# Chiral Photochemistry



- Crystals
- Zeolites
- Solution

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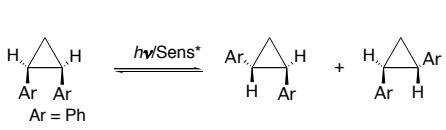
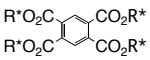
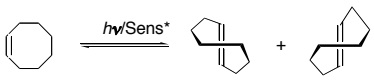
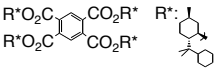
## Controlling products during asymmetric photoreactions



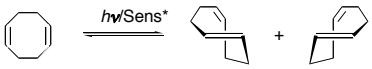

**Sens:** 

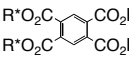
**ee: 10.4%** R* = (–)-menthyl




**Sens:** 

**ee: 49%**




**Sens:** 

**ee: 4.4%** R - (*R*)-1-methylheptyl

- Because of very little difference in rates of formation of the two enantiomeric products normally there is 'zero' selectivity; ee: 0.
- The best chiral induction in photoreactions are obtained in solid state.

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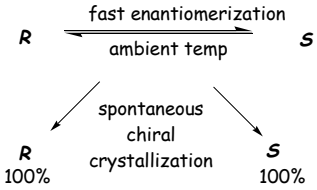
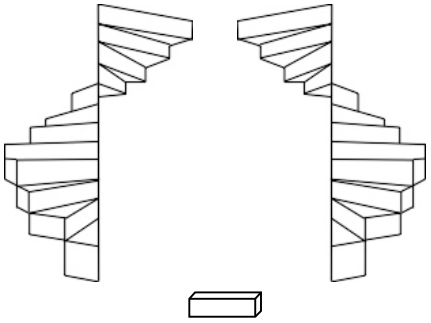
## Chiral crystallization

Achiral molecule may crystallize in achiral space group.
e.g., quartz, urea, maleic anhydride,




Chiral crystallization of achiral materials



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The most common space groups of organic crystalline compounds based upon a survey of 29059 crystal structure determinations

| space group | number | percentage |
|---|---|---|
| $P2_1/c$ | 10450 | 36.0 |
| $P\bar{1}$ | 3986 | 13.7 |
| $P2_12_12_1$* | 3359 | 11.6 |
| $P2_1$* | 1957 | 6.7 |
| $C2/c$ | 1930 | 6.6 |
| $Pbca$ | 1261 | 4.3 |
| $Pnma$ | 548 | 1.9 |
| $Pna2_1$ | 513 | 1.8 |
| $Pbcn$ | 341 | 1.2 |
| $P1$* | 305 | 1.1 |

*Chiral space group.

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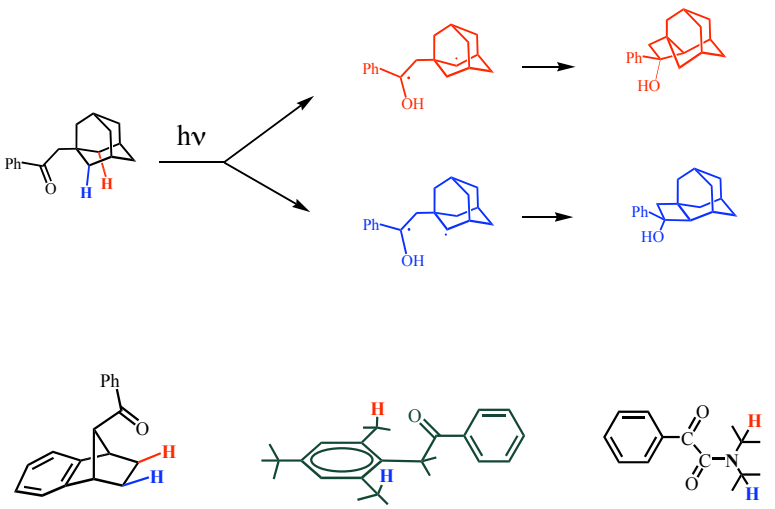


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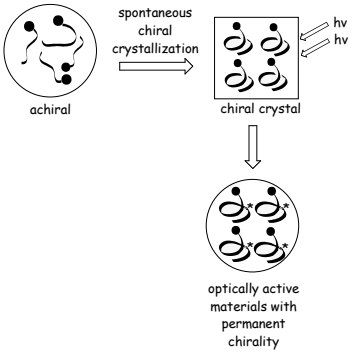
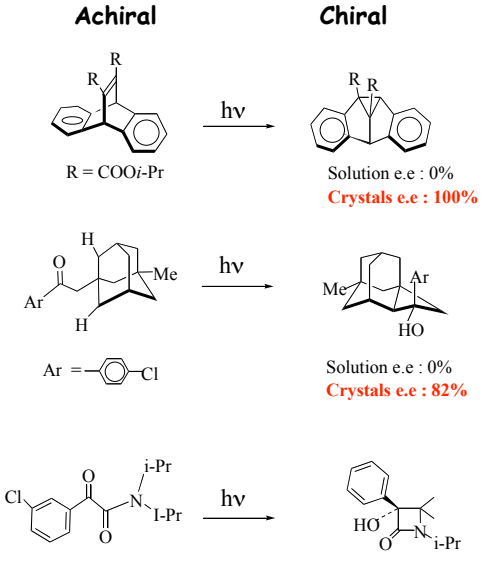
# Chiral crystallization




Absolute asymmetric synthesis in the chiral crystalline environment

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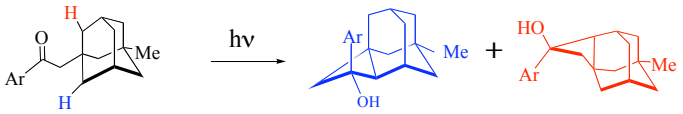
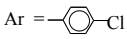
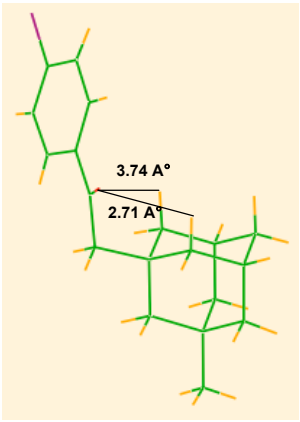



Ar = 


Solution e.e : 0%

**Crystals e.e : 82%**




Note that the two prochiral hydrogens are not equidistant from the carbonyl chromophore.

The molecule being present in a chiral space group does not have another molecule that is mirror symmetric.

Since only one prochiral hydrogen would be abstracted only one cyclobutanol enantiomer would be formed.

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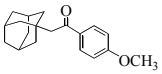
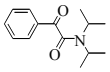
## Essential Criteria for Asymmetric Photochemistry in the Crystalline State

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

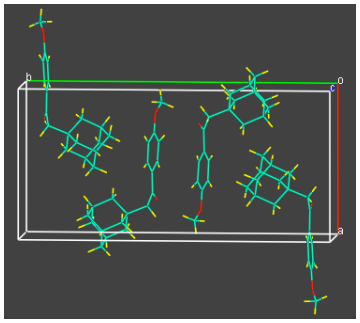
**Majority of achiral molecules crystallize in a non chiral space group (symmetric packing)**

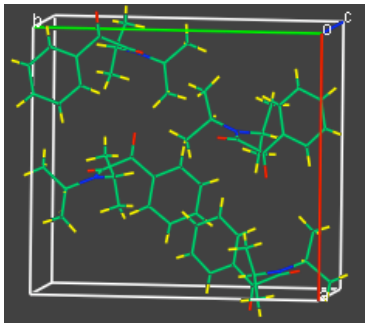



**% ee: 0**




**% ee: 100**





**$P2_1/n$**

**centrosymmetric**

**$P2_12_12_1$**

**non-centrosymmetric**

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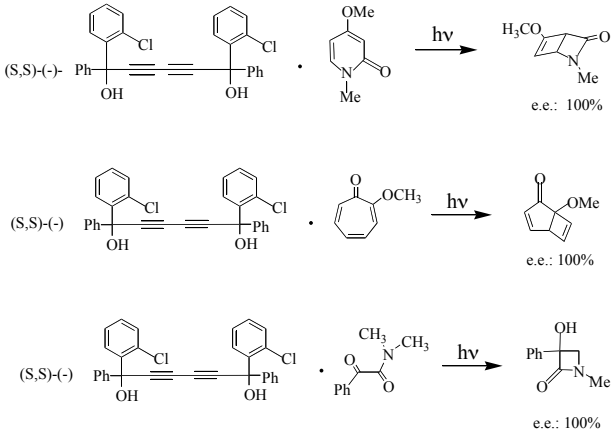
## Use of chiral hosts: Solid state photochemistry

Chiral hosts upon inclusion of an achiral molecule may induce chirality on the achiral molecule.

