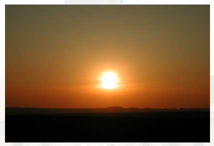
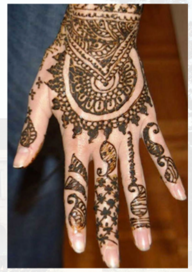
Chiral Photochemistry

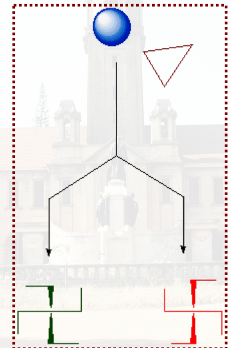


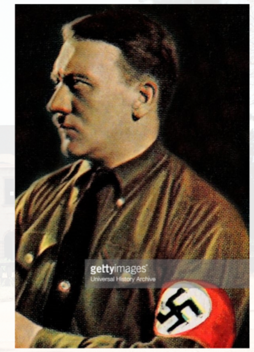


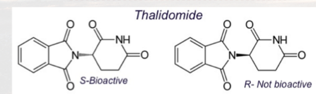
- Crystals
- Zeolites
- Solution

2

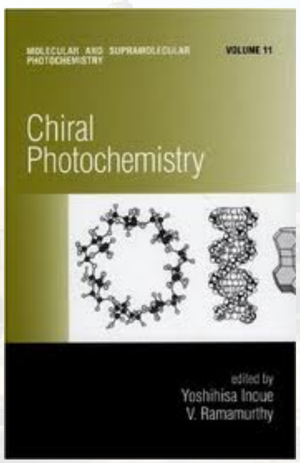
Why Chiral Chemistry







3



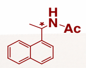
4

Photochemistry in Solution

Sunset in Kovalam Beach

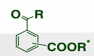
The beginnings of chiral organic photochemistry

Hammond, G. S. and Cole, R. S.
J. Am. Chem. Soc. **1965**, p-3256



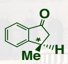
ee = 6.7%

Horner, L. and Klaus, J.
Liebigs Ann. Chem., **1979**, p-1232



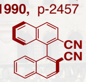
ee = 4.0 %

Ouannes, C. Beugelmans, R. and Roussi, G.
J. Am. Chem. Soc., **1973**, p-8472



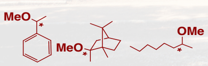
ee = 3.0%

Vondenhof, M. and Mattay, J.
Chem. Ber., **1990**, p-2457



ee = 3.5%

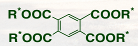
Faljoni, A. Zinner, K. and Weiss, R. G.
Tetrahedron lett., **1974**, p-1127



As chiral solvents

ee = 2.3%

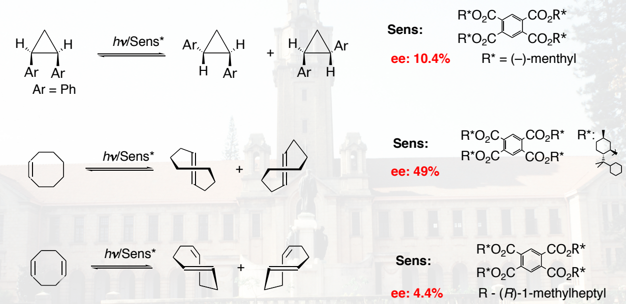
Inoue, Y. Shimoyama, H. Yamasaki, N. and Tai, A.
Chem, lett., **1991**, p-593



ee = 10.4 %

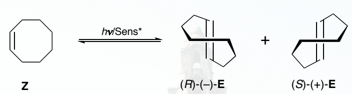
6

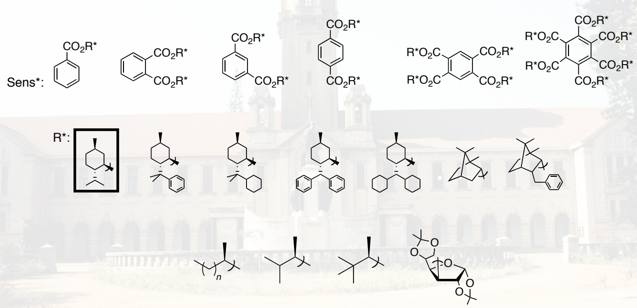
Controlling products during asymmetric photoreactions



- 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.

7



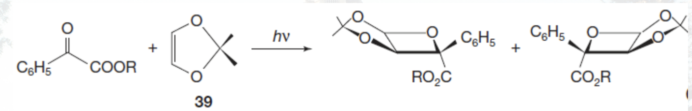


Temperature
Pressure
Solvent

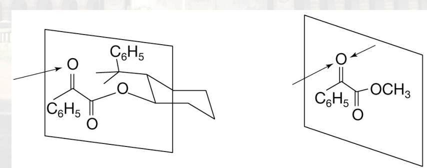
73% ee at -110° C in pentane

8

Chiral photochemistry in solution through covalent chiral auxiliary

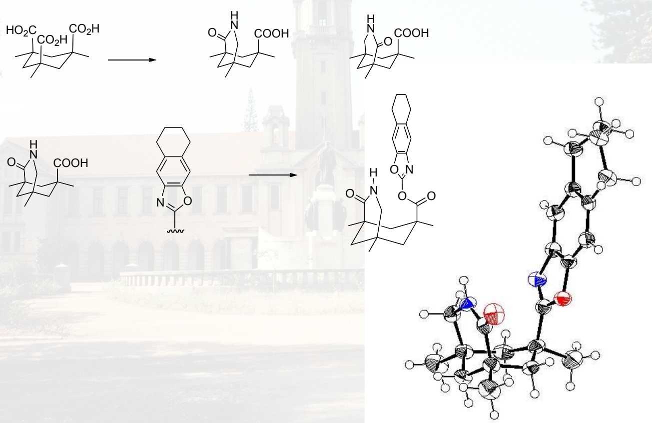


R	de
(–)-8-C_6H_5-Menthyl	≥96%
(–)-Menthyl	57%

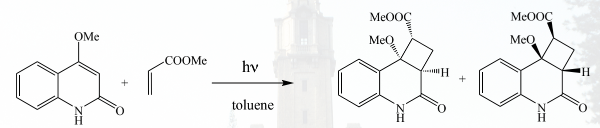


(a) (b)

