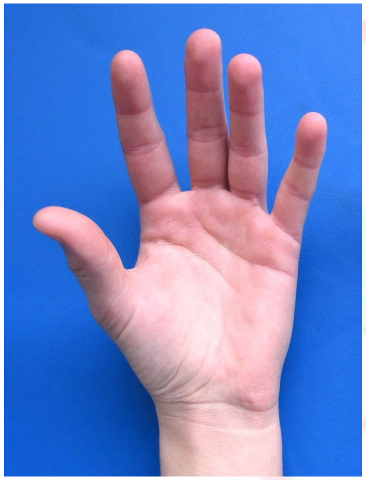
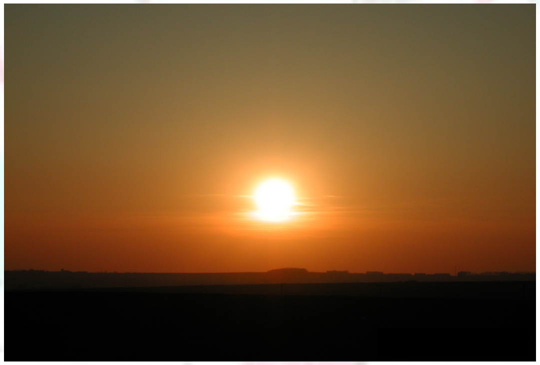
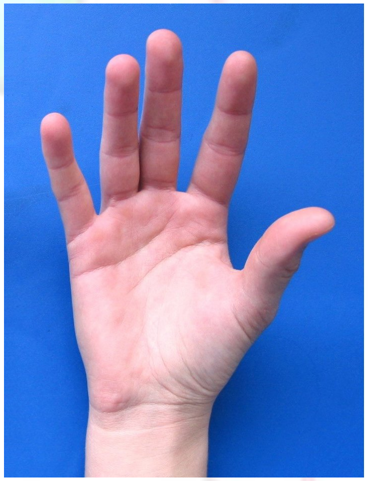
Chiral Photochemistry



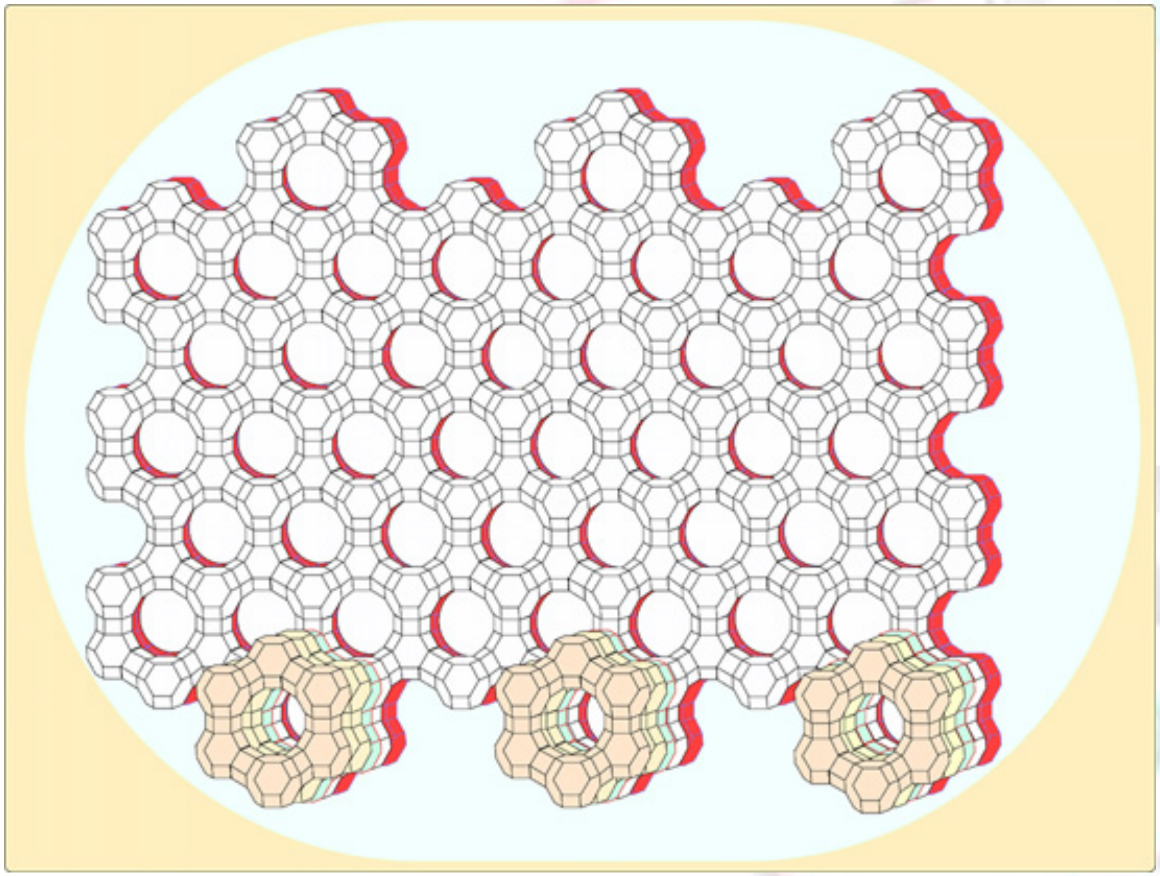


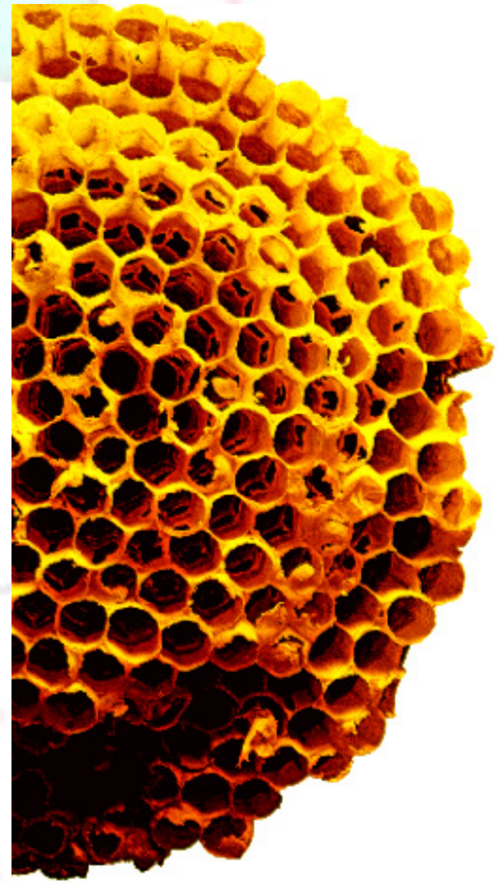


- Crystals
- Zeolites
- Solution

Chemistry in Confined Spaces

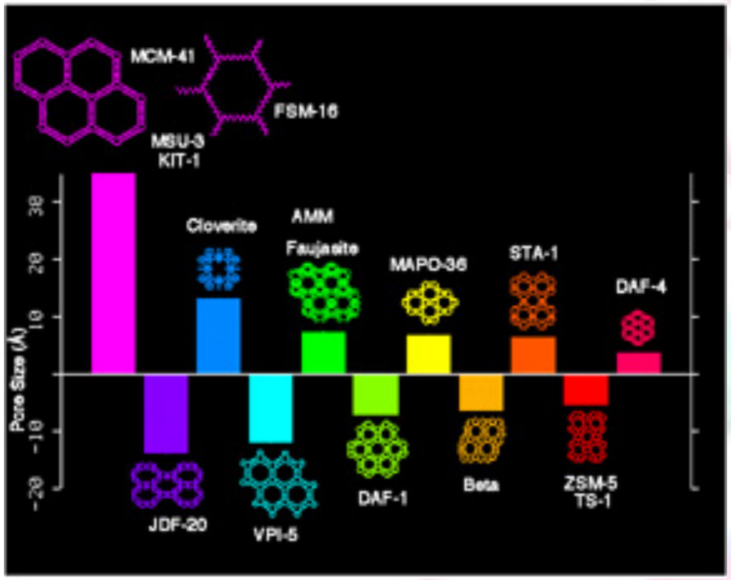
-- a single cupful has enough surface area to cover 20 football fields.