The above host-guest complexation would lead to diastereomeric (instead of enantiomeric) transition states .




In solution no chiral induction is obtained.

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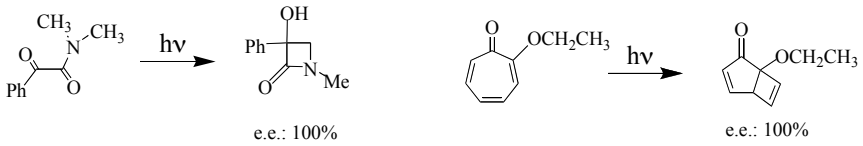
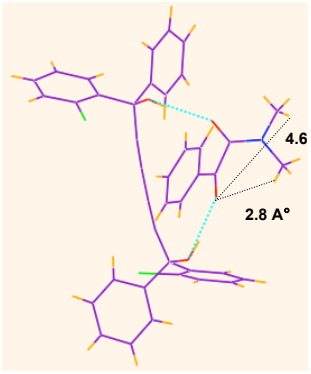
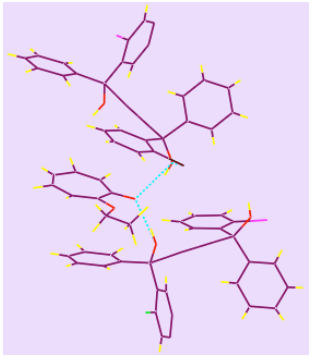
## Use of chiral hosts: Unimolecular reactions



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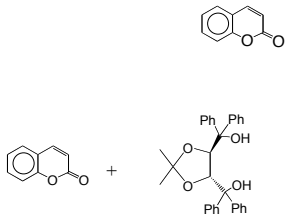
## Use of chiral hosts: Bimolecular reactions

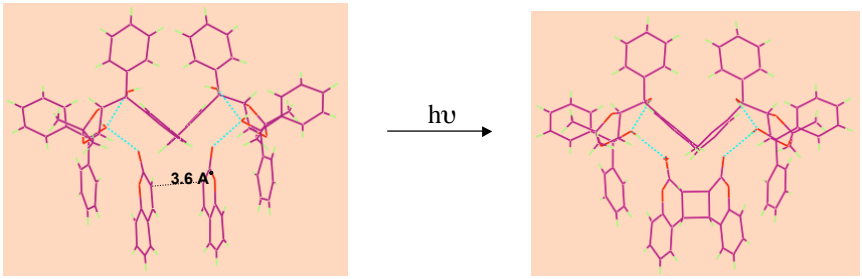






1:1 complex

96% ee

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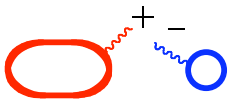
## Most commonly occurring space groups

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)

| Space group | Total no. of crystals | % |
|---|---|---|
| $P2_1/c$ | 10450 | 36.0 |
| $P_{\bar{1}}$ | 3986 | 13.7 |
| **$P2_12_12_1$** | 3359 | 11.6 |
| **$P2_1$** | 1957 | 6.7 |
| $C_2/c$ | 1930 | 6.6 |
| $P_{bca}$ | 1261 | 4.3 |
| Pnma | 548 | 1.9 |
| $Pna2_1$ | 513 | 1.8 |
| $P_{bcn}$ | 341 | 1.2 |
| **P1** | 305 | 1.1 |

Chiral space group

### Ionic Chiral Auxillary Approach




Reactive part  Chiral auxliary

### Covalent Chiral Auxillary Approach

Reactive part  Chiral auxliary

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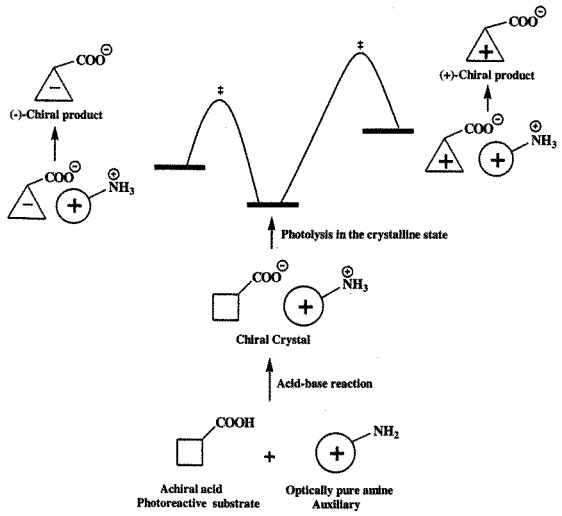
## Ionic chiral auxiliary approach: Solid state photochemistry

The chiral auxiliary ensures that the reactant molecule crystallizes in a chiral space group.

This would make the two diastereomeric reaction pathways to have different activation energies.

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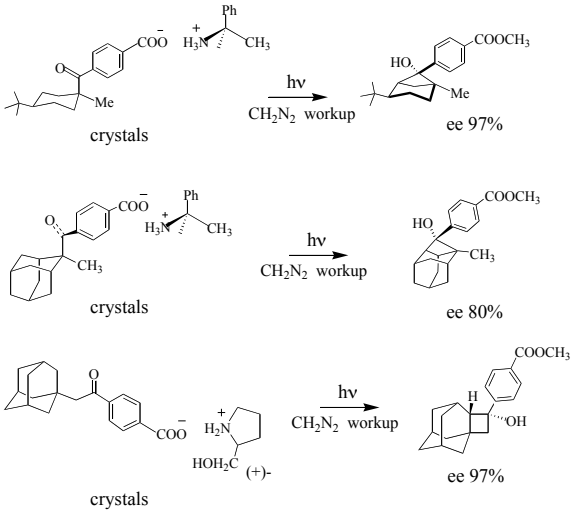
## Ionic chiral auxiliary approach




The two prochiral hydrogens are distinguishable in the crystalline state. In solution no chiral induction is obtained.

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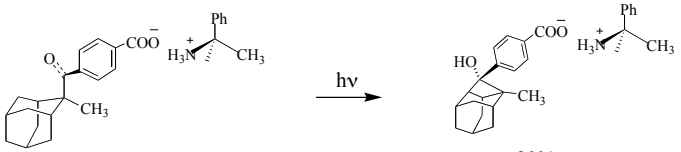


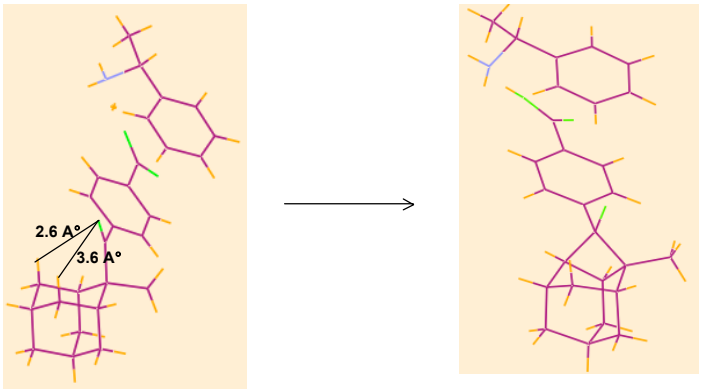


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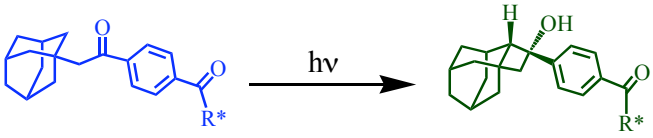
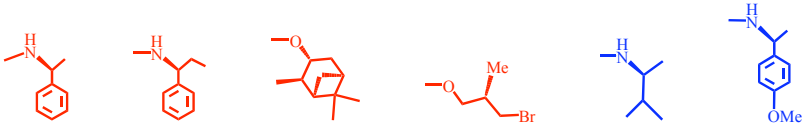
## Covalent chiral auxiliary approach



| R* | | | | | | |
|---|---|---|---|---|---|---|
| % de | 97 | 90 | 92 | 80 | 22 | 5 |