Chiral photochemistry in solution through templation



Chiral photochemistry in solution through templation

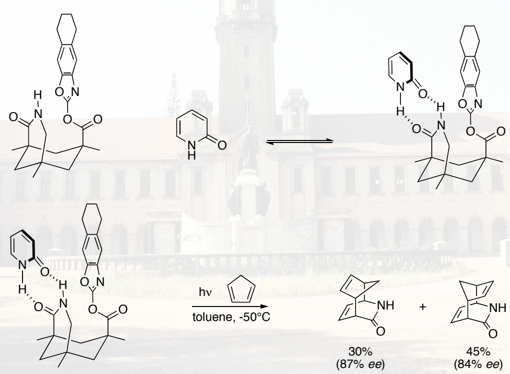


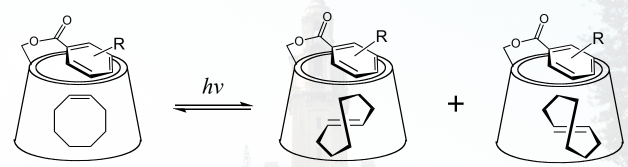
In the absence of template; e.e.: 0

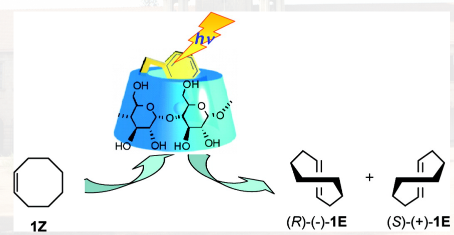
In the presenceof template; e.e.: 82%

One mode of approach blocked

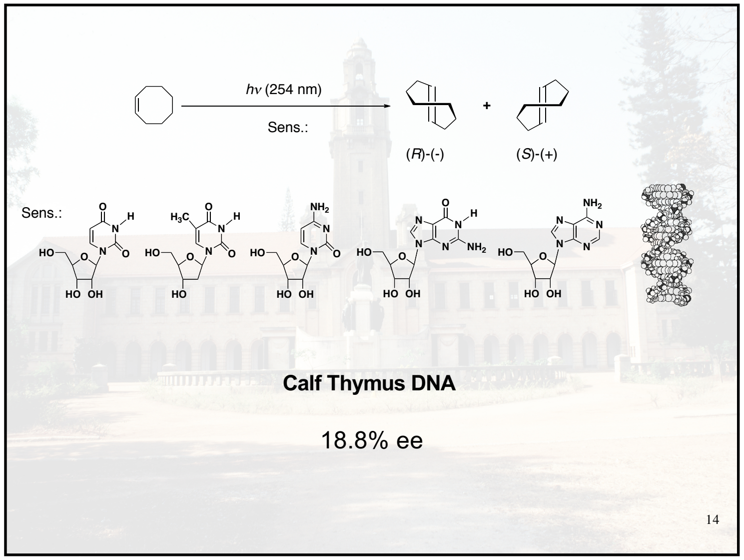
Chiral photochemistry in solution through templation

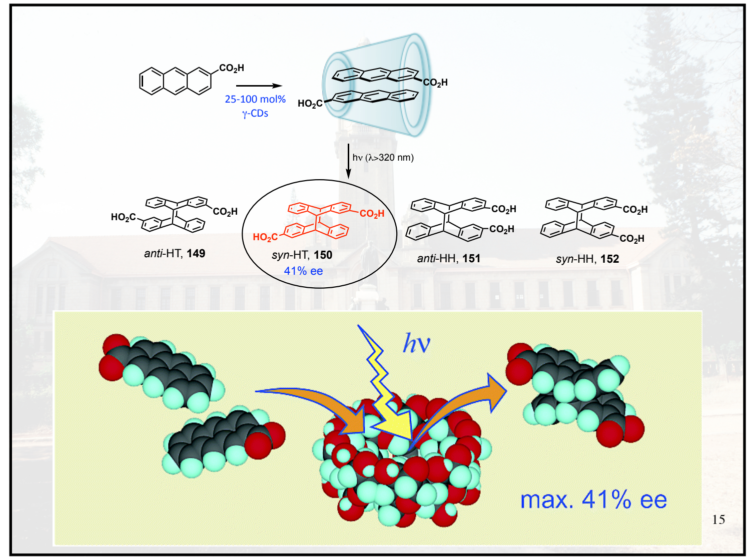


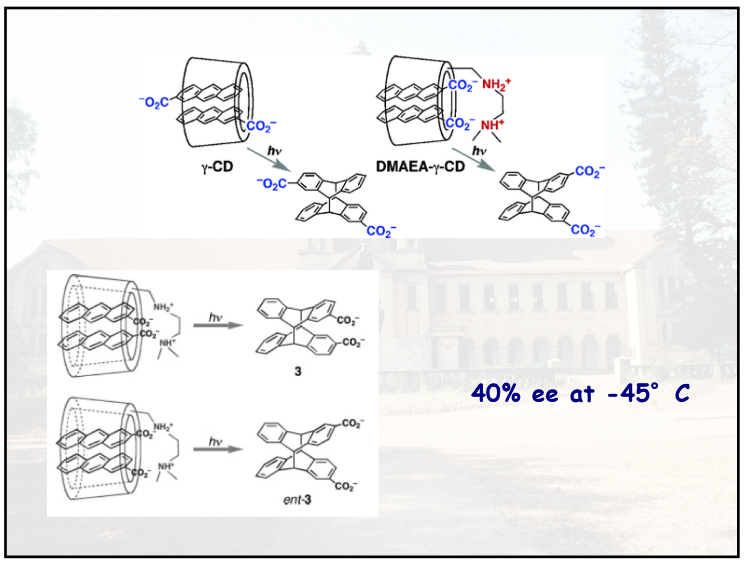


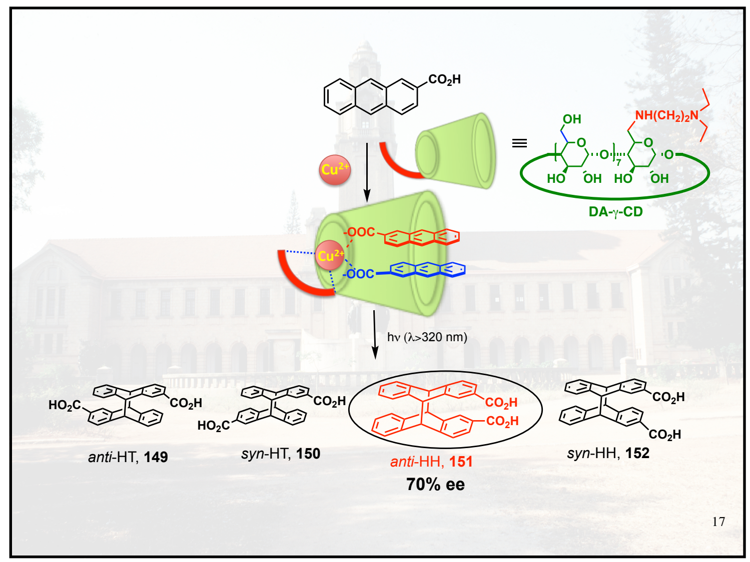


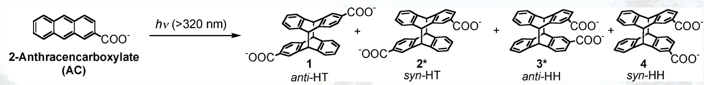
46% ee

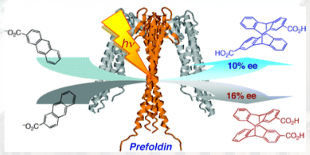

hν (254 nm)
Sens.:
(R)-(-)
(S)-(+)
Sens.:
Calf Thymus DNA
18.8% ee
14

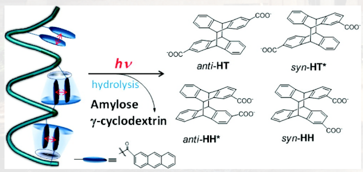

25-100 mol% γ-CDs
hν (λ>320 nm)
anti-HT, 149
syn-HT, 150
41% ee
anti-HH, 151
syn-HH, 152
hν
max. 41% ee
15

