td>
<td>&lt;1</td>
<td>7</td>
<td>340</td>
</tr>
</tbody>
</table>

R= Methyl (S)-α
Ethyl (S)-γ
iPropyl (S)-δ

[trans-Rh(\(\text{H}_2\text{CO}\))\(\alpha\)C4(BArF)\(_3\)]

\(\alpha\)(Zn-TPP)\(_3\)

Chiral Metal–Ligand Assembly

Figure 38. Stereochemical relationships between a chiral racemic guest and assembly 17.

Revisiting the Aza-Cope

**Table 1. Evaluation of Asymmetric Induction in the Aza-Cope Rearrangement Catalyzed by 1**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Yield (%)</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>H</td>
<td>Me</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>2b</td>
<td>Et</td>
<td>H</td>
<td>58</td>
<td>64</td>
</tr>
<tr>
<td>2c</td>
<td>H</td>
<td>Et</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>2d</td>
<td>Pr</td>
<td>H</td>
<td>68</td>
<td>9</td>
</tr>
<tr>
<td>2e</td>
<td>H</td>
<td>Pr</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>2f</td>
<td>H</td>
<td>iPr</td>
<td>74</td>
<td>60</td>
</tr>
<tr>
<td>2f$^b$</td>
<td>H</td>
<td>iPr</td>
<td>49</td>
<td>78</td>
</tr>
<tr>
<td>2g$^c$</td>
<td>H</td>
<td>nBu</td>
<td>82</td>
<td>6</td>
</tr>
</tbody>
</table>

$^a$ Yields measured by $^1$H NMR spectroscopy using CHCl$_3$ as an internal standard. $^b$ Reaction conducted at 5 °C over 8 days. $^c$ Catalyst loading was 50%.
Assembly of Single Diastereomeric Host

Figure 1. Relationship of racemic 1 to diastereo- and enantioenriched $\text{Ga}_{14}$ supramolecular assembly.

Table 1. Enantioselective and Chemoselective Monoterpellike Cyclization of Neutral Substrates Catalyzed by $\Delta\Delta\Delta\Delta$-6

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>pD</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>yield (trans/cis)</th>
<th>ee of 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>8</td>
<td>25</td>
<td>50</td>
<td>92% (8:1)</td>
<td>61%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>5</td>
<td>25</td>
<td>16</td>
<td>94% (7.5:1)</td>
<td>-58%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>5</td>
<td>-20</td>
<td>168</td>
<td>70% (8:1)</td>
<td>69%</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>5</td>
<td>60</td>
<td>24</td>
<td>33% (8:1)</td>
<td>58%</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>8</td>
<td>60</td>
<td>16</td>
<td>12% (nd)</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>5</td>
<td>60</td>
<td>16</td>
<td>92% (8:1)</td>
<td>65%</td>
</tr>
</tbody>
</table>

*Reaction performed with $\Delta\Delta\Delta\Delta$-6 (2.5 mol %). †0.3 mol % of $\Delta\Delta\Delta\Delta$-6 was used (99 TON).
Encapsulation results in an increase in basicity of imine allowing for activation of the leaving group without the need of strong acid. Clear difference in stereochemical outcome for reaction in bulk solution vs encapsulated.
The substitution reactions performed on enantiopure 3 and enantioenriched 7 proceed with retention regardless of absolute configuration.

The low enantioinduction on racemic 3 and 7 suggests that the stereochemistry of the reaction predominates over the effect of the chiral capsule.

Model for stereochemical retention
Overview

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Enantioselective

Dual-Catalytic
Chemical Assembly Line

[Chemical structures and reactions as shown in the diagram]

Enzyme Dual Catalysis

Table 1 | Tandem esterase- or lipase-mediated acetate hydrolysis followed by Me₃PAu⁺- or Me₃PAuCl-catalysed hydroalkoxylation.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Enzyme</th>
<th>[Au] cat.</th>
<th>Product ratio (4:2:3)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3</td>
<td>Rabbit liver esterase ¹</td>
<td>Me₃PAu⁺-</td>
<td>(0:0:100)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Hog liver esterase ⁶</td>
<td>Me₃PAuCl</td>
<td>(14:24:62)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Horse liver esterase ⁵</td>
<td>Me₃PAu⁺-</td>
<td>(2:4:94)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Mucor miehei lipase ⁵</td>
<td>Me₃PAu⁺-</td>
<td>(35:22:44)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Mucor miehei lipase ⁸</td>
<td>Me₃PAu⁺-</td>
<td>(4:43:53)</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Mucor miehei lipase ⁵</td>
<td>Me₃PAu⁺-</td>
<td>(11:35:54)</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>Mucor miehei lipase ⁸</td>
<td>Me₃PAu⁺-</td>
<td><strong>(0:0:100)</strong></td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>Mucor miehei lipase ⁵</td>
<td>Me₃PAu⁺-</td>
<td>(38:2:60)</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>Mucor miehei lipase ⁸</td>
<td>Me₃PAu⁺-</td>
<td>(32:2:66)</td>
</tr>
</tbody>
</table>