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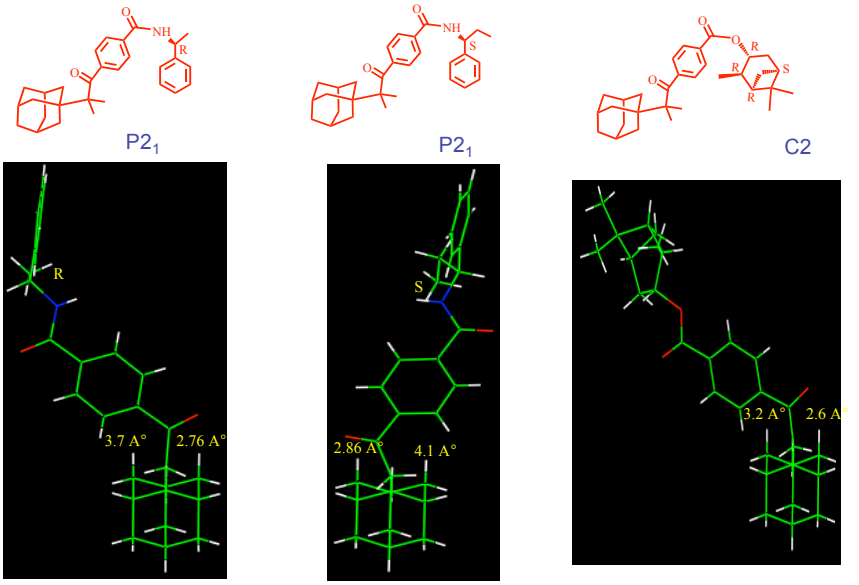


| | Trans CB | Trans CB | Trans CB |
|---|---|---|---|
| % de | 97 | 90 | 92 |

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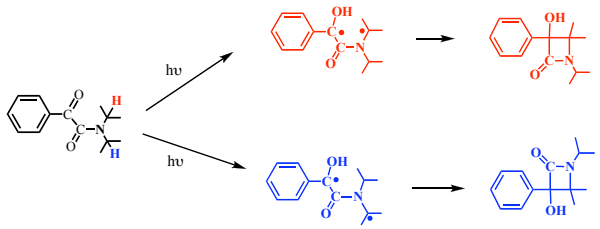
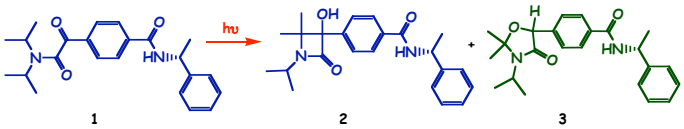
## Covalent chiral auxiliary approach: Photochemistry of α-Oxoamides




| Medium | 1 | 2 | 3 |
|---|---|---|---|
| Solution ($CH_3CN$) | 19 | 35 | 46 |
| Crystal | 0 | 100 | 0 |

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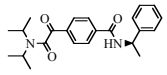
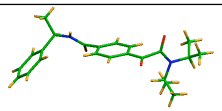
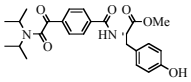
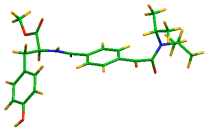
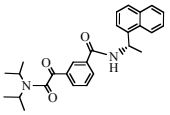
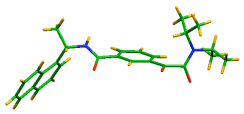
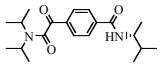
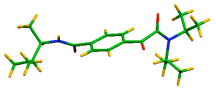
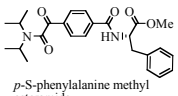
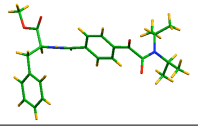
## Diastereoselectivity obtained with various chiral auxiliaries in solid state

| | | Crystal structures | C=O....γ-$H_1$ | C=O....γ-$H_2$ | %de of β-lactam |
|---|---|---|---|---|---|
| a) |  *p*-R-phenylethylamide |  | 2.814 A° | 5.077 A° | >99(A) |
| b) |  p-S-tyrosine methylesteramide |  | 2.562 A° | 5.091 A° | >99(B) |
| c) |  m-S-napthylethylamide |  | 2.737 A° | 5.214 A° | >99(B) |
| d) |  *p*-R-secondarybutylmide |  | 2.781 A° | 5.052 A° | 96(B) |
| e) |  *p*-S-phenylalanine methyl esteramide |  | 2.618A° | 5.130 A° | 82(A) |

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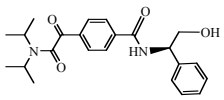
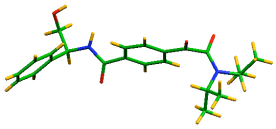
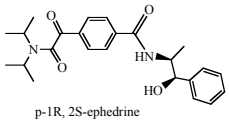
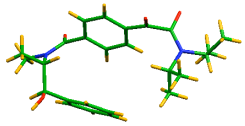
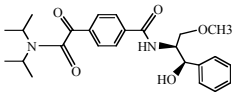
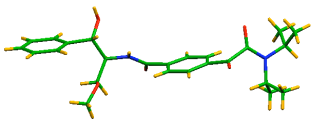
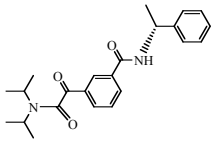
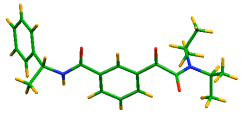
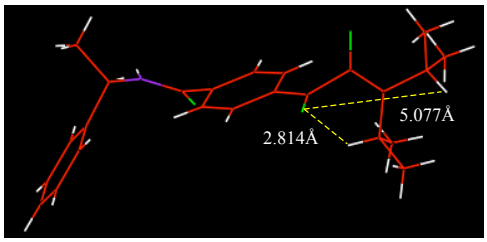
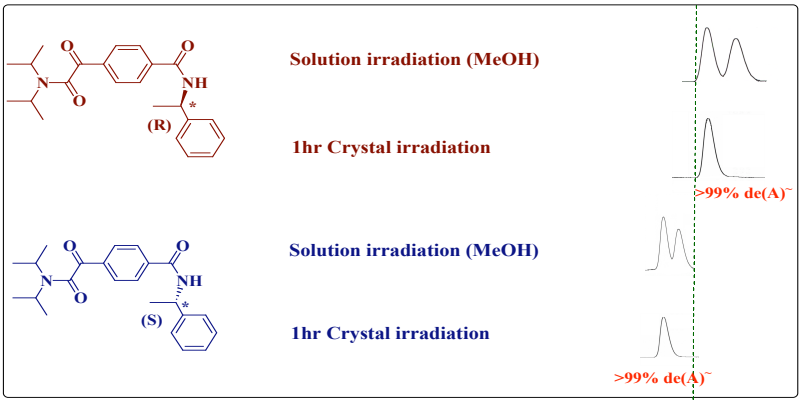
| | | Crystal structures | C=O....γ-$H_1$ | C=O....γ-$H_2$ | %de of β-lactam |
|---|---|---|---|---|---|
| f) |  p-R-phenylglycinol |  | 2.776 A° | 5.025 A° | 93(B) |
| g) |  p-1R, 2S-ephedrine |  | 2.804 A° | 5.030 A° | 87(B) |
| h) |  p-S-amidomethylphenylpropanol |  | 2.662 A° | 5.034 A° | 85(B) |
| i) |  m-R-phenylethylamide |  | 2.713 A° | 4.850 A° | 80(A) |