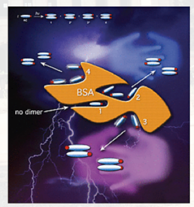

γ-CD
DMAEA-γ-CD
hν
3
ent-3
40% ee at -45° C


hν (λ>320 nm)
DA-γ-CD
anti-HT, 149
syn-HT, 150
anti-HH, 151
70% ee
syn-HH, 152
17





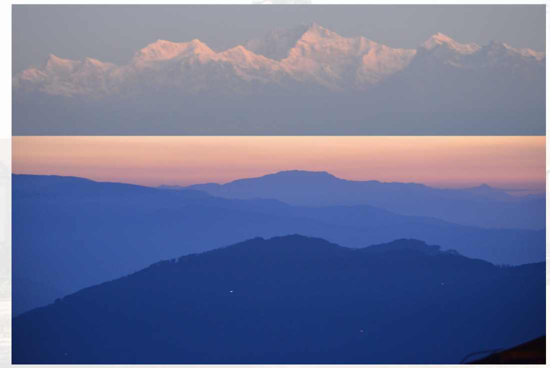




15% ee for syn HT amylose
37% ee for syn HT amylose + γ-cyclodextrin

38% ee for syn HT
58% ee for anti HH

Photochemistry in Solid State



Sunrise at Himalayan range

Chiral crystallization

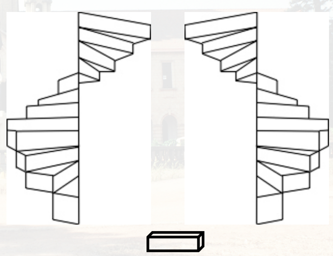
Achiral molecule may crystallize in achiral space group.
e.g., quartz, urea, maleic anhydride,

R ⇌ S (fast enantiomerization, ambient temp)

spontaneous chiral crystallization

R 100% — S 100%

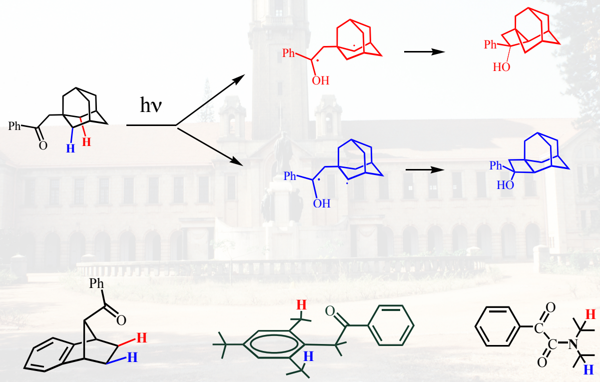
Chiral crystallization of achiral materials



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

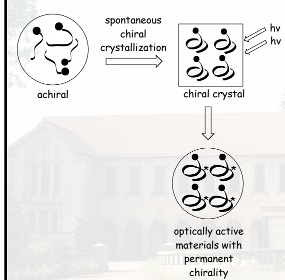
space group	number	percentage
$P2_1/c$	10450	36.0
P-1	3986	13.7
$P2_12_12_1$*	3359	11.6
$P2_1$*	1957	6.7
$C2/c$	1930	6.6
$Pbca$	1261	4.3
$Pnma$	548	1.9
$Pna2_1$	513	1.8
$Pbcn$	341	1.2
$P1$*	305	1.1

*Chiral space group.

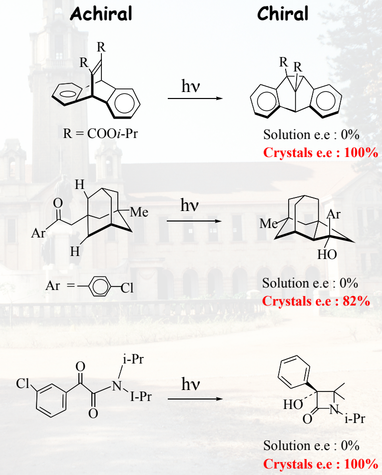


22

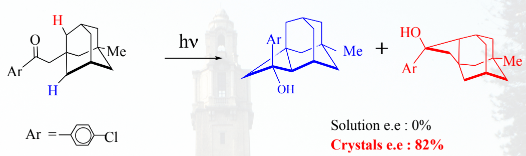
Chiral crystallization



Absolute asymmetric synthesis in the chiral crystalline environment

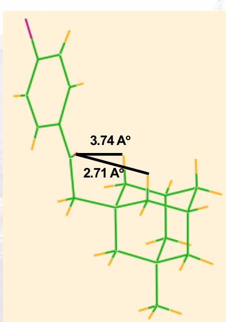


23



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.

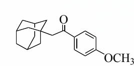
Since only one prochiral hydrogen would be abstracted only one cyclobutanol enantiomer would be formed.

24

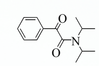
Essential Criteria for Asymmetric Photochemistry in the Crystalline State

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

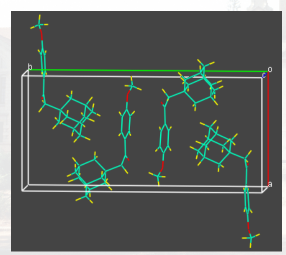
Majority of achiral molecules crystallize in a non chiral space group (symmetric packing)

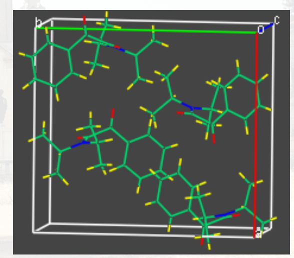


% ee: 0



% ee: 100





P21/n
centrosymmetric

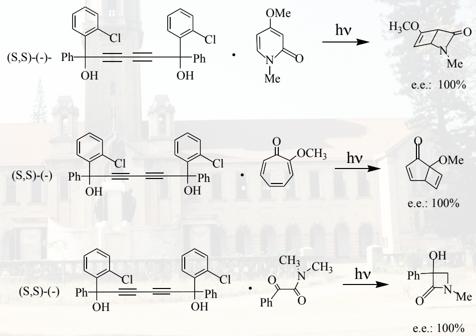
P212121
non-centrosymmetric

25

Use of chiral hosts: Solid state photochemistry

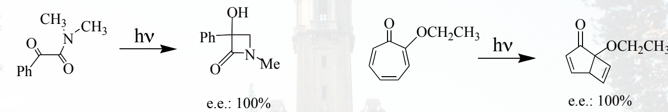
Chiral hosts upon inclusion of an achiral molecule may induce chirality on the achiral molecule.

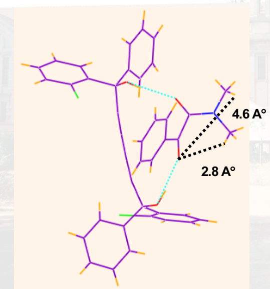
The above host-guest complexation would lead to diastereomeric (instead of enantiomeric) transition states .

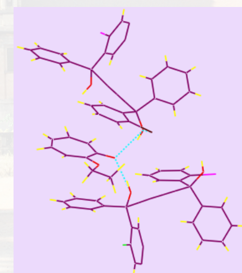


In solution no chiral induction is obtained.