¹Tris buffer pH 8 was used in the esterase reactions and phosphate buffer pH 7 was used in the lipase reactions. 5% DMSO or MeOH was also used in all the reactions to increase the solubility of 4 in aqueous buffer. The substrate concentration was 2.2 mM. ²Determined by proton NMR spectroscopy (see the Supplementary Information for NMR yields relative to internal standard).
³Six units of enzyme used at 37 °C. ⁴One unit of esterase used at 23 °C. ⁵Three units of enzyme used at 37 °C cat = catalyst.
Enzyme Dual Catalysis

Table 2 | Tandem enzymatic kinetic resolution and cyclization with Me₃PAu⁺ C 1 or Me₃PAuCl.

<table>
<thead>
<tr>
<th>Product</th>
<th>Enzyme</th>
<th>[Au] cat.</th>
<th>Conversion (%)</th>
<th>d.e. (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Amano</td>
<td>Me₃PAu⁺ C 1</td>
<td>32</td>
<td>26</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>lipase PS</td>
<td>Me₃PAuCl</td>
<td>20</td>
<td>21</td>
<td>88</td>
</tr>
<tr>
<td>10</td>
<td>Hog liver</td>
<td>Me₃PAu⁺ C 1</td>
<td>32</td>
<td>15</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>esterase</td>
<td>Me₃PAuCl</td>
<td>30</td>
<td>20</td>
<td>38</td>
</tr>
<tr>
<td>11</td>
<td>Amano</td>
<td>Me₃PAu⁺ C 1</td>
<td>33</td>
<td>30</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>lipase PS</td>
<td>Me₃PAuCl</td>
<td>32</td>
<td>37</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td>Hog liver</td>
<td>Me₃PAu⁺ C 1</td>
<td>19</td>
<td>29</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>esterase</td>
<td>Me₃PAuCl</td>
<td>22</td>
<td>38</td>
<td>27</td>
</tr>
</tbody>
</table>

*Moderate diastereoselectivity and good-to-excellent enantioselectivity are exhibited. Tris buffer pH 8 was used in the esterase reactions and phosphate buffer pH 7 was used in the lipase reactions. 5% DMSO was used in all the reactions and the substrate concentration was 2.2 mM. Determined by gas chromatography analysis. Determined from the minor cis diastereomer. Two units of enzyme were used at rt. d.e. = diastereomeric excess, e.e. = enantiomeric excess.

Figure 2 | Reaction progress of the hydrolysis of 12 with hog liver esterase in the presence of Me₃PAu⁺ C 1, Me₃PAuCl (free Au) or no additional gold complex. Free gold(i) complexes significantly reduce the activity of hog liver esterase, but encapsulated gold(i) complexes have no measurable effect on the rate of enzyme catalysis. Error bars represent the error inherent in the integration of ¹⁹F NMR signals used to determine conversion.

Nature Chemistry. 2013, vol 5, 100–103
Limitations and problems

J. Am. Chem. Soc. 2017, 139, 6090−6093

56% yield
endo/exo = >20:1
93% ee
Increasing the Rate of Reductive Elimination

- Substitution of PMe$_3$ for PPh$_3$ resulted in no observable acceleration
- Addition of Et$_4$P cation shut down acceleration
- Observed catalyst deactivation
- Increase in steric bulk of phosphine greatly enhances TON

- Encapsulation can increase the rate of reductive elimination for metals other than Au

*Science. 2015, Vol. 350, 1235-1238*
Increasing the Rate of Reductive Elimination
Future Directions and Limitation

Selectivity:
• Further exploration of inverting regioselectivities
• Design of new capsules for enantioselective processes

Dual catalysis:
• The ability to protect catalysts from necessary reaction conditions can open new reactivity
• Slow release of reactive functionality could allow increased control of reactivity and selectivities
• Telescoped reactions can lead to greater efficiency and yield
• Using encapsulation to catalyze the slow step of a reaction.

Limitations
• Low enantioselectivity
• Flasks have extremely low substrate generality
• Atom economy
• Product inhibition
Questions
Limitations and problems

http://www.cchem.berkeley.edu/toste/publications/JACS_2017_139_8013.pdf
Limitations and problems

http://www.cchem.berkeley.edu/toste/publications/ja202055v.pdf
http://www.cchem.berkeley.edu/toste/publications/ja308254k_2.pdf