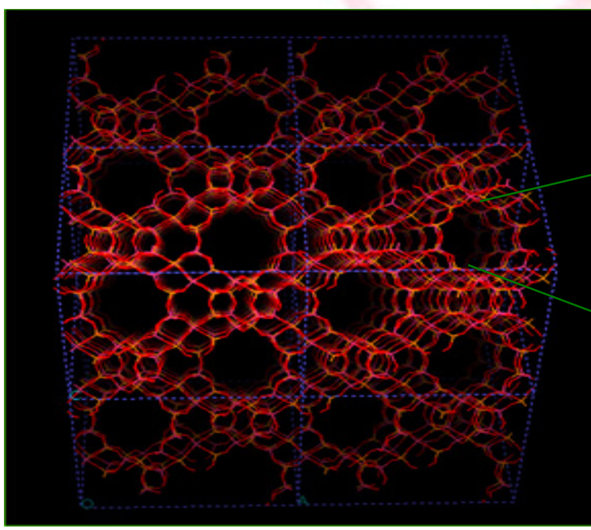


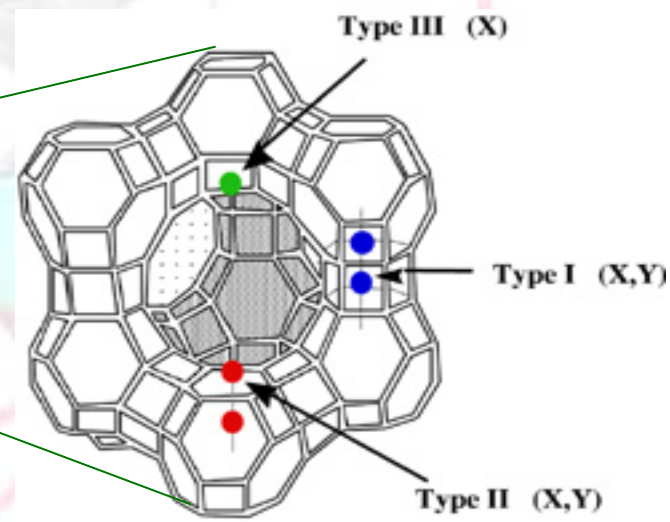
Characteristics of Zeolites

$$M_x(AlO_2)_x(SiO_2)_y.z\ H_2O$$

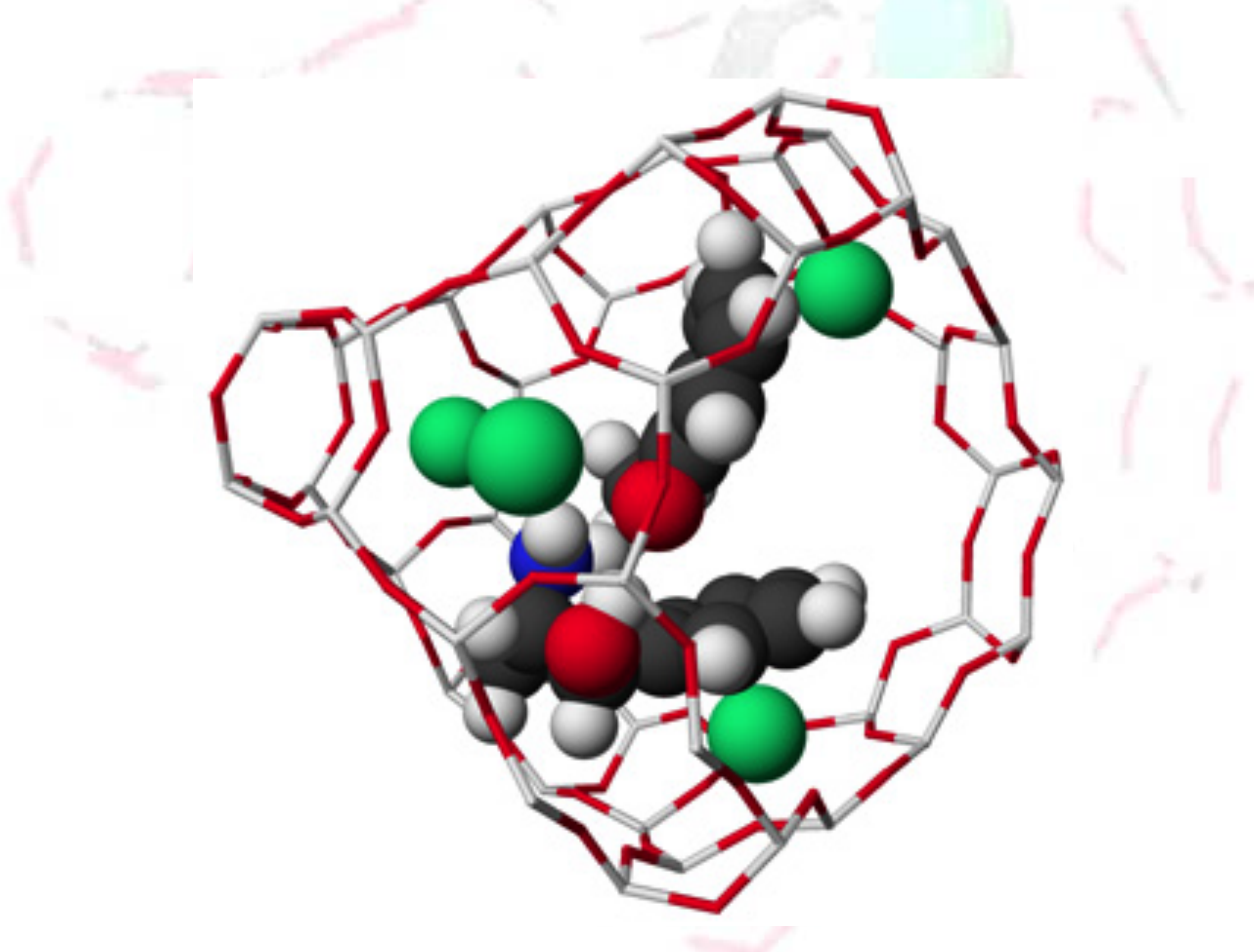


- Crystalline white powder
- Microporous solid
- Large surface area
- Well defined large pores
- Channels and cages