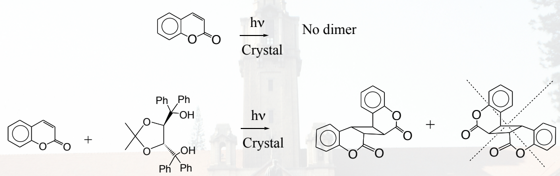
Use of chiral hosts: Unimolecular reactions



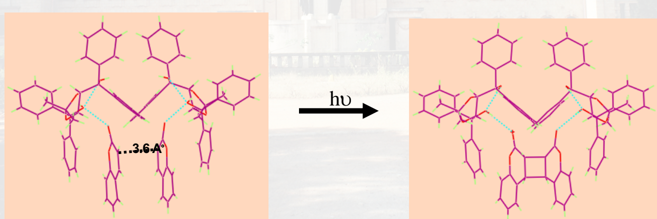




Use of chiral hosts: Bimolecular reactions



1:1 complex



Most commonly occurring space groups

230 unique space groups of which only 65 are chiral space groups

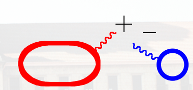
Chiral space groups (symmetry elements are rotational, translational and combinations of these)

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

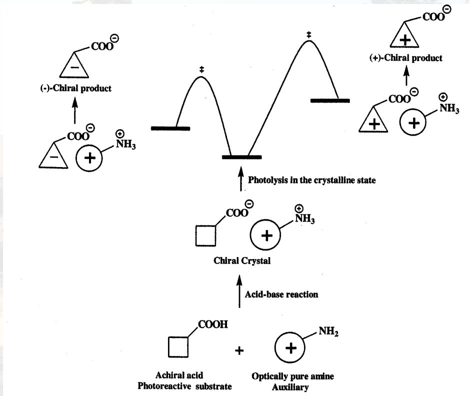
Covalent Chiral Auxillary Approach

Reactive part   Chiral auxliary

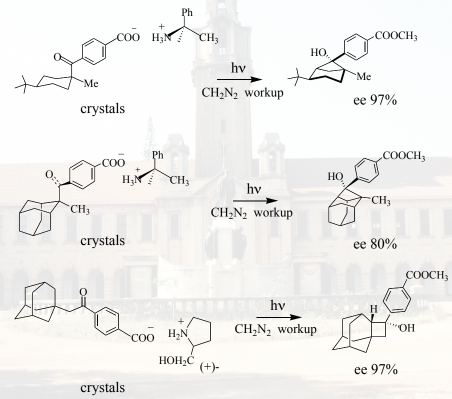
Ionic chiral auxiliary approach: Solid state photochemistry

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

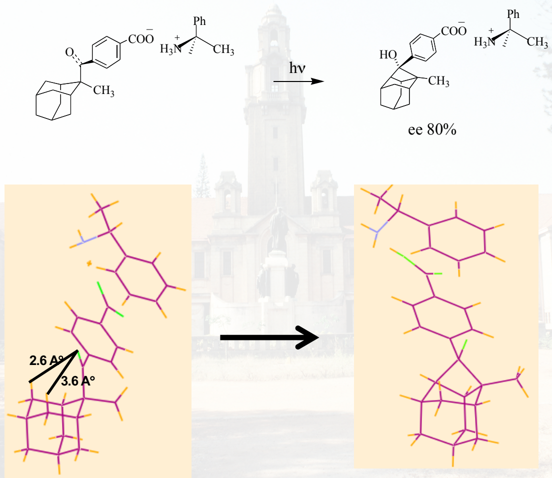
This would make the two diastereomeric reaction pathways to have different activation energies.



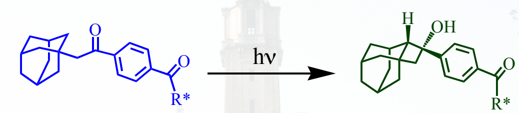
Ionic chiral auxiliary approach



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

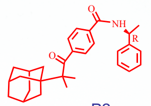


Covalent chiral auxiliary approach

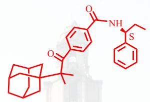


R*

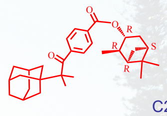
% de	97	90	92	80	22	5



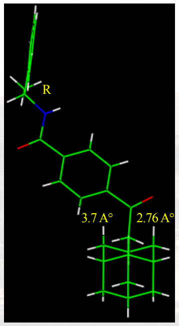
$P2_1$

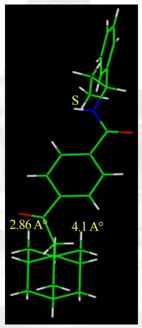


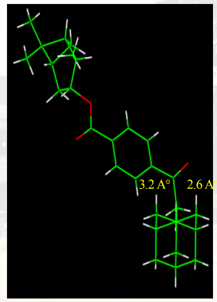
$P2_1$



C2

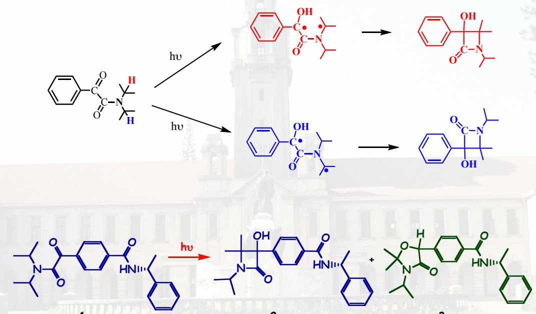






	Trans CB	Trans CB	Trans CB
% de	97	90	92

Covalent chiral auxiliary approach: Photochemistry of α-Oxoamides

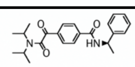
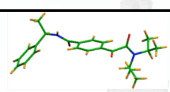
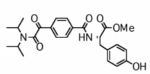
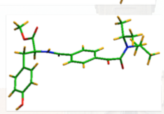
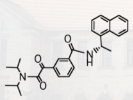
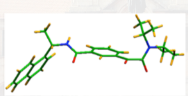
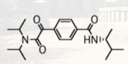
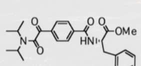
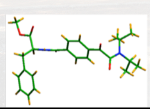


1 2 3

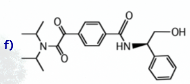
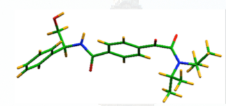
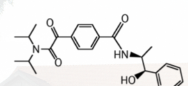
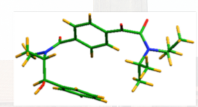
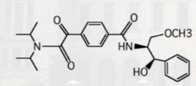
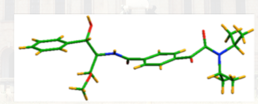
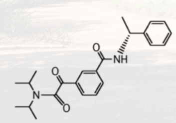
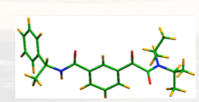
Medium	1	2	3
Solution (CH_3CN)	19	35	46
Crystal	0	100	0

35

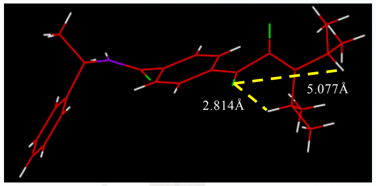
Diastereoselectivity obtained with various chiral auxiliaries in solid state