20




$P\,2_1$

β-lactam photoproduct#




# Photoproducts analyzed on HPLC chiralcel-OD
~ A: First peak on HPLC

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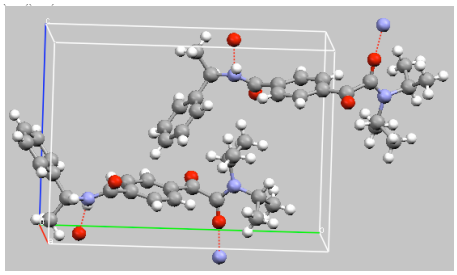
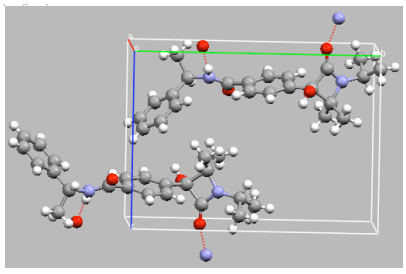
## Single crystal-to-Single Crystal Phototransformation





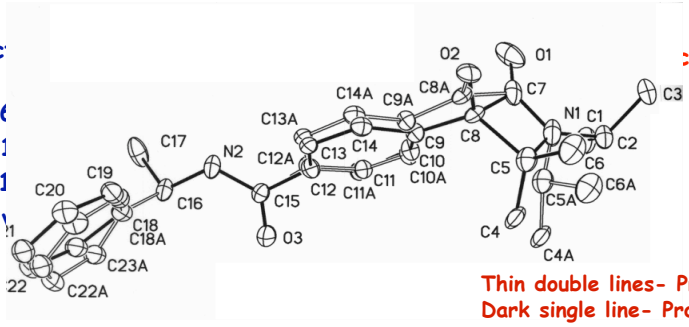
Reac ...crystal; $P2_1$)

*a* = (

*b* = 1

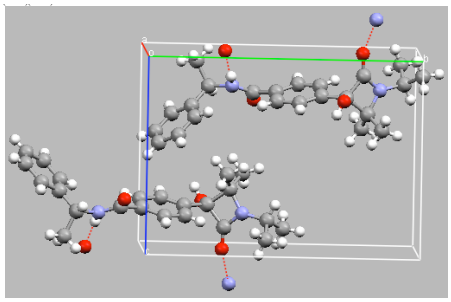
*c* = 1

Cell V ... Å$^3$



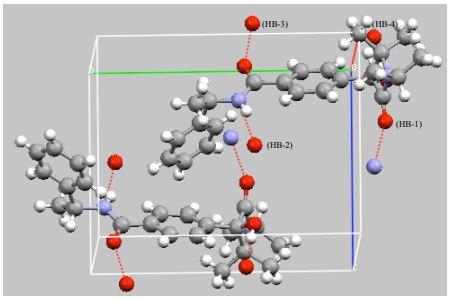

Thin double lines- Precursor
Dark single line- Product

22



Photoproduct as Formed ($P2_1$)

*a* = 6.4821 Å
*b* = 14.967 Å
*c* = 10.7528 Å
β = 98.52°
Cell volume 1031.71 Å$^3$




Photoproduct Recrystallized ($P2_1$)

*a* = 8.5684 Å
*b* = 12.8865Å
*c* = 9.8260 Å
β = 107.98°
Cell volume 1031.99(30) Å$^3$

23

## Soild State Photochemical Reactions

Topochemical Reactions: Reaction in the solid state is preferred and occurs with a minimum amount of atomic and molecular movement.

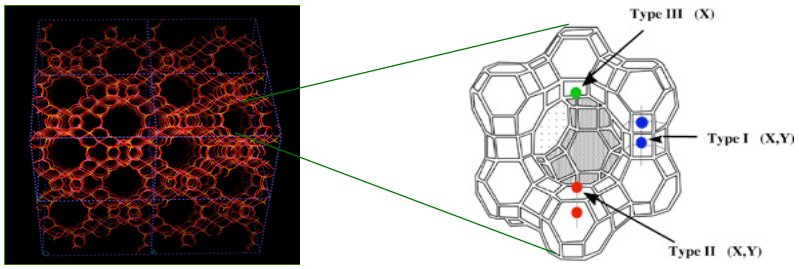
Topotactic Reactions: A phenomenon in which X ray quality single crystals of the reactant are continuously and quantitatively converted into single crystals of the product.

Topotactic reactions are not common

24

## Asymmetric photoreactions within zeolites

- Key is the cation binding to the included organic molecule. Confined space also imposes restrictions.
- Details yet to be understood.

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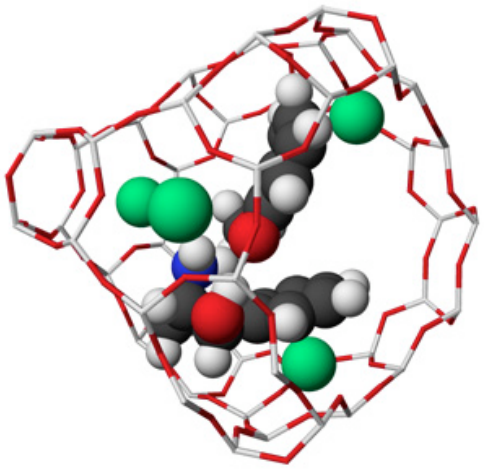
## Asymmetric Photoreactions Within Zeolites



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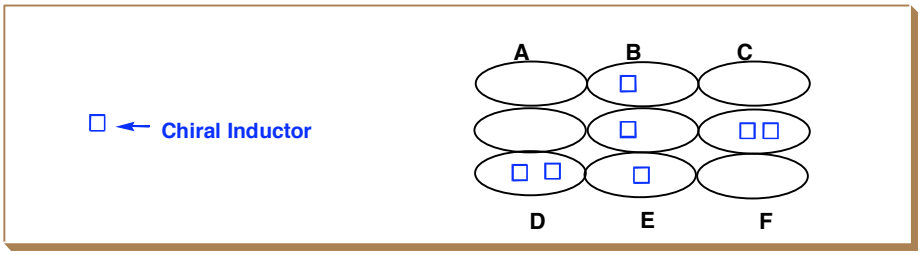
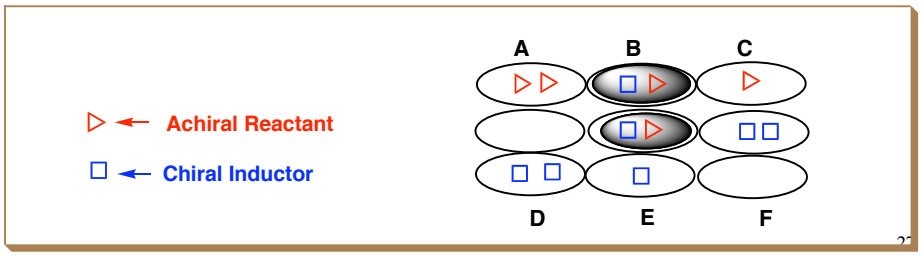
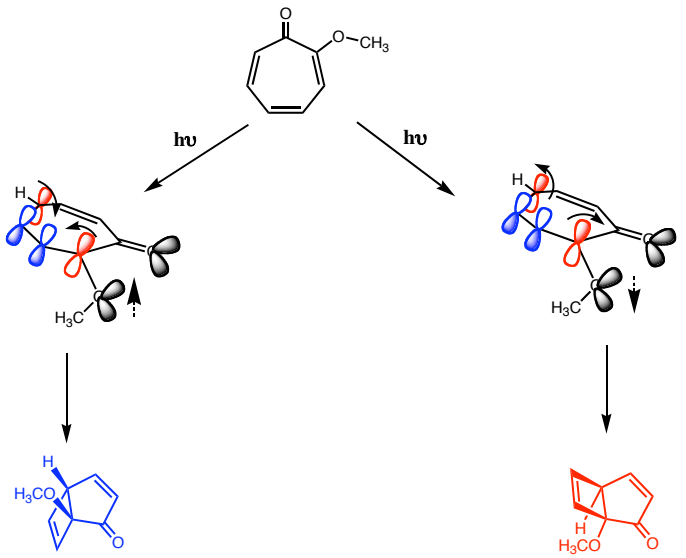
## Chiral inductor approach