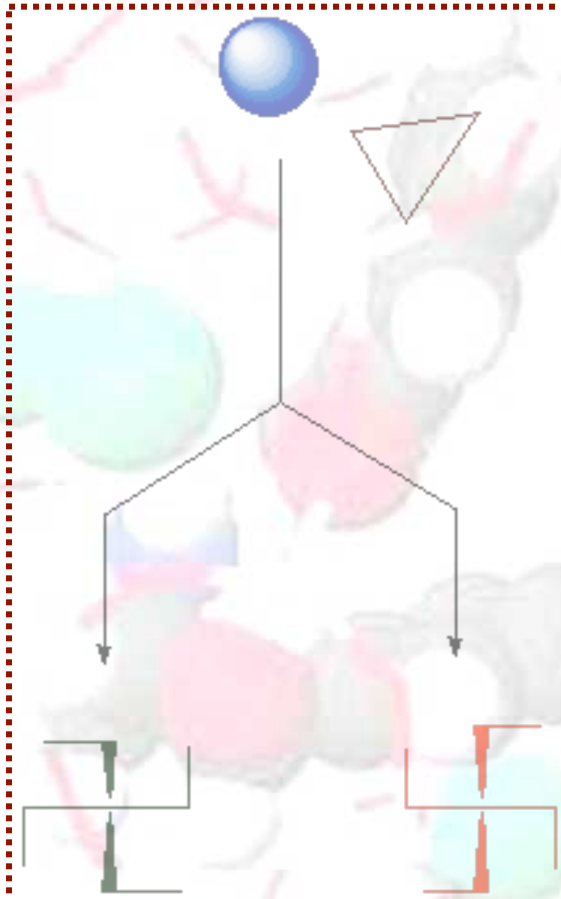




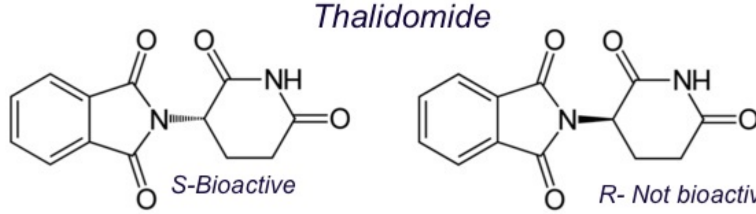
Asymmetric Photoreactions Within Chirally Modified Zeolites



