The Nobel Prize in Chemistry 1964
"for her determinations by X-ray techniques of the structures of important biochemical substances"
Photoreactions in Crystals

“A crystal is a chemical cemetery”
Nobel Laureate L. Ruzika (1930s)

Esher’s drawings
Photodimerization of *trans*-Cinnamic acids

\[
\text{Ar}=\text{COOH} \xrightarrow{\text{hv}} \text{Solid} \xrightarrow{\alpha - \text{form}} \text{COOH} \\
\text{Ar}=\text{COOH} \xrightarrow{\text{hv}} \text{Solution} \xrightarrow{\beta - \text{form} \ (3.9 - 4.1\text{Å} ; \text{Translation})} \text{COOH} \\
\text{Ar}=\text{COOH} \xrightarrow{\gamma - \text{form} \ (4.7 - 5.1\text{Å} ; \text{Translation})} \text{No reaction}
\]

\[\text{Double bond separation: 3.6 - 4.1Å} \]

Nearest neighbour relation: Centric
**α-trans-Cinnamic acid**
Leads to centrosymmetric dimer

**β-trans-Cinnamic acid**
Leads to mirror symmetric dimer
Topochemical principle: Reactions in the solid state take place with minimum atomic movements.

“The next decade will surely see ----- large-amplitude molecular motions in the solid state.”

J. D. Dunitz, V. Schomaker and K. N. Trueblood (1988)

“A crystal is a chemical cemetry”

L. Ruzika (1930s)

Harada and Ogawa, JACS (2004).
Photodimerization of criss-cross alkenes

\[
\begin{align*}
\text{NH}_3^+ \cdot \text{OOC} & \quad \rightarrow \quad \text{NH}_3^+ \cdot \text{OOC} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

\[\text{hv}\]

Crystals

\[
\begin{align*}
\beta\text{-truxinate}
\end{align*}
\]
Large motions are tolerated in the crystal

- Pedal-like conformational change by one of the cinnamic acid molecules is required for β-dimer formation.
Pre-organization with a guest: Non reactive molecule made to react

MacGillivray et. al., JACS, 2000, 122, 7817.
Overview of templated dimerization of olefins in solid-state

For ex:

- $M = \text{metal}$
- $\sim 4 \text{ Å}$
Thiourea as a possible template (Cambridge Structural Database)
An overview of photochemistry of stilbazoles in thiourea co-crystals

$^{1}$H NMR (CDCl$_3$) of cyclobutane protons in dimer products
Anomalous orientation of 4-cyanostilbazole in thiourea co-crystals
Does Not Dimerize

Does Not Dimerize
Cis-Trans Photoisomerization in Crystals

<table>
<thead>
<tr>
<th>Temp °C</th>
<th>Duration</th>
<th>% Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>12</td>
<td>100</td>
</tr>
<tr>
<td>50°C</td>
<td>6</td>
<td>100</td>
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<tr>
<td>RT</td>
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<td>15</td>
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<tr>
<td>50°C</td>
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<td>RT</td>
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</tr>
<tr>
<td>50°C</td>
<td>21</td>
<td>100</td>
</tr>
</tbody>
</table>
Photoisomerization of *cis*-8-fluoranthenyl styrene

Large distance between the reactive double bonds 6.77 Å precludes cyclobutane intermediate.
Supramolecular Containers

Guest

Boundary

Reaction cavity

Free Space

Cohen and Schmidt
Role of Weak Interactions

Cation---π

π---π

C-H---π

Hydrogen bond

van der Waals

Charge transfer
Asymmetric Photochemistry in Crystals
Adamantyl acetophenone derivatives

\[
\begin{array}{c}
\text{Adamantyl acetophenone} \\
\begin{array}{c}
\text{derivatives}
\end{array}
\end{array}
\]

% ee = 0

3.75 Å

2.7 Å

P2_1/n

centrosymmetric
Most commonly occurring space groups

230 unique space groups of which only 65 are chiral space groups
Chiral space groups (symmetry elements are rotational, translational and combinations of these)
achiral space groups (symmetry elements are mirror, glide plane or center of inversion)