## Enantioselective Electrocylization of Achiral Tropolones

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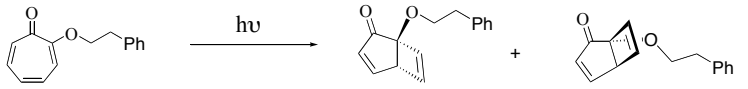
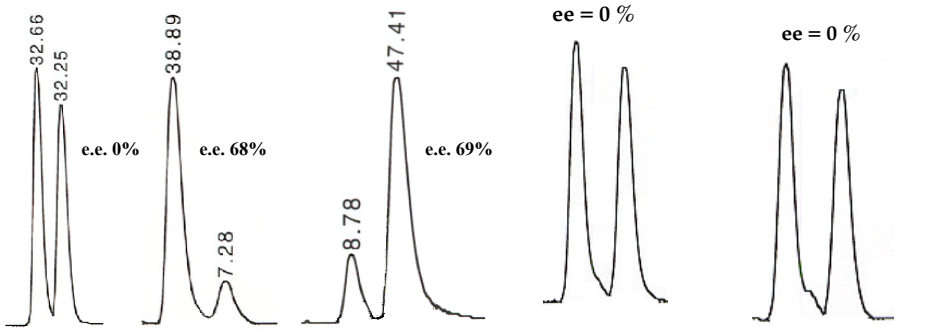
## Chiral Induction: Solution *vs.* Zeolite

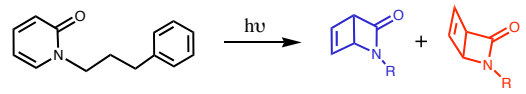


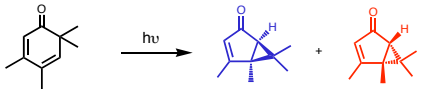

NaY | NaY / (-)-Ephedrine | NaY / (+)-Ephedrine | Hexane-methylene chloride/(-)-Ephedrine | Silica gel/(-)-Ephedrine

29

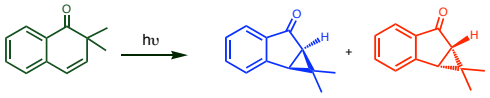
## Enantioselectivity in Photoreactions-Generality



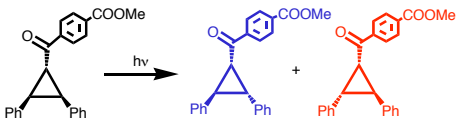

NaY, Norephedrine, RT: 50%ee



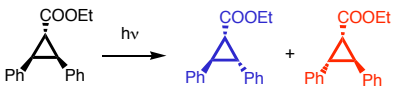

NaY, Ephedrine, -55°C: 50%ee




NaY, Ephedrine: 15%ee



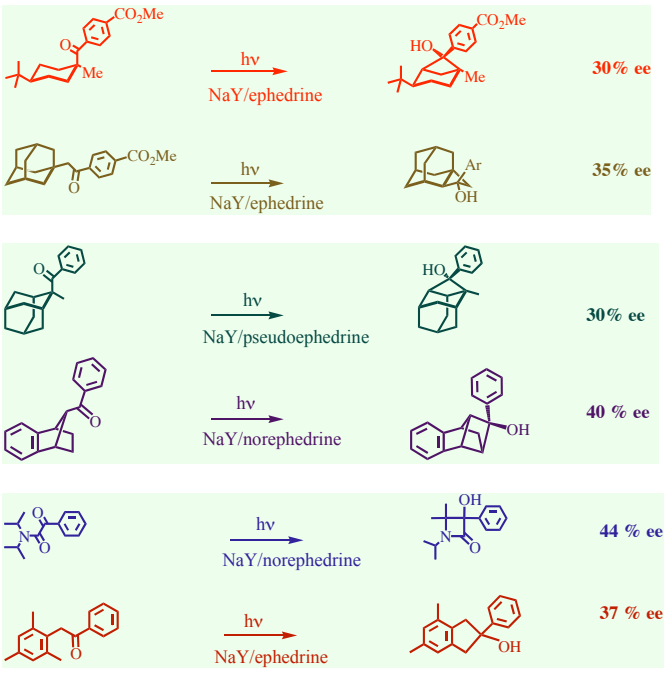

NaY, Norephedrine, RT: 20%ee




NaY, Cyclohexyl ethyl amine, RT: 17%ee

30

Solution ee was zero % in all the above cases

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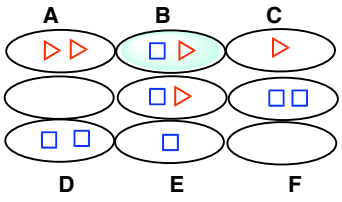
## Chiral inductor approach

Achiral Reactant

Chiral Inductor

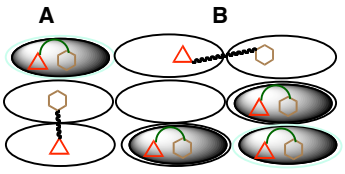



## Chiral auxiliary approach

Achiral Reactant

Covalent bond

Chiral Auxiliary

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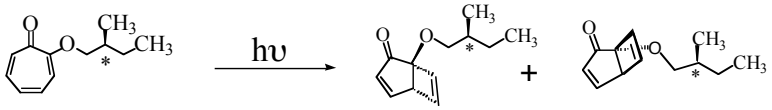
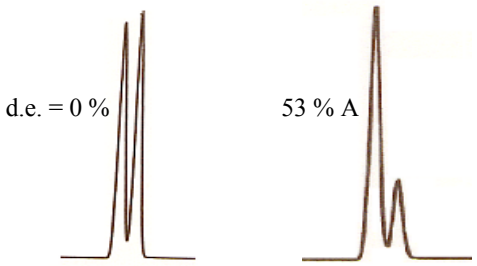
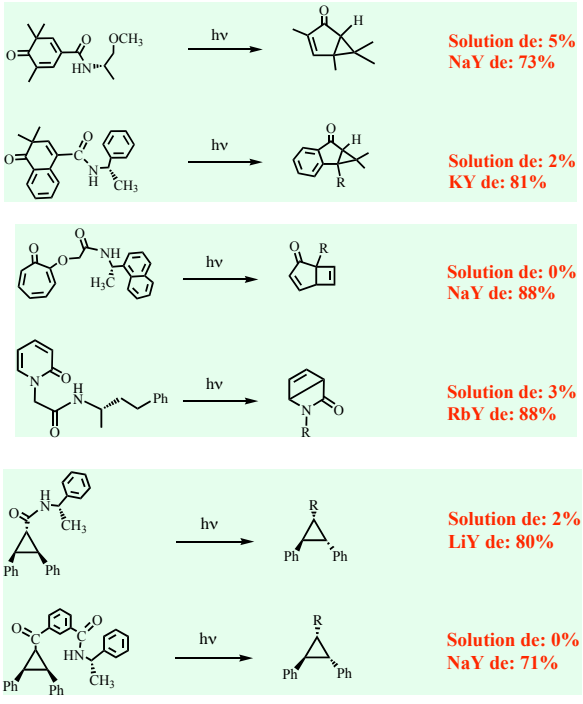
## Chiral Induction (Diastereoselectivity)
## Solution *vs.* Zeolite