Why Chiral Chemistry



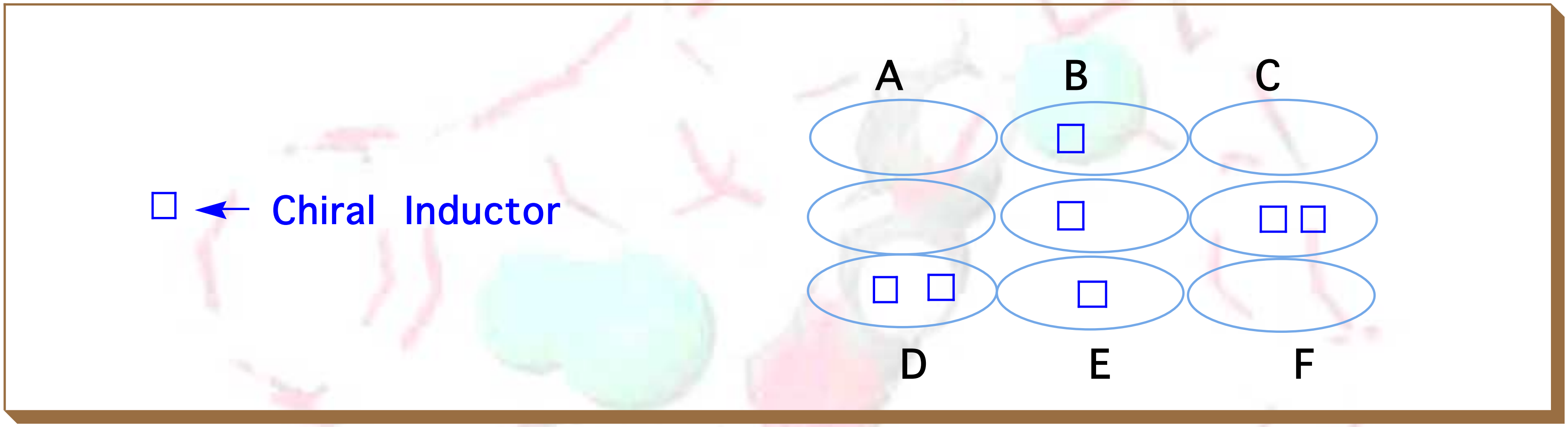
Thalidomide

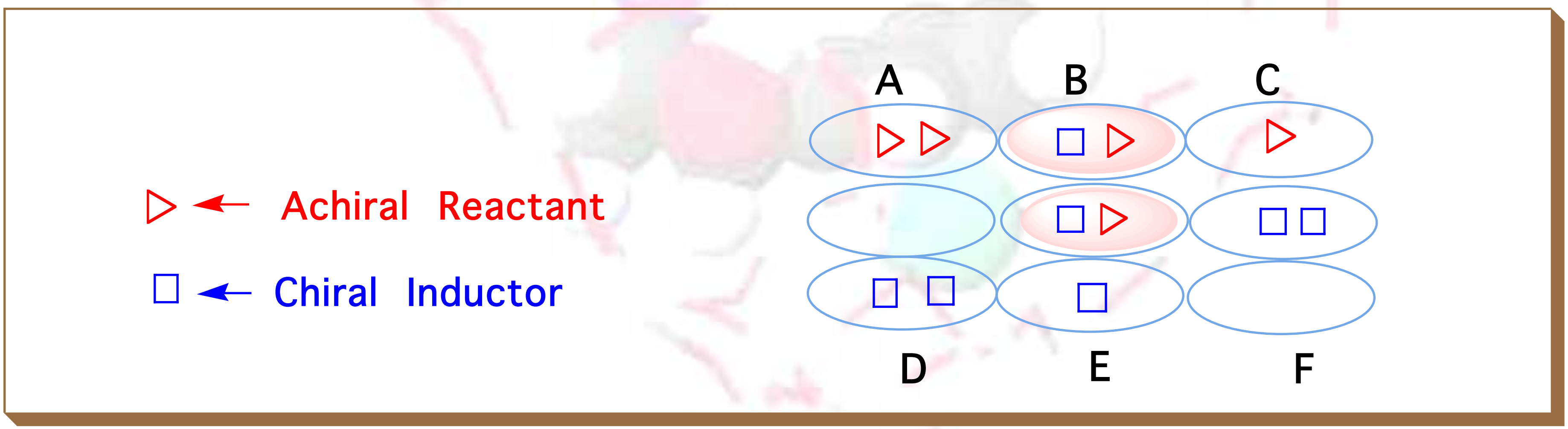


S-Bioactive

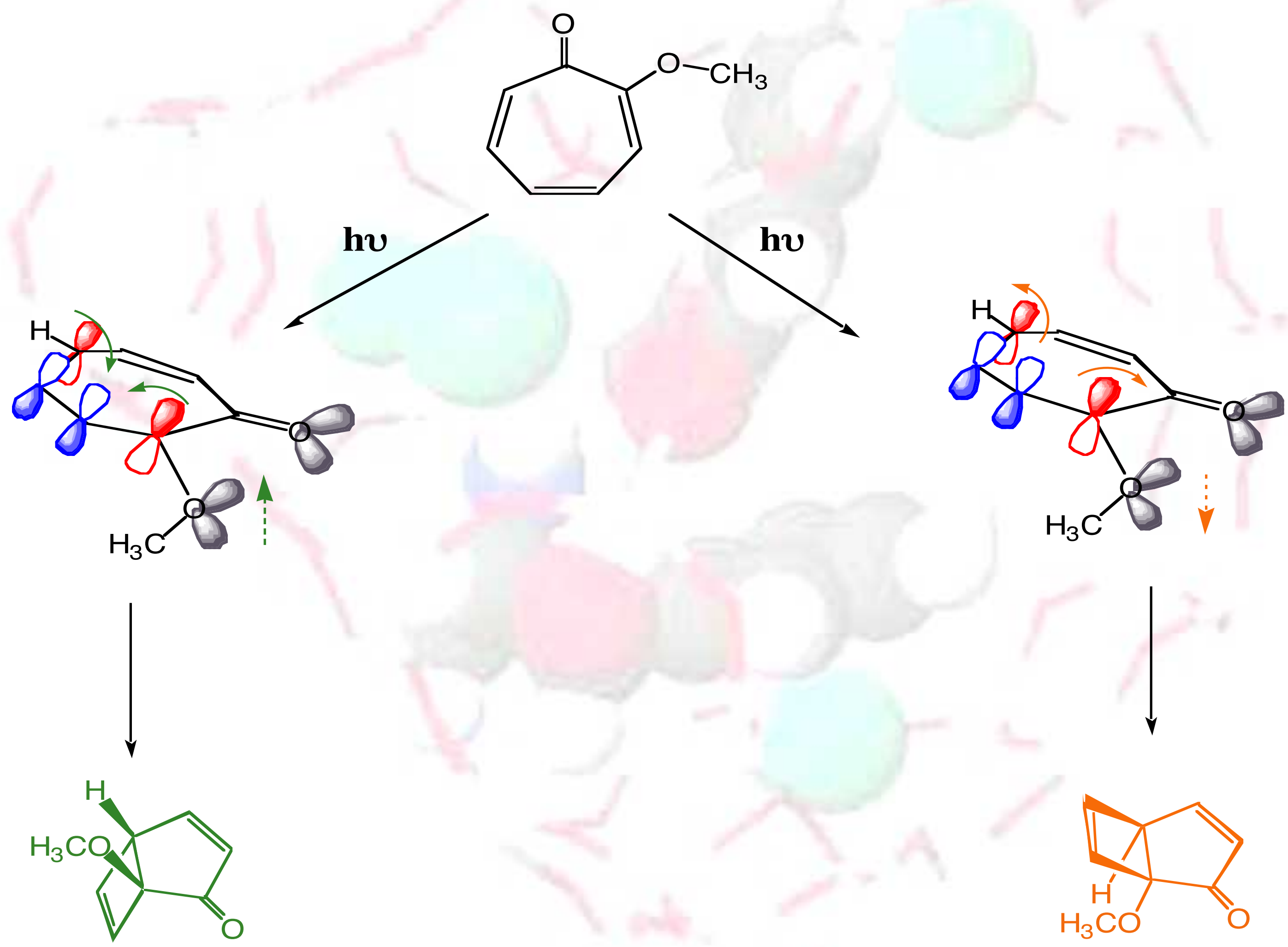
R- Not bioactive

Chiral inductor approach

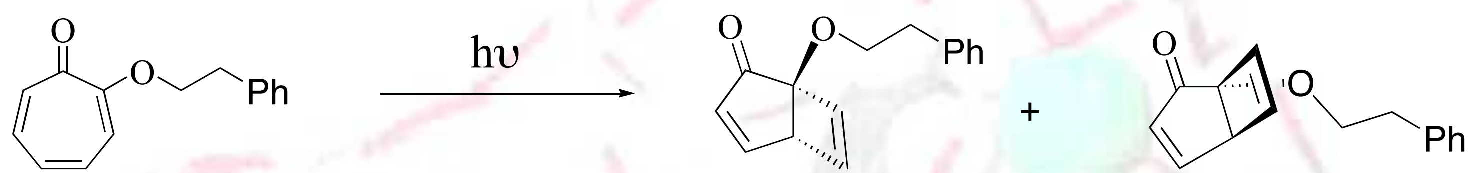


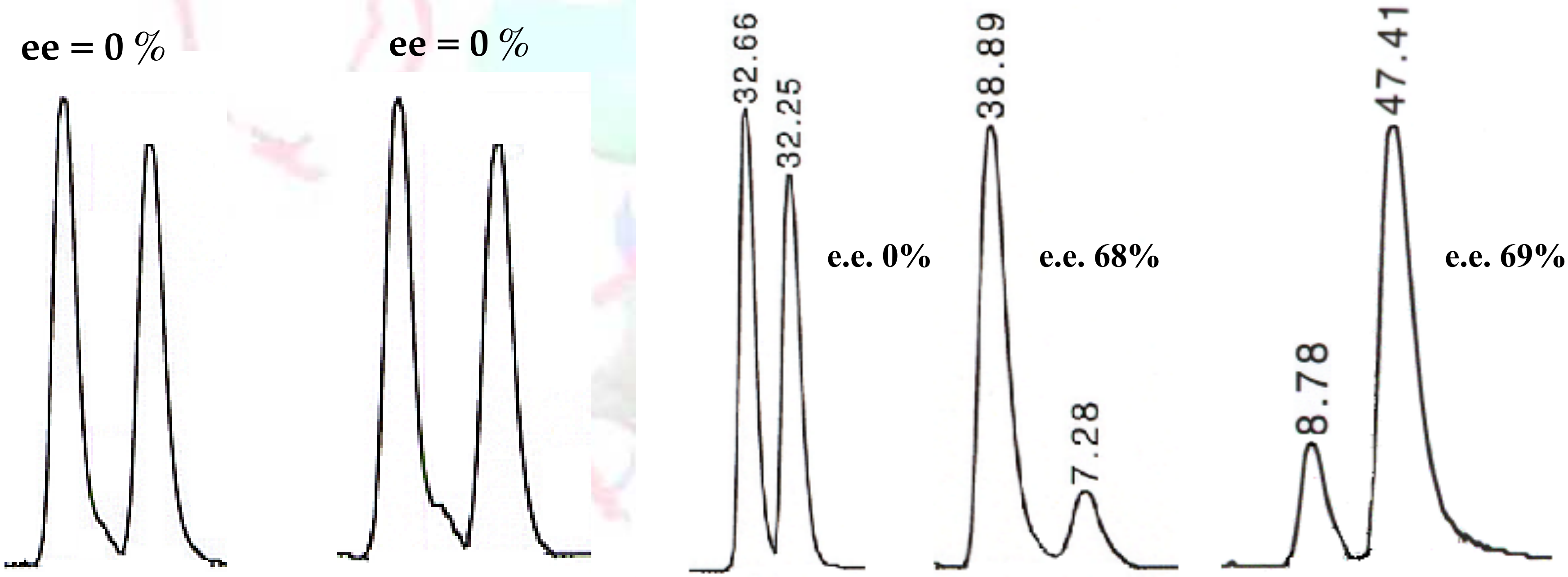


Enantioselective Electrocylization of Tropolones



Chiral induction: Solution vs. Zeolite





Hexane-methylene chloride/(-)-Ephedrine