		Crystal structures	C=O....γ-H1	C=O....γ-H2	%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)

36

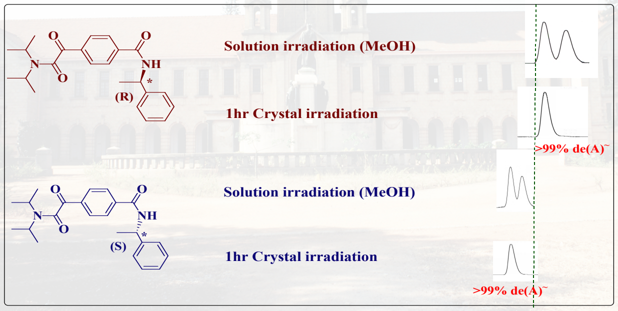
		Crystal structures	C=O....γ-H1	C=O....γ-H2	%de of β-lactam
f)	 p-R-phenylglycinol		2.776 A°	5.025 A°	93(B)
g)	 p-1R, 2S-ephedrine		2.804 A°	5.030 A°	87(B)
h)	 p-S-amidomethylphenylpropanol		2.662 A°	5.034 A°	85(B)
i)	 m-R-phenylethylamide		2.713 A°	4.850 A°	80(A)

37



$P\ 2_1$

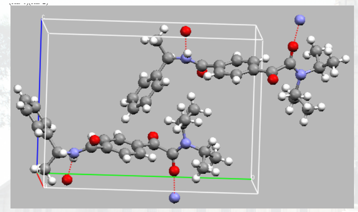
β-lactam photoproduct#

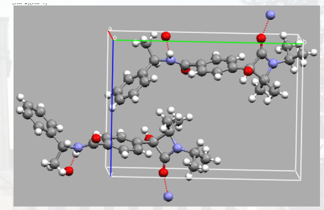


38

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

Single crystal-to-Single Crystal Phototransformation





Reac

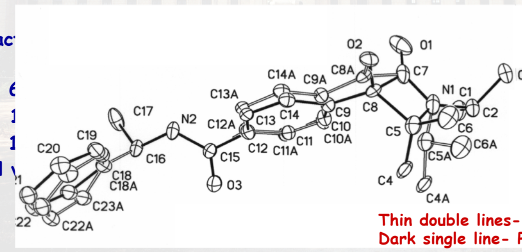
a = 6

b = 1

c = 1

Cell v

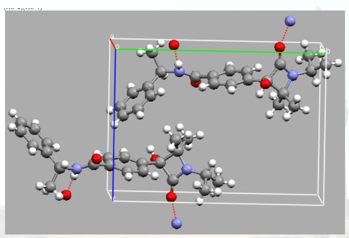
crystal; $P2_1$)



$Å^3$

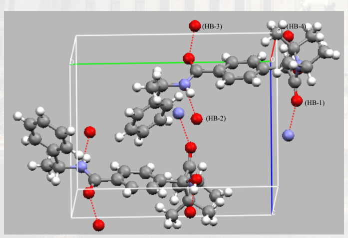
Thin double lines- Precursor
Dark single line- Product

39



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) $Å^3$

40

Soild State Photochemical Reactions

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

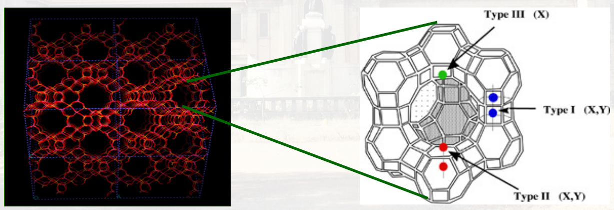
Topotactic Reactions: A phenomenon in which X ray quality single crystals of the reactant are continuously and quantitatively converted into single crystals of the product.

Topotactic reactions are not common

41

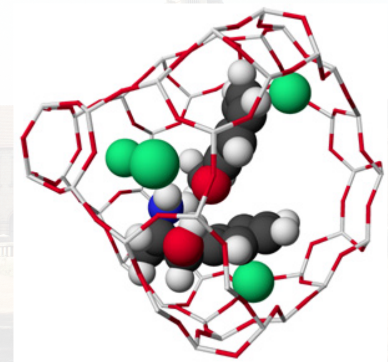
Asymmetric photoreactions within zeolites

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



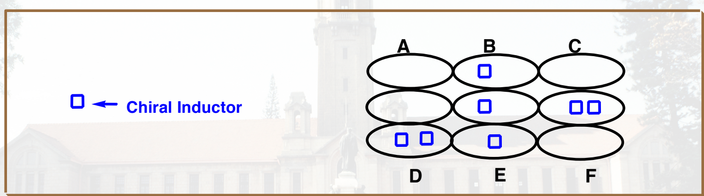
42

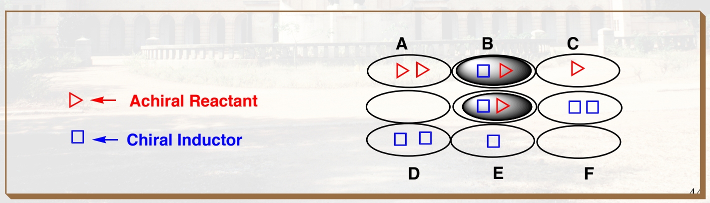
Asymmetric Photoreactions Within Zeolites