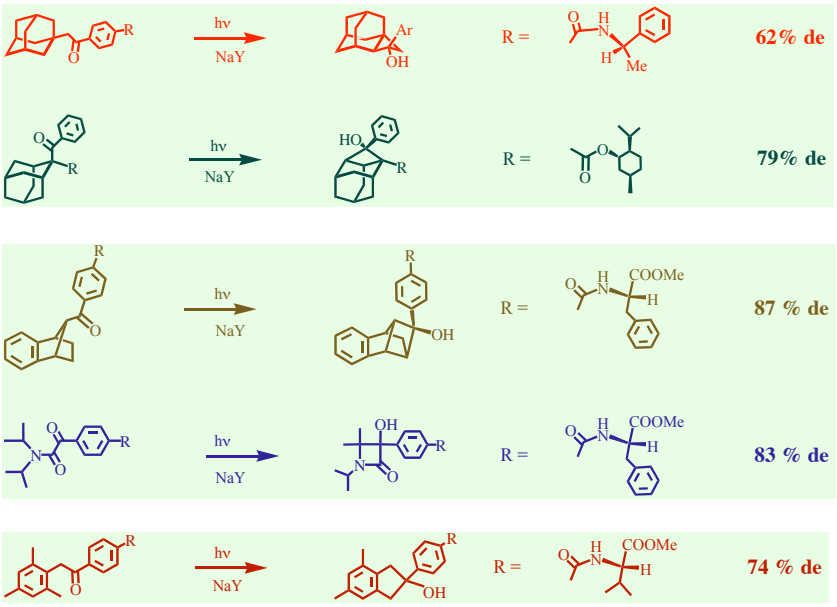


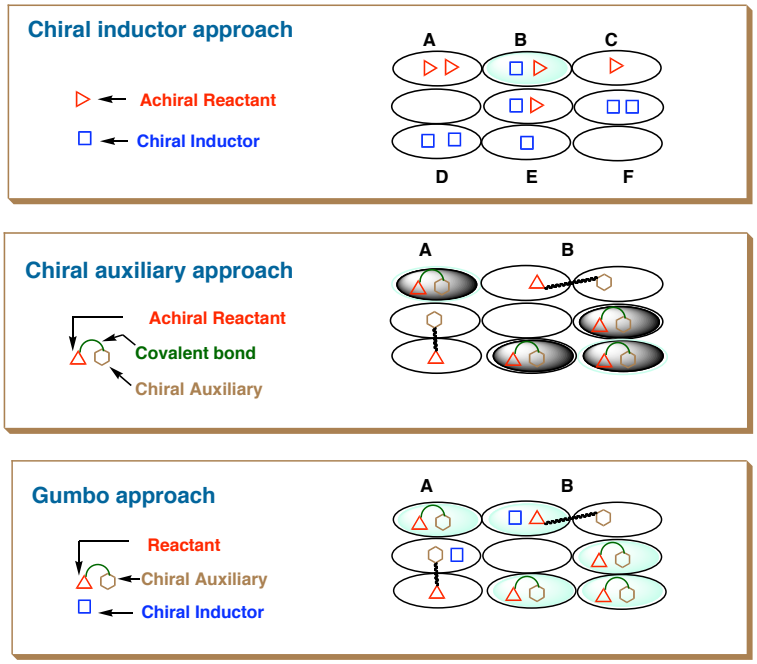

33




34

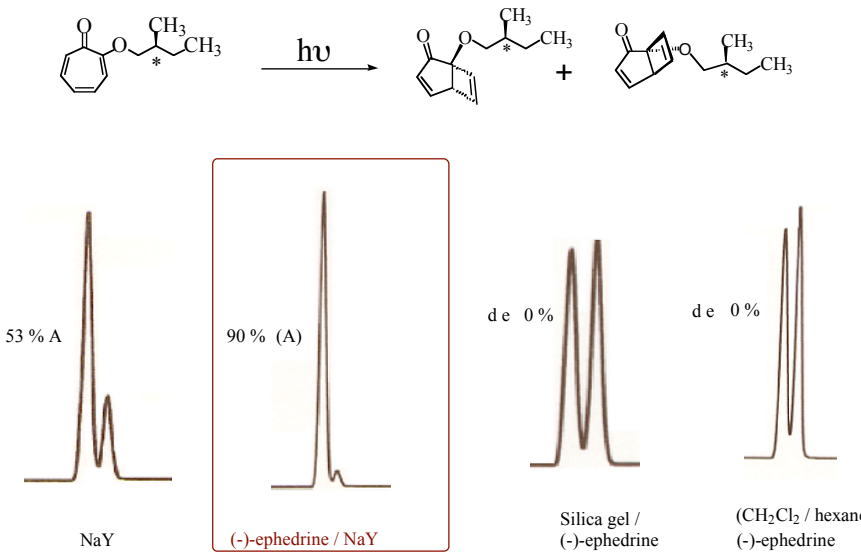

hv
NaY
R =
62% de
79% de
87 % de
83 % de
74 % de
Me
COOMe

35


Chiral inductor approach
Achiral Reactant
Chiral Inductor
A
B
C
D
E
F
Chiral auxiliary approach
Achiral Reactant
Covalent bond
Chiral Auxiliary
A
B
Gumbo approach
Reactant
Chiral Auxiliary
Chiral Inductor
A
B

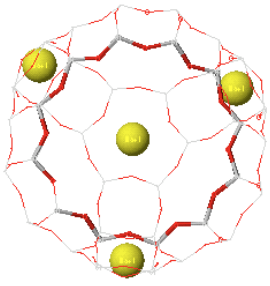
36

## Chiral induction within a chirally modified zeolite




37

## Asymmetric Photoreactions Within Zeolites



- Chiral Induction Depends on
  - Nature of the Cation
  - Number of Cations (Si/Al ratio)
  - Water Content

**Cation is the Key**

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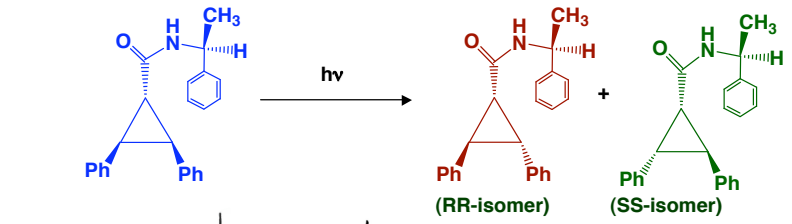
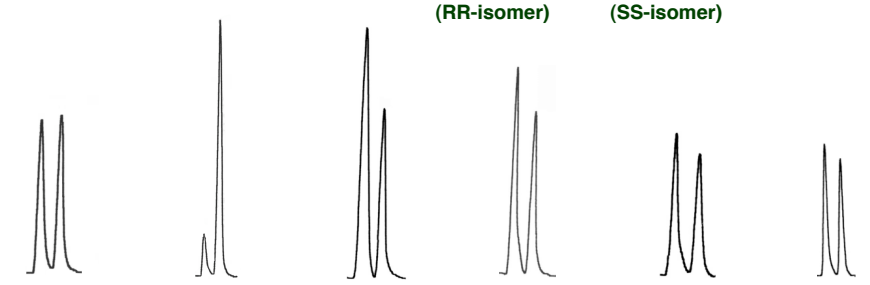
## Chiral Induction Depends on the Nature Alkali Metal Ion



| Solution | LiY | NaY | KY | RbY | CsY |
|---|---|---|---|---|---|
| 2 (SS) | 80 (SS) | 28 (RR) | 14 (RR) | 5 (RR) | 5 (RR) |