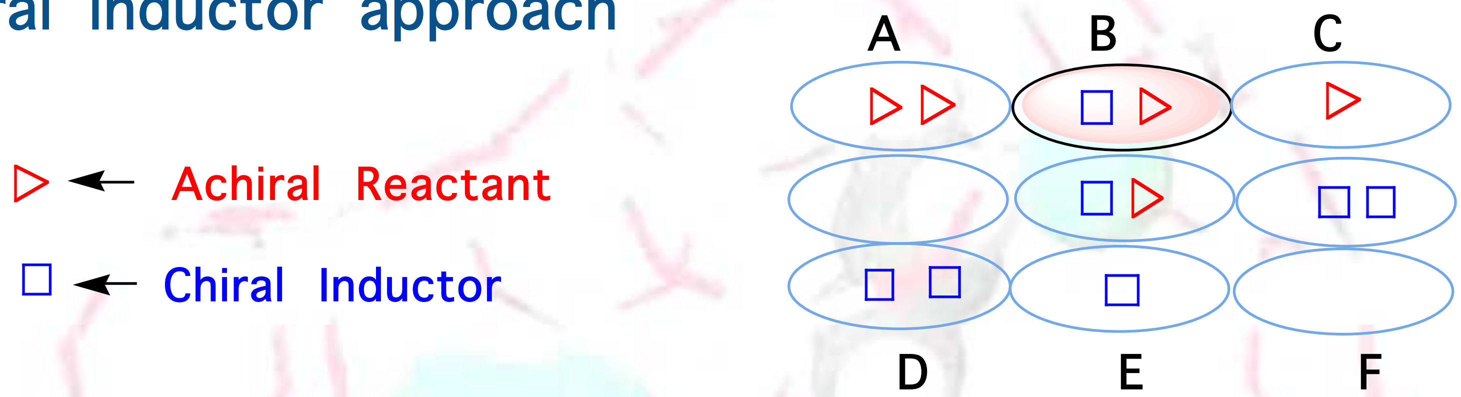
Silica gel/(-)-Ephedrine

NaY

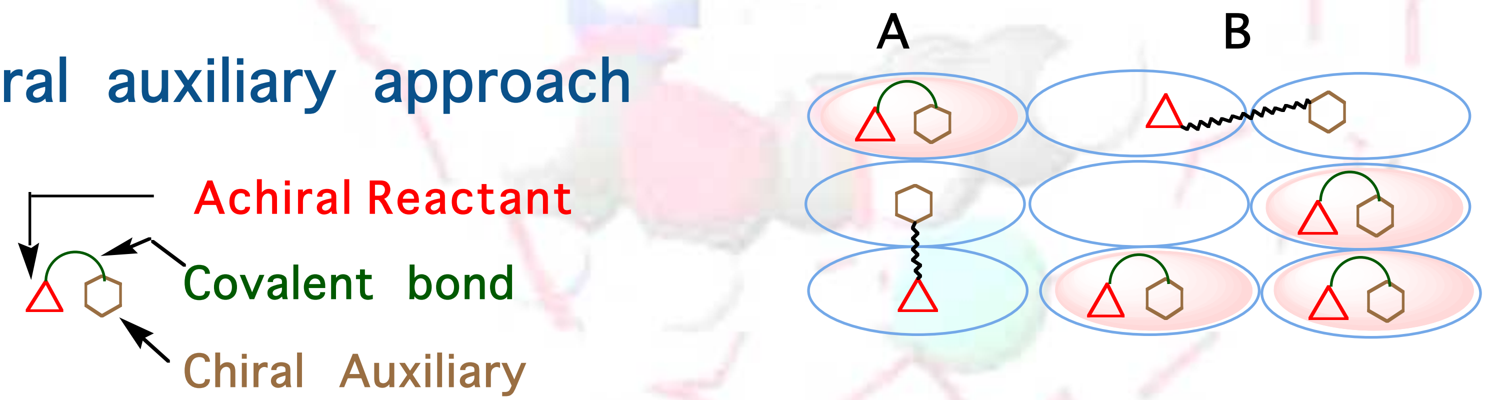
NaY / (-)-Ephedrine

NaY / (+)-Ephedrine

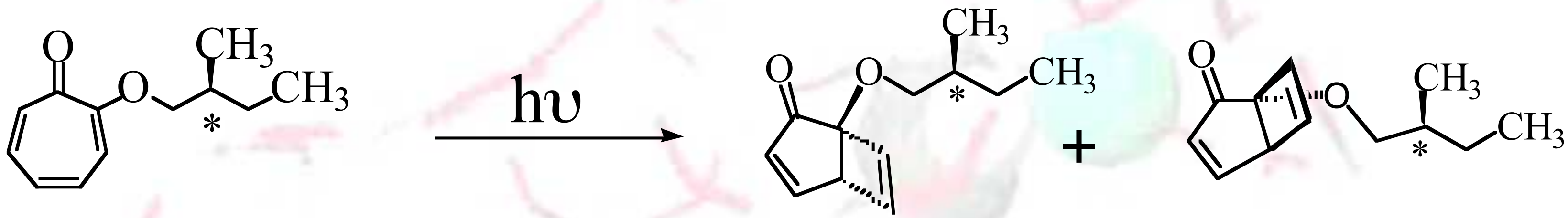
Chiral inductor approach

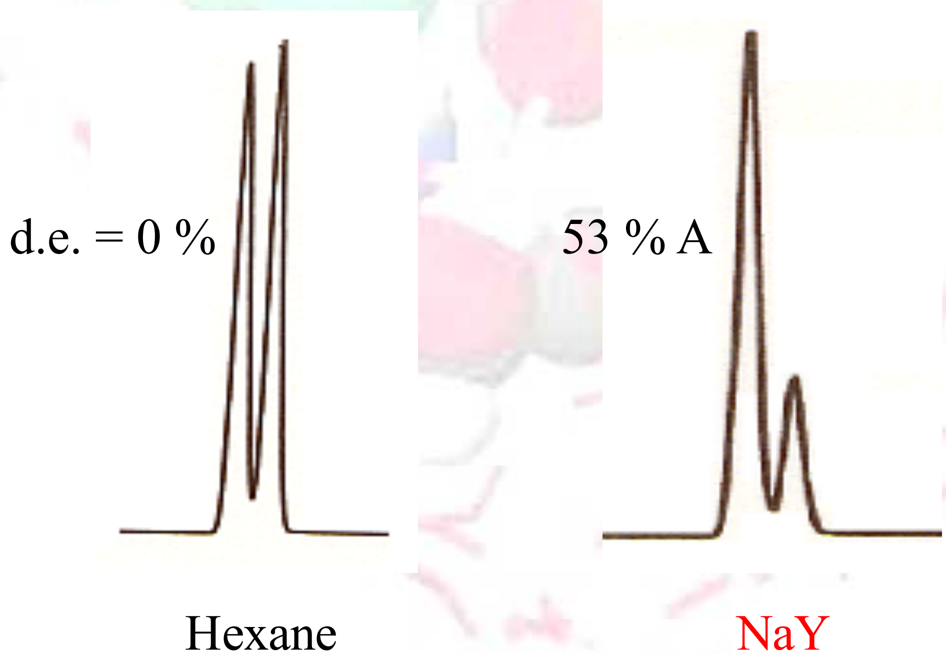


Chiral auxiliary approach

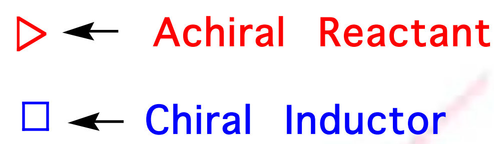


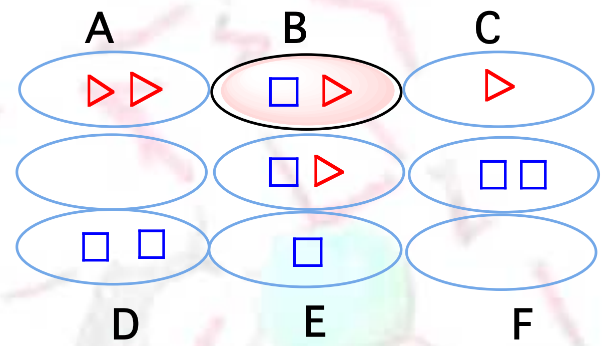
Chiral induction: Solution vs. Zeolite