<table>
<thead>
<tr>
<th>Space group</th>
<th>Total no. of crystals</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2₁/ c</td>
<td>10450</td>
<td>36.0</td>
</tr>
<tr>
<td>P₁</td>
<td>3986</td>
<td>13.7</td>
</tr>
<tr>
<td>P2₁2₁2₁</td>
<td>3359</td>
<td>11.6</td>
</tr>
<tr>
<td>P2₁</td>
<td>1957</td>
<td>6.7</td>
</tr>
<tr>
<td>C₂/ c</td>
<td>1930</td>
<td>6.6</td>
</tr>
<tr>
<td>P_bca</td>
<td>1261</td>
<td>4.3</td>
</tr>
<tr>
<td>Pnma</td>
<td>548</td>
<td>1.9</td>
</tr>
<tr>
<td>Pna2₁</td>
<td>513</td>
<td>1.8</td>
</tr>
<tr>
<td>P_bcn</td>
<td>341</td>
<td>1.2</td>
</tr>
<tr>
<td>P1</td>
<td>305</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Covalent Chiral Auxillary Approach

Chiral space group

Reactive part

Chiral auxiliary
<table>
<thead>
<tr>
<th></th>
<th>Trans CB</th>
<th>Trans CB</th>
<th>Trans CB</th>
</tr>
</thead>
<tbody>
<tr>
<td>% de</td>
<td>97</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.7 Å°</td>
<td>2.86 Å°</td>
<td>3.2 Å°</td>
</tr>
<tr>
<td></td>
<td>2.76 Å°</td>
<td>4.1 Å°</td>
<td>2.6 Å°</td>
</tr>
</tbody>
</table>
Conformational isomerism

$p$L-phenylalaninol

$p$-L-phenylalaninol

$\text{P2}_1$

$p$-1R,2R-pseudoephedrine

“Crystallization with equal amounts of two independent and mirror image related conformers”
Essential Criteria for Asymmetric Photochemistry in the Crystalline State

Molecules must crystallize in a chiral space group (non-centro symmetric form).

Majority of achiral molecules crystallize in a non-chiral space group (symmetric packing).

\[
\text{P2}_1/n \quad \text{centrosymmetric}
\]

\[
\text{P2}_1\text{2}_1\text{2}_1 \quad \text{non-centrosymmetric}
\]

\%
\text{ee: 0}

\%
\text{ee: 100}
Diastereoselective Photoreactions in the Crystalline State

R*  
\[ \begin{array}{cccccc}
\text{NH} & \text{NH} & \text{O} & \text{O} & \text{H} \\
\text{N} & \text{N} & \text{O} & \text{Me} & \text{Me} \\
\text{H} & \text{H} & \text{H} & \text{H} & \text{H} \\
\end{array} \]

% de  
97  90  92  80  22  5
Generality and limitation of covalent chiral auxiliary strategy

![Chemical structures and reactions](image)

<table>
<thead>
<tr>
<th>R*</th>
<th>% Conversion</th>
<th>%de (endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 1" /></td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td><img src="image" alt="Structure 2" /></td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td><img src="image" alt="Structure 3" /></td>
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<tr>
<td><img src="image" alt="Structure 4" /></td>
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<td>73</td>
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<tr>
<td><img src="image" alt="Structure 5" /></td>
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<td>1</td>
</tr>
<tr>
<td><img src="image" alt="Structure 6" /></td>
<td>20</td>
<td>3</td>
</tr>
</tbody>
</table>
Crystal irradiation of Benzonorbornadiene derivatives

*p-L-valinol

*p-R-cyclohexylethylamide

%de 100

91
Mirror image related conformers

“In the asymmetric unit”

“Independent view”

%de 1
Photochemistry of $\alpha$-Oxoamides

\[ \text{Medium} \begin{array}{c|c|c|c} \hline 
 & 1 & 2 & 3 \\ 
\hline 
\text{Solution (CH}_3\text{CN)} & 19 & 35 & 46 \\
\hline 
\text{Crystal} & 0 & 100 & 0 \\
\hline 
\end{array} \]
Diastereoselectivity obtained with various chiral auxiliaries in solid state