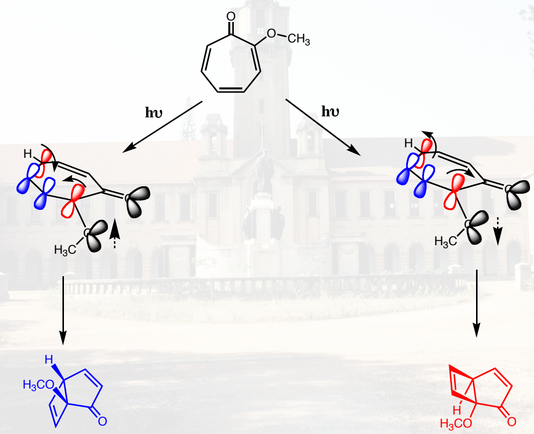
43

Chiral inductor approach

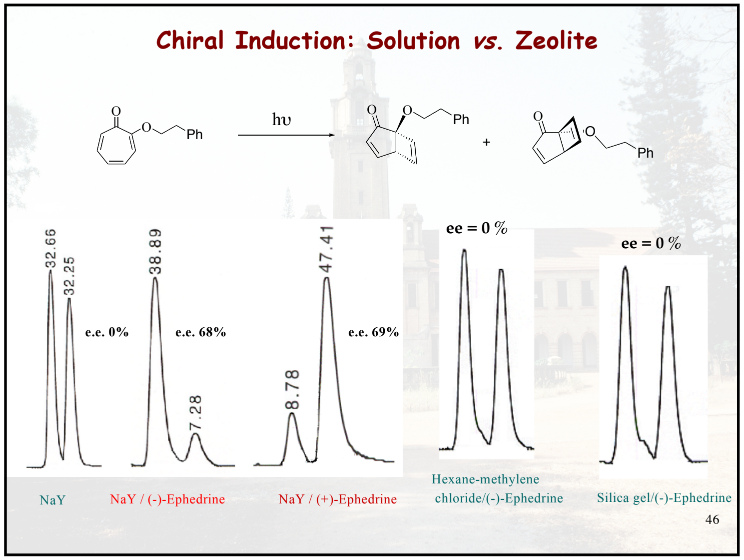


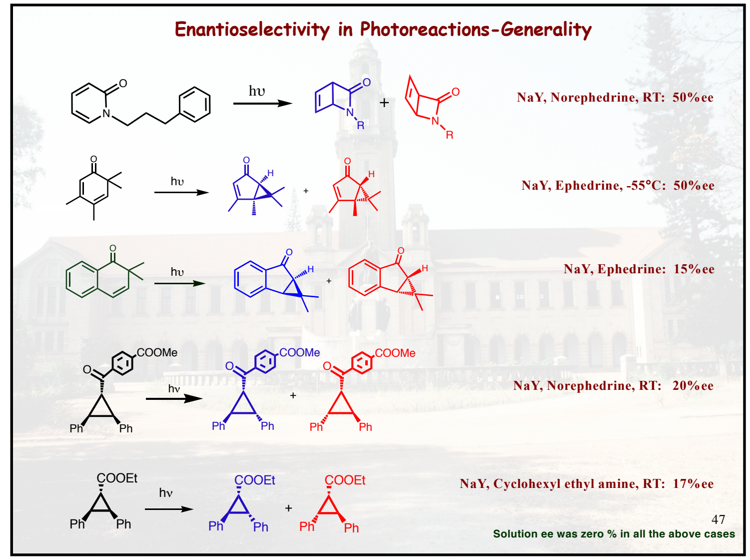


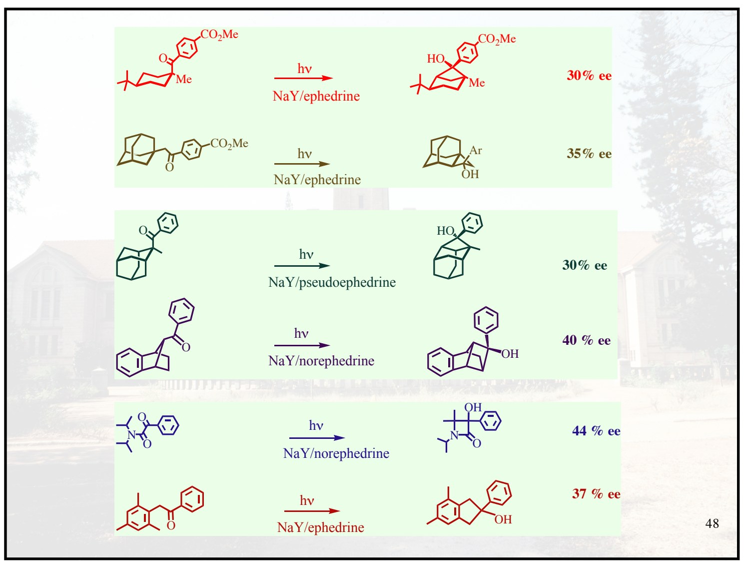
Enantioselective Electrocylization of Achiral Tropolones

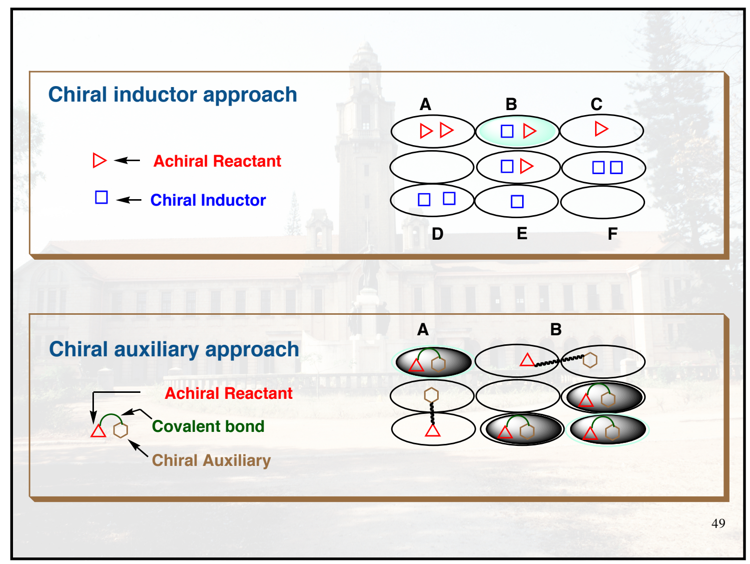


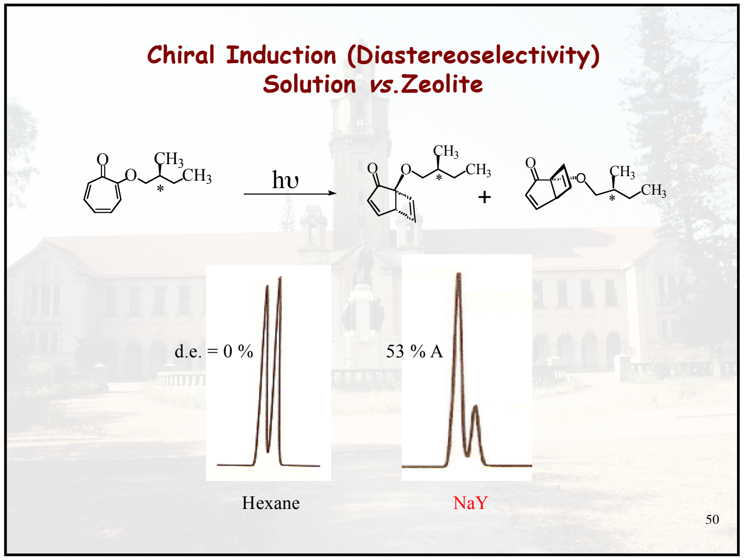
45

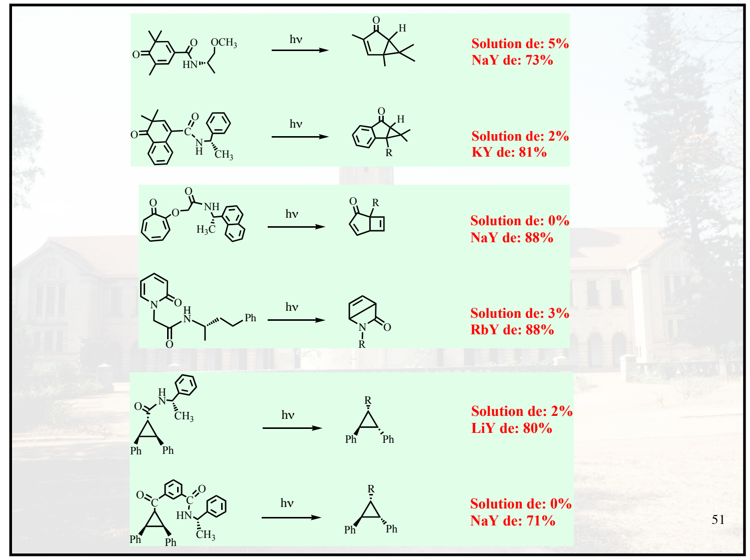

Chiral Induction: Solution vs. Zeolite
hυ
Ph
O
+
32.66
32.25
e.e. 0%
38.89
7.28
e.e. 68%
8.78
47.41
e.e. 69%
ee = 0 %
ee = 0 %
NaY
NaY / (-)-Ephedrine
NaY / (+)-Ephedrine
Hexane-methylene chloride/(-)-Ephedrine
Silica gel/(-)-Ephedrine
46