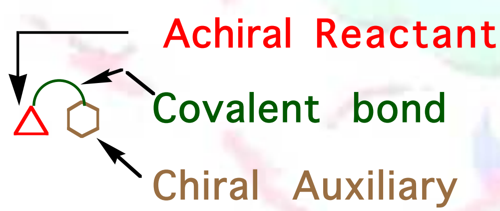


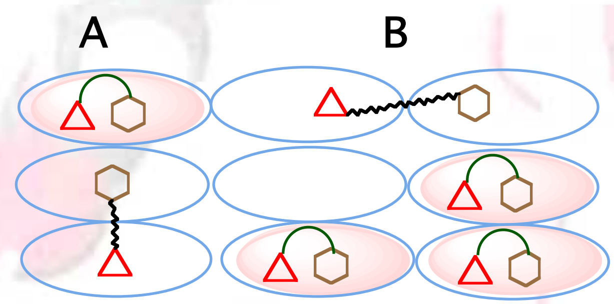
Chiral inductor approach



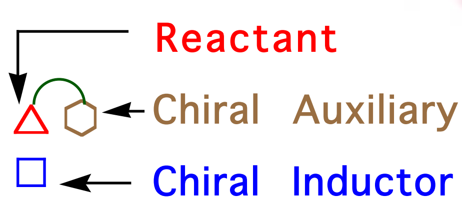


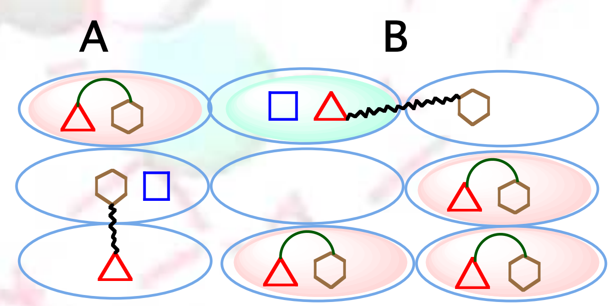
Chiral auxiliary approach



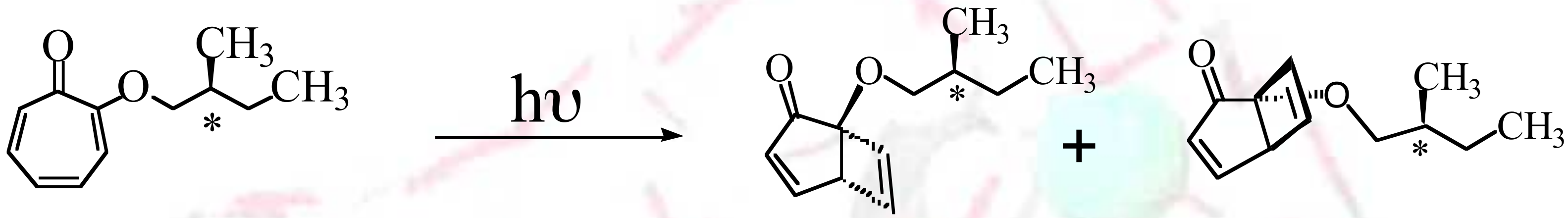


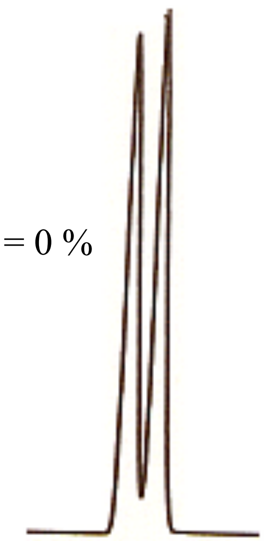
Gumbo approach





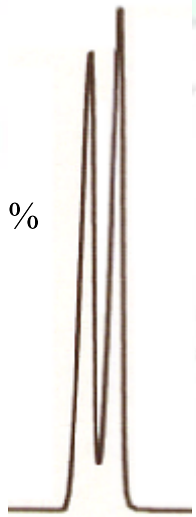
Chiral induction within a chirally modified zeolite