<table>
<thead>
<tr>
<th>Crystal structures</th>
<th>C=O\ldots\gamma-H_1</th>
<th>C=O\ldots\gamma-H_2</th>
<th>%de of β-lactam</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure a)" /></td>
<td><img src="image" alt="Image a)" /></td>
<td><img src="image" alt="Image a)" /></td>
<td><img src="image" alt="Image a)" /></td>
</tr>
<tr>
<td>p-R-Phenylethylamide</td>
<td>2.562 Å</td>
<td>5.091 Å</td>
<td>&gt;99(B)</td>
</tr>
<tr>
<td><img src="image" alt="Structure b)" /></td>
<td><img src="image" alt="Image b)" /></td>
<td><img src="image" alt="Image b)" /></td>
<td><img src="image" alt="Image b)" /></td>
</tr>
<tr>
<td>p-S-Tyrosine methyl esteramide</td>
<td>2.781 Å</td>
<td>5.052 Å</td>
<td>96(B)</td>
</tr>
<tr>
<td><img src="image" alt="Structure c)" /></td>
<td><img src="image" alt="Image c)" /></td>
<td><img src="image" alt="Image c)" /></td>
<td><img src="image" alt="Image c)" /></td>
</tr>
<tr>
<td>m-S-Naphthylethylamide</td>
<td>2.618 Å</td>
<td>5.130 Å</td>
<td>82(A)</td>
</tr>
<tr>
<td>Crystal structures</td>
<td>C=O...γ-H₁</td>
<td>C=O...γ-H₂</td>
<td>%de of β-lactam</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><img src="image" alt="f" /> p-R-phenylglycinol</td>
<td><img src="image" alt="f" /></td>
<td>2.776 Å⁰</td>
<td>5.025 Å⁰</td>
</tr>
<tr>
<td><img src="image" alt="g" /> p-1R, 2S-ephrine</td>
<td><img src="image" alt="g" /></td>
<td>2.804 Å⁰</td>
<td>5.030 Å⁰</td>
</tr>
<tr>
<td><img src="image" alt="h" /> p-S-amidomethylphenylpropanol</td>
<td><img src="image" alt="h" /></td>
<td>2.662 Å⁰</td>
<td>5.034 Å⁰</td>
</tr>
<tr>
<td><img src="image" alt="i" /> m-R-phenylethylamide</td>
<td><img src="image" alt="i" /></td>
<td>2.713 Å⁰</td>
<td>4.850 Å⁰</td>
</tr>
</tbody>
</table>
\[ \beta\text{-lactam photoproduct}^{\#} \]

Solution irradiation (MeOH)

1hr Crystal irradiation

Solution irradiation (MeOH)

1hr Crystal irradiation

\# Photoproducts analyzed on HPLC chiralcel-OD

\sim A: First peak on HPLC
Single crystal-to-Single Crystal Phototransformation

Reactant (Single crystal; P2₁)

\[ a = 6.4935 \, \text{Å} \]
\[ b = 15.047 \, \text{Å} \]
\[ c = 10.7907 \, \text{Å} \]

Cell volume \(1044.65 \, \text{Å}^3\)

Photoproduct (Single crystal-Single crystal; P2₁)

\[ a = 6.4821 \, \text{Å} \]
\[ b = 14.967 \, \text{Å} \]
\[ c = 10.7528 \, \text{Å} \]

Cell volume \(1031.71 \, \text{Å}^3\)

Thin double lines- Precursor
Dark single line- Product
Photoproduct as Formed (P2₁)

\[ a = 6.4821 \text{ Å} \]
\[ b = 14.967 \text{ Å} \]
\[ c = 10.7528 \text{ Å} \]
\[ \beta = 98.52° \]
\[ \text{Cell volume} \quad 1031.71 \text{ Å}^3 \]

Photoproduct Recrystallized (P2₁)

\[ a = 8.5684 \text{ Å} \]
\[ b = 12.8865 \text{ Å} \]
\[ c = 9.8260 \text{ Å} \]
\[ \beta = 107.98° \]
\[ \text{Cell volume} \quad 1031.99(30) \text{ Å}^3 \]
A crystal is a chemical cemetery

Reactions in the solid state take place with minimum atomic movements.

The next decade will surely see large- amplitude molecular motions in the solid state.
Acknowledgements