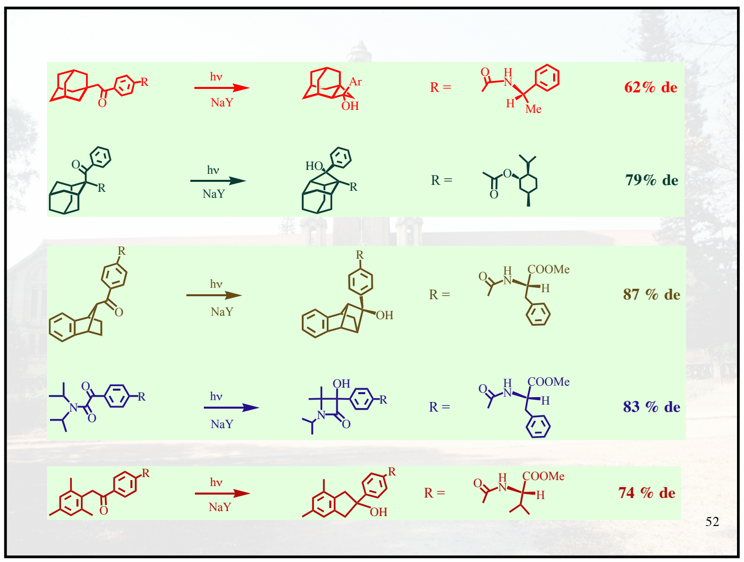

Enantioselectivity in Photoreactions-Generality
hυ
NaY, Norephedrine, RT: 50%ee
NaY, Ephedrine, -55°C: 50%ee
NaY, Ephedrine: 15%ee
COOMe
NaY, Norephedrine, RT: 20%ee
COOEt
Ph
NaY, Cyclohexyl ethyl amine, RT: 17%ee
47
Solution ee was zero % in all the above cases

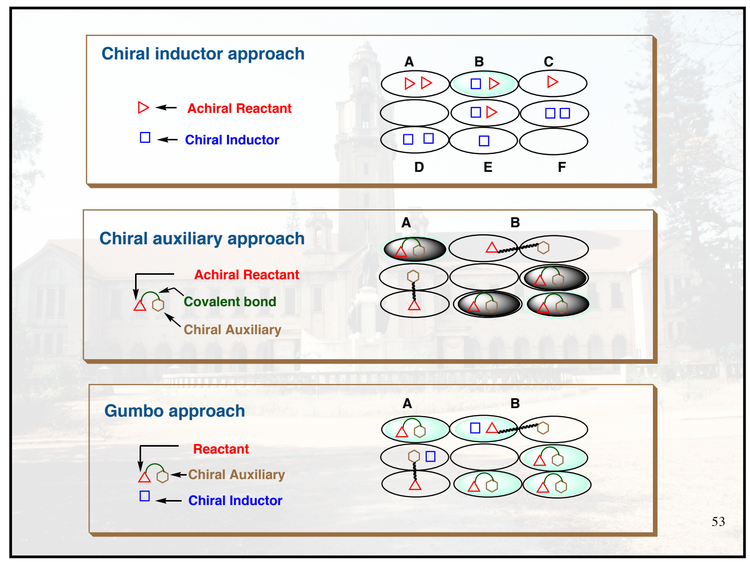

hv
NaY/ephedrine
30% ee
NaY/ephedrine
35% ee
NaY/pseudoephedrine
30% ee
NaY/norephedrine
40 % ee
NaY/norephedrine
44 % ee
NaY/ephedrine
37 % ee
48


Chiral inductor approach
Achiral Reactant
Chiral Inductor
A
B
C
D
E
F
Chiral auxiliary approach
Achiral Reactant
Covalent bond
Chiral Auxiliary
49

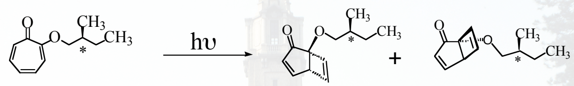

Chiral Induction (Diastereoselectivity)
Solution vs. Zeolite
hυ
d.e. = 0 %
53 % A
Hexane
NaY
50

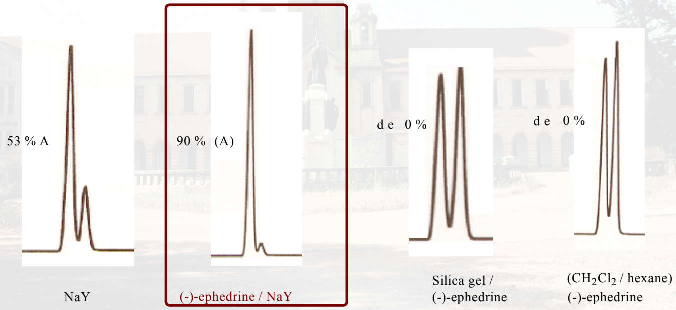

hν
Solution de: 5%
NaY de: 73%
Solution de: 2%
KY de: 81%
Solution de: 0%
NaY de: 88%
Solution de: 3%
RbY de: 88%
Solution de: 2%
LiY de: 80%
Solution de: 0%
NaY de: 71%
51


hν
NaY
R =
62% de
79% de
87 % de
83 % de
74 % de
52


Chiral inductor approach
Achiral Reactant
Chiral Inductor
A
B
C
D
E
F
Chiral auxiliary approach
Achiral Reactant
Covalent bond
Chiral Auxiliary
Gumbo approach
Reactant
Chiral Auxiliary
Chiral Inductor
53

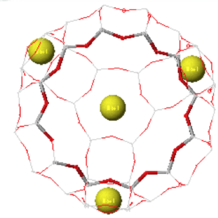
Chiral induction within a chirally modified zeolite





54

Asymmetric Photoreactions Within Zeolites

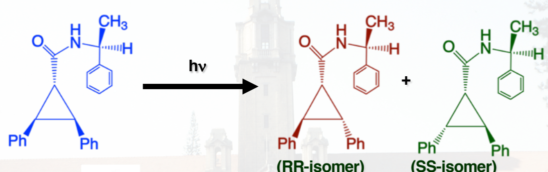


- Chiral Induction Depends on
  - Nature of the Cation
  - Number of Cations (Si/Al ratio)
  - Water Content

Cation is the Key

55

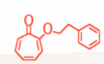
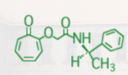
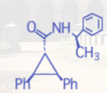
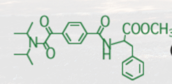
Chiral Induction Depends on the Nature Alkali Metal Ion