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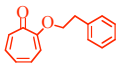
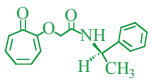
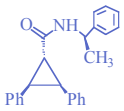
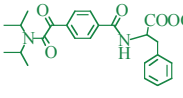
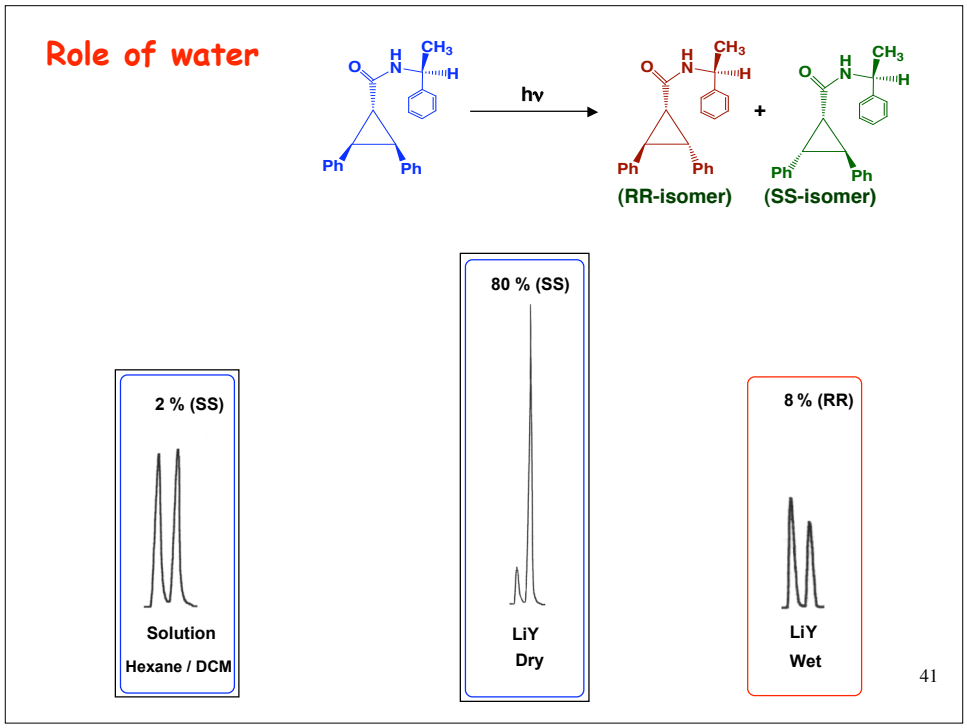
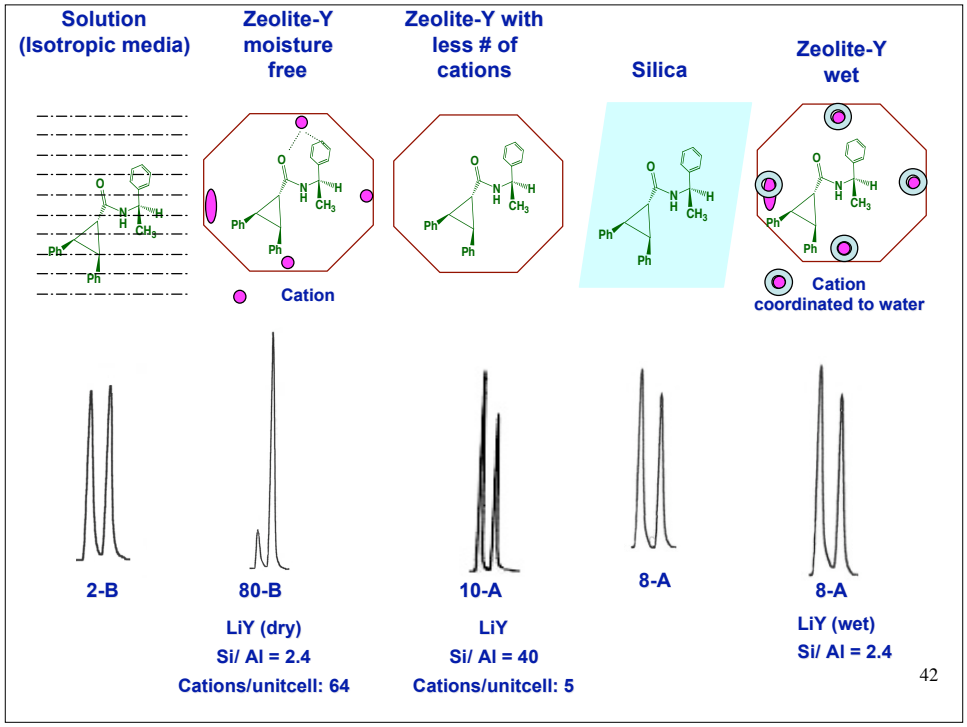
## Enantio and Diastereomeric Excess Depends on the Number of Cations

| Si/Al Ratio | | 2.4 | 6 | 15 | 40 |
|---|---|---|---|---|---|
|  | ($Na^+$) | 70 | 24 | 13 | 5 |
|  | ($Na^+$) | 80 | 22 | 16 | 4 |
|  | ($Li^+$) | 68 | 25 | 12 | 10 |
|  | ($Na^+$) | 78 | 10 | 13 | 10 |

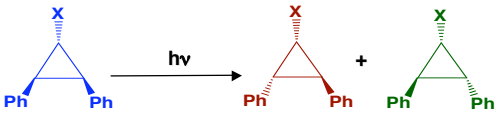
40

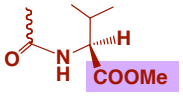

Role of water
hν
(RR-isomer)
(SS-isomer)
2 % (SS)
Solution
Hexane / DCM
80 % (SS)
LiY
Dry
8 % (RR)
LiY
Wet
41

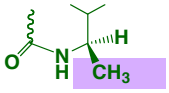

Solution
(Isotropic media)
Zeolite-Y
moisture
free
Zeolite-Y with
less # of
cations
Silica
Zeolite-Y
wet
Cation
Cation
coordinated to water
2-B
80-B
LiY (dry)
Si/ Al = 2.4
Cations/unitcell: 64
10-A
LiY
Si/ Al = 40
Cations/unitcell: 5
8-A
8-A
LiY (wet)
Si/ Al = 2.4
42

## Role of Cation-Carbonyl Dipolar Interaction

### Carboalkoxy *vs* Alkyl




| Zeolite | % d.e. | % d.e. |
|---|---|---|
| LiY | 83-B | 7-A |
| NaY | 28-A | 7-A |
| KY | 80-A | 7-B |
| RbY | 47-A | 12-B |
| Solution | 2-B | 2-B |

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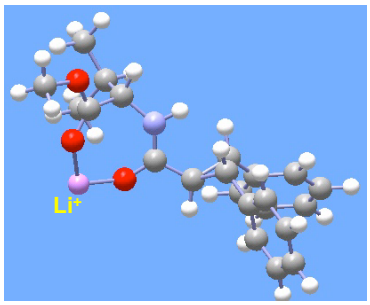
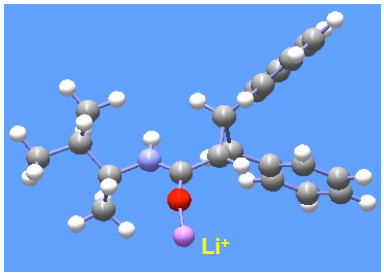
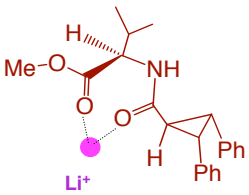
## Role of Cation-Carbonyl Dipolar Interaction (HF / 3-21G)

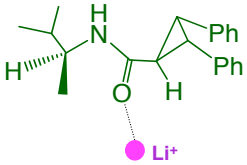



BA = 104.10 kcal/mol




BA = 79.63 kcal/mol

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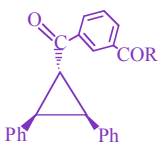
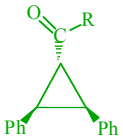
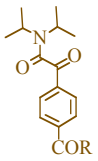
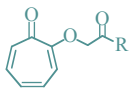
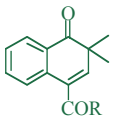
## Importance of Cation-Chiral Auxiliary Binding: Phenyl vs Cyclohexyl

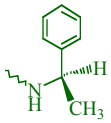
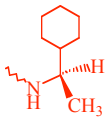



| | NaY | LiY | NaY | NaY | KY |
|---|---|---|---|---|---|
|  | 71 | 80 | 62 | 85 | 81 |
|  | 30 | 29 | 22 | 45 | 45 |

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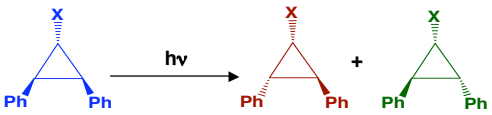
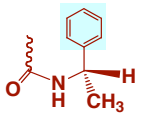
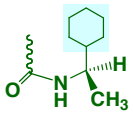
## Role of Cation-π Quadrupolar Interaction