d e = 0 %

Hexane

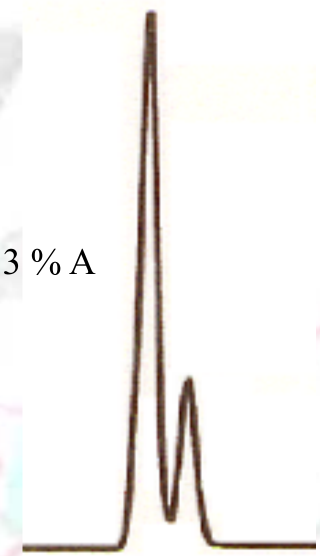


d e 0 %

(CH_2Cl_2 / hexane)
(-)-ephedrine

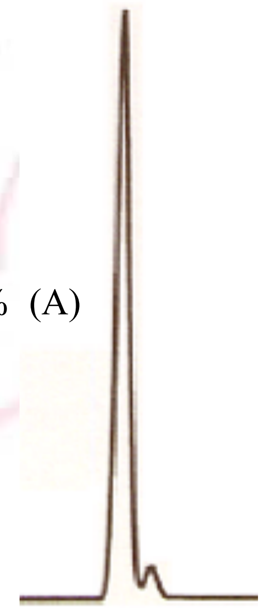
d e 0 %

Silica gel /
(-)-ephedrine



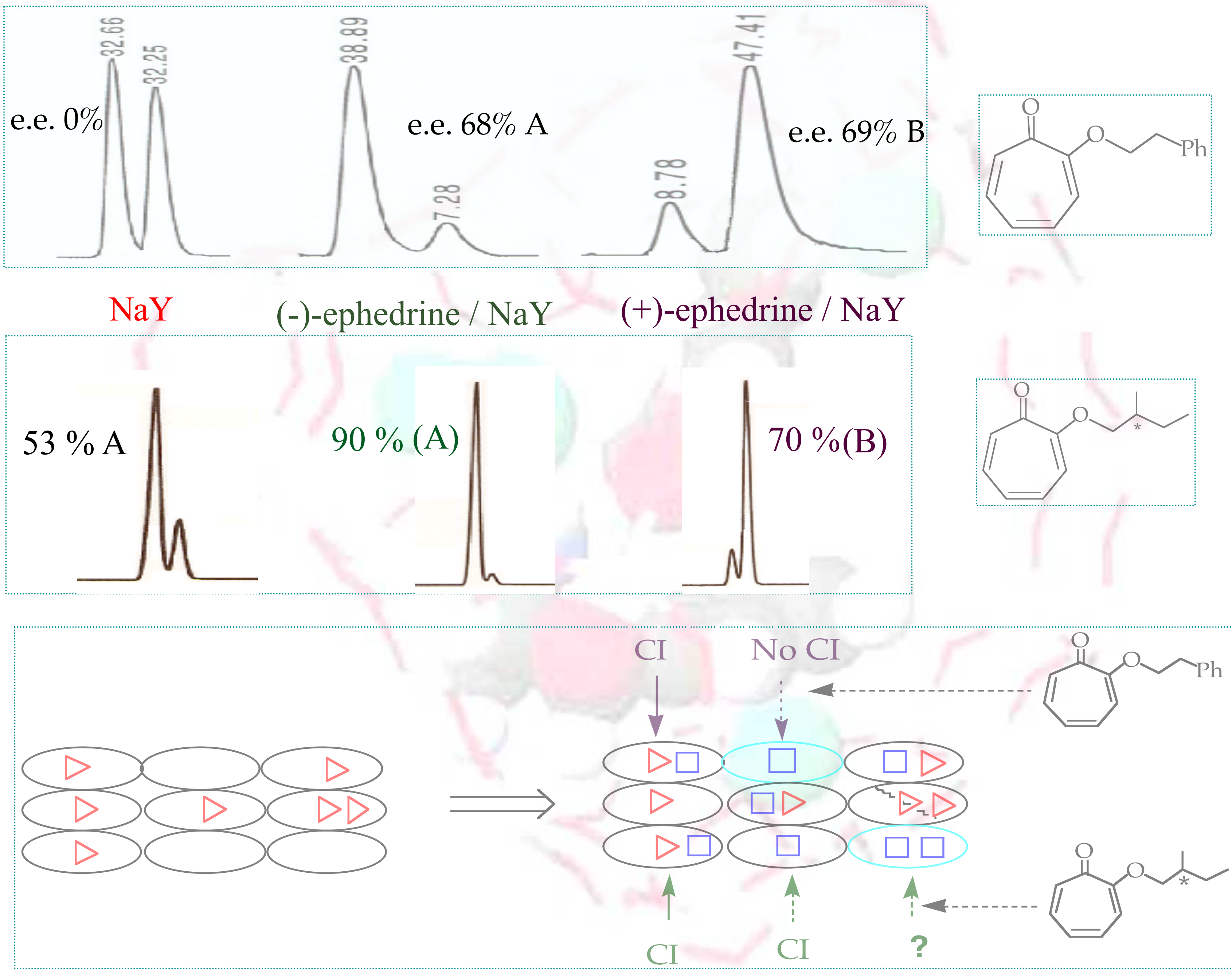
53 % A

NaY

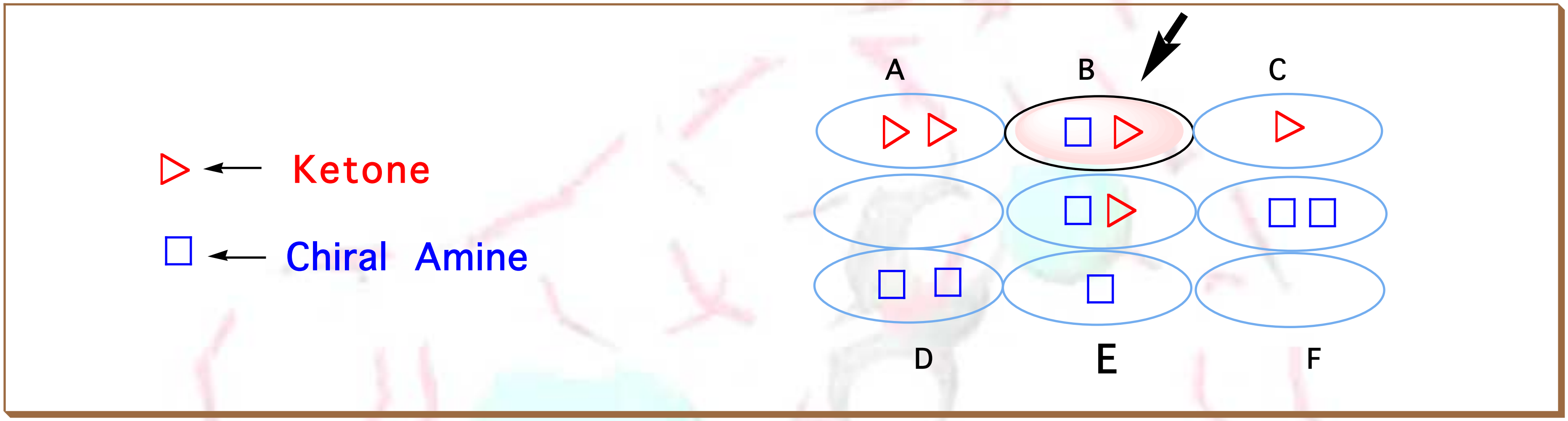


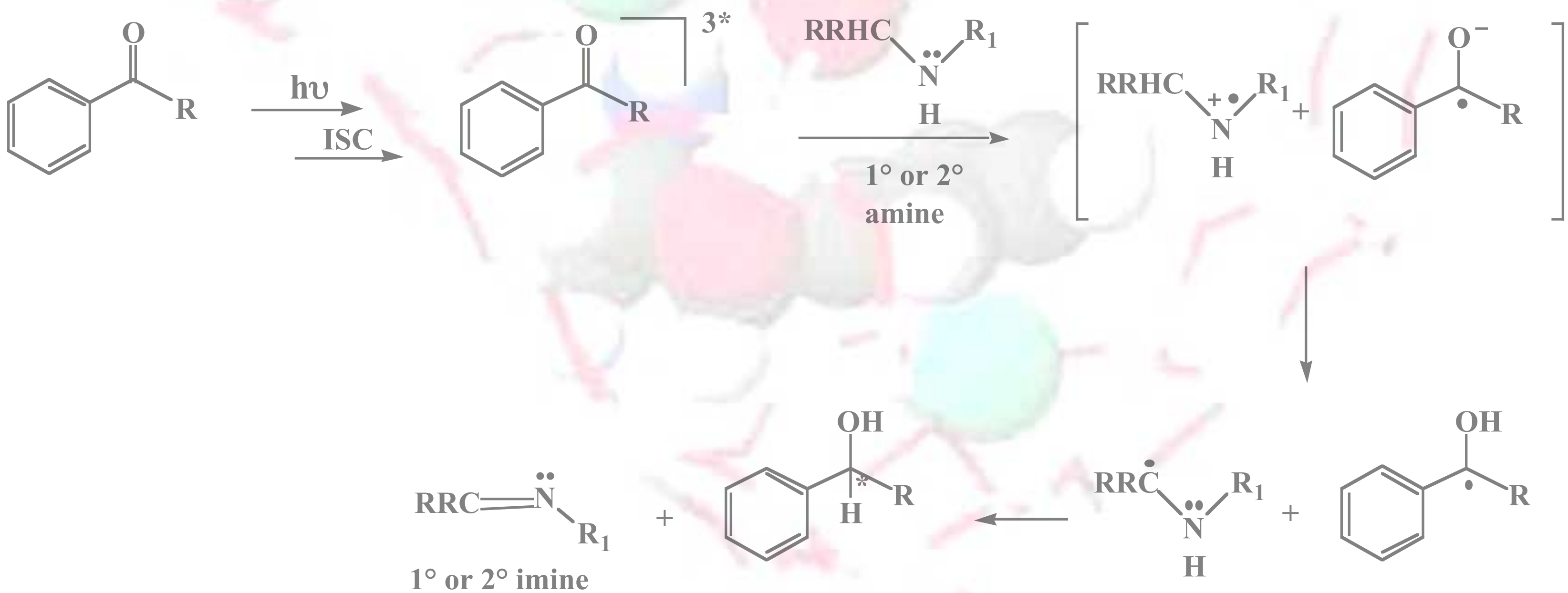
90 % (A)