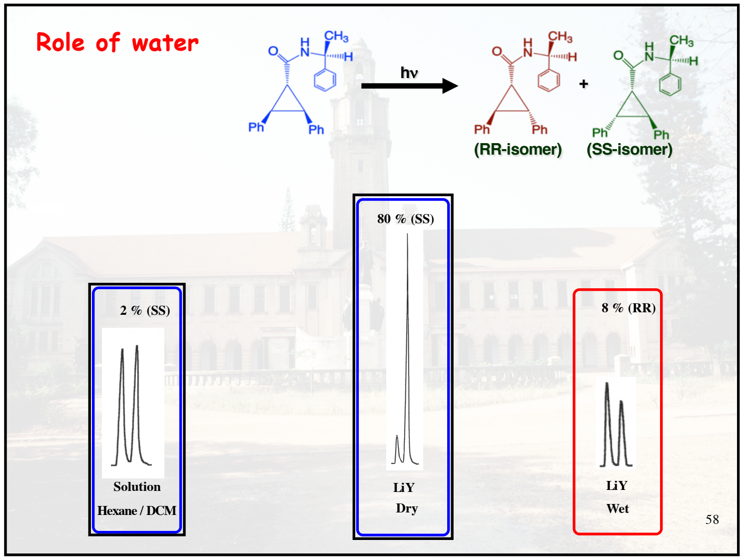
Solution	LiY	NaY	KY	RbY	CsY
2 (SS)	80 (SS)	28 (RR)	14 (RR)	5 (RR)	5 (RR)

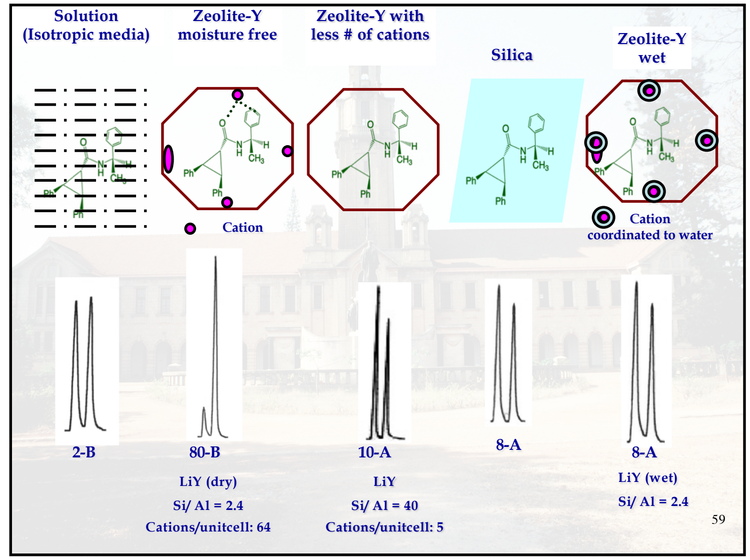
56

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

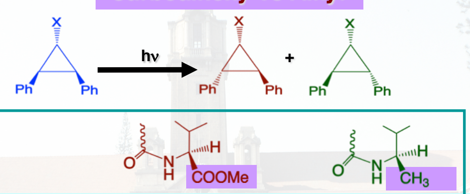
57





Role of Cation-Carbonyl Dipolar Interaction

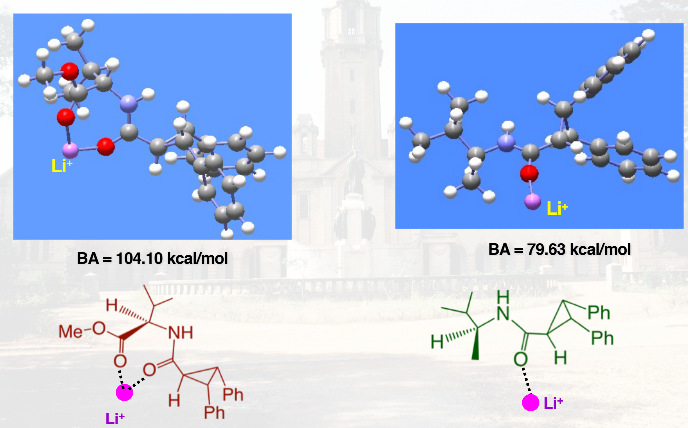
Carboalkoxy *vs* Alkyl



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

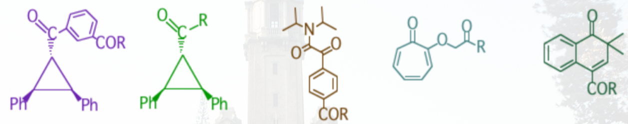
60

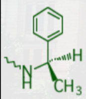
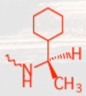
Role of Cation-Carbonyl Dipolar Interaction (HF / 3-21G)



61

Importance of Cation-Chiral Auxiliary Binding: Phenyl vs Cyclohexyl

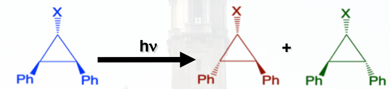


	NaY	LiY	NaY	NaY	KY
	71	80	62	85	81
	30	29	22	45	45

62

Role of Cation-π Quadrupolar Interaction

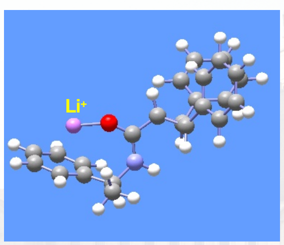
Phenyl *vs* Cyclohexyl



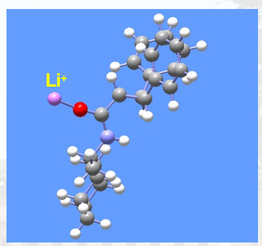
Zeolite	% d.e.	% d.e.
LiY	80-B	29-B
NaY	28-A	24-A
KY	14-A	26-A
RbY	5-A	29-A
CsY	5-A	37-A
Solution	2-B	2-B

63

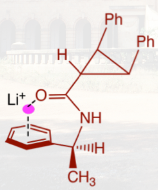
Role of Cation-π Quadrupolar Interaction$_{(HF / 3-21G)}$

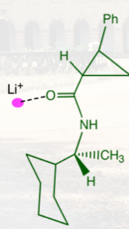


BA = 91.3 kcal/mol



BA = 80.26 kcal/mol

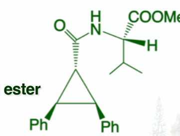


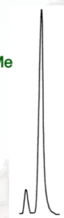


64

Cation Dependent Diastereomer Switch

Amide of L-Valine methyl ester

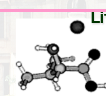




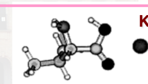
LiY 83 (SS)

KY 80 (RR)

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



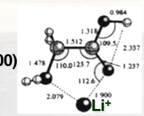
Valine



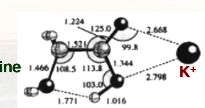
NO - Co-ordination

OO - Co-ordination

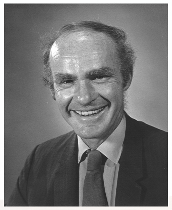
Bowers, M. T. et. al., JACS, 2001, 122, 3458-3464, (2000)



Glycine

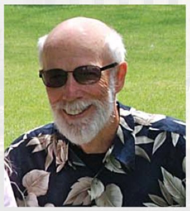


65


G. S. Hammond


M. Lahav


F. Toda


J. R. Scheffer


T. Bach


Y. Inoue