### Phenyl *vs* Cyclohexyl




| Zeolite | % d.e. | % d.e. |
|---|---|---|
| LiY | 80-B | 29-B |
| NaY | 28-A | 24-A |
| KY | 14-A | 26-A |
| RbY | 5-A | 29-A |
| CsY | 5-A | 37-A |
| Solution | 2-B | 2-B |

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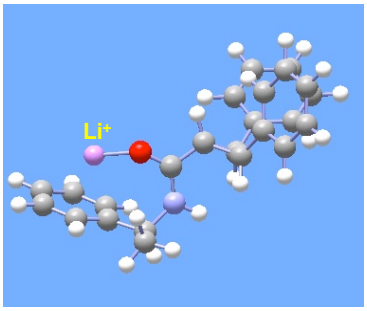
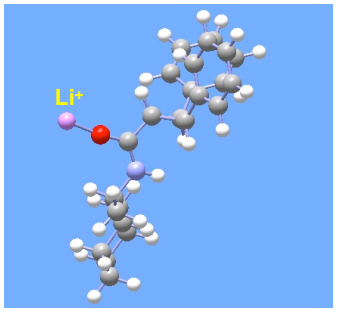
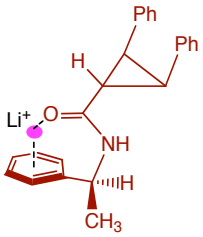
## Role of Cation-π Quadrupolar Interaction (HF / 3-21G)

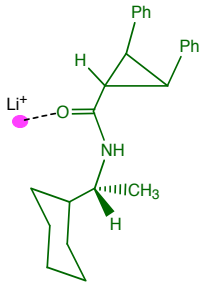



BA = 91.3 kcal/mol




BA = 80.26 kcal/mol

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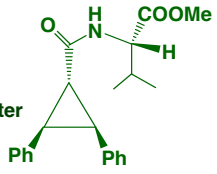
## Cation Dependent Diastereomer Switch

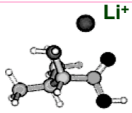
Amide of
L-Valine methyl ester



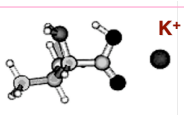

LiY
83 (SS)

KY
80 (RR)

Williams, E. A. et. al.,
JACS, 123, 12255-12265, (2001)



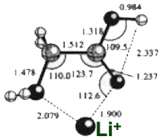

Valine



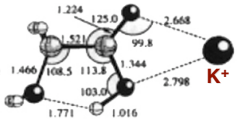

NO - Co-coordination

OO - Co-coordination

Bowers, M. T. et. al.,
JACS, 2001, 122, 3458-3464, (2000)




Glycine

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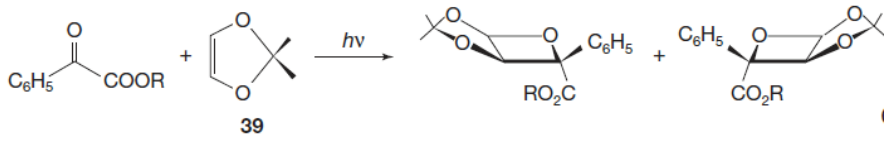
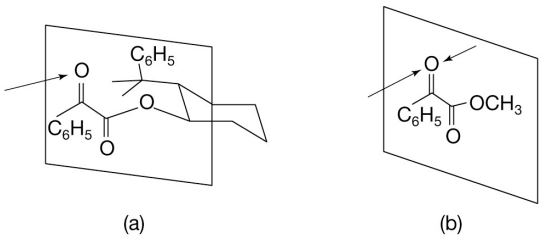
## Chiral photochemistry in solution through covalent chiral auxiliary

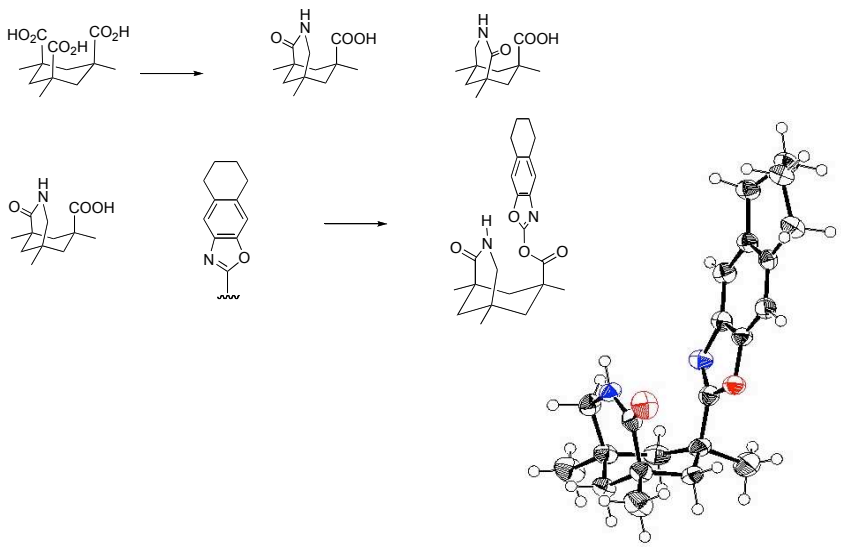



| R | *de* |
|---|---|
| (–)-8-$C_6H_5$-Menthyl | ≥96% |
| (–)-Menthyl | 57% |

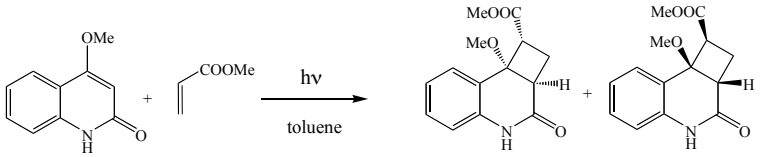



(a) (b)

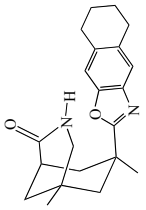
## Chiral photochemistry in solution through templation



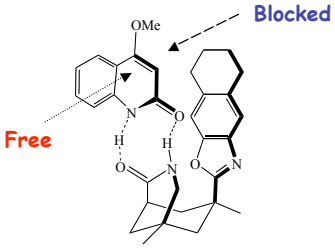
## Chiral photochemistry in solution through templation




**In the absence of template; e.e.: 0**
**In the presenceof template; e.e.: 82%**



Template




One mode of approach blocked

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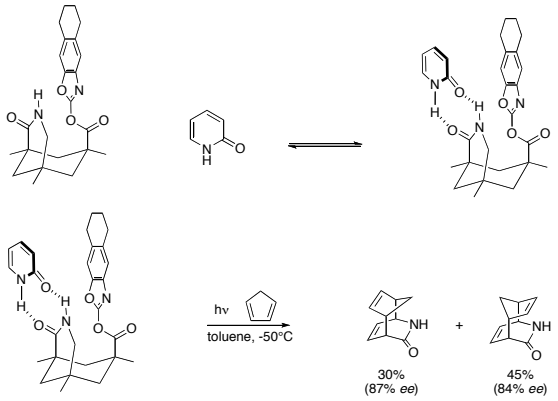
## Chiral photochemistry in solution through templation

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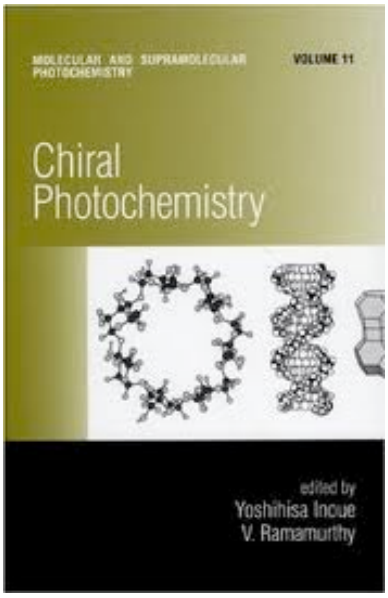
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