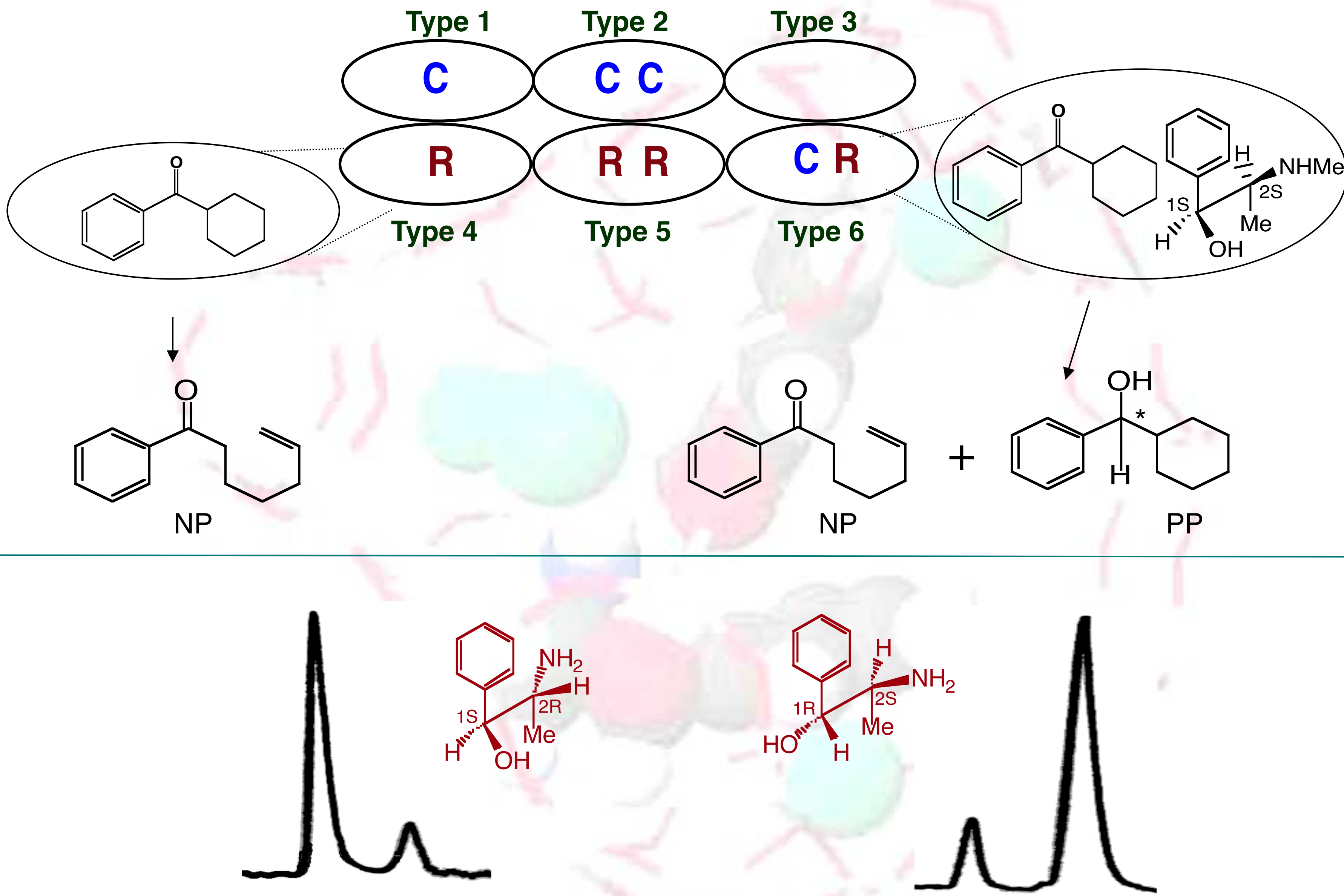
(-)-ephedrine / NaY



e.e. 0%
32.66
32.25
38.89
e.e. 68% A
7.28
8.78
47.41
e.e. 69% B
O
O
Ph
NaY
(-)-ephedrine / NaY
(+)-ephedrine / NaY
53 % A
90 % (A)
70 %(B)
O
O
*
CI
No CI
O
O
Ph
O
O
*
CI
CI
?


Ketone
Chiral Amine
A
B
C
D
E
F

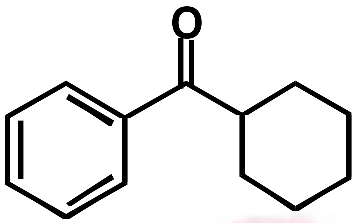

hυ
ISC
3*
RRHC
R1
H
1° or 2° amine
1° or 2° imine



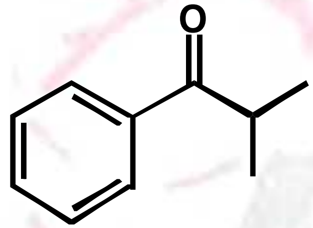
(+) Norephedrine 68% R
R(+)Cyclohexyl benzyl alcohol

(-) Norephedrine 67% S
S(-)-Cyclohexyl benzyl alcohol

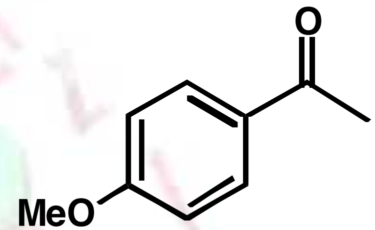
Photoreduction of Aryl alkyl ketones: Generality



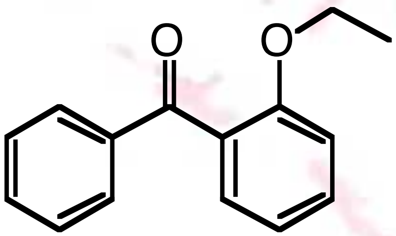
Norephedrine - 68%ee



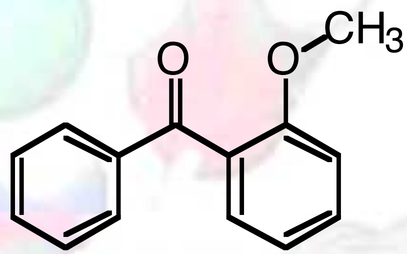
Norephedrine-50%ee



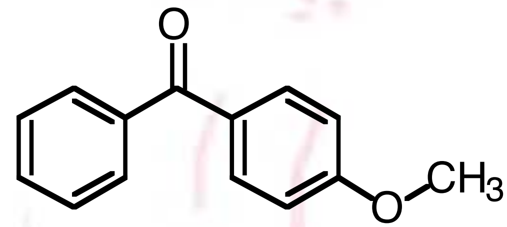
Ephedrine - 47%ee



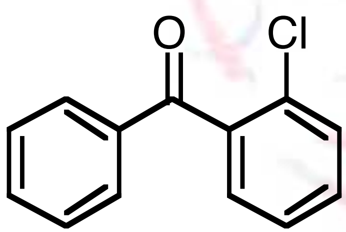
Pseudoephedrine -43%ee



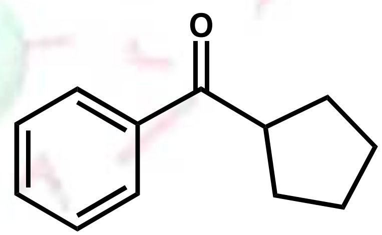
1,2-Diaminocyclohexane-44%ee



Ephedrine-45%ee



Ephedrine-34%ee

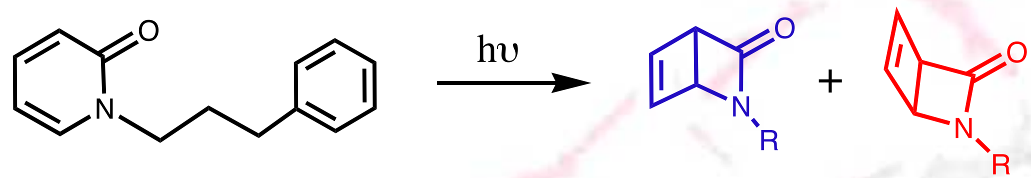


Pseudoephedrine - 30%ee

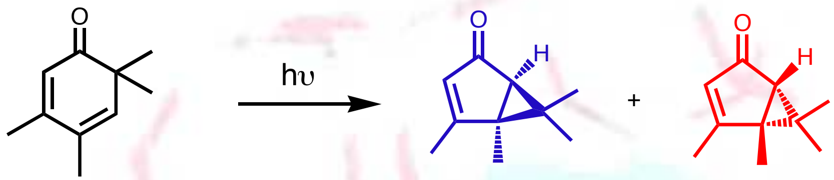
Asymmetric Photoreactions Within Zeolites

- **Modest to Good Chiral Induction**
- **Chiral Induction Depends on**
  - Reaction and Reactant
  - **Chiral Inductor and Chiral Auxiliary**
  - **Nature of the Cation**
  - **Number of Cations (Si/Al ratio)**
  - **Water Content**
  - **Mechanism of the Reaction**
  - **Reactive State (S_1 vs T_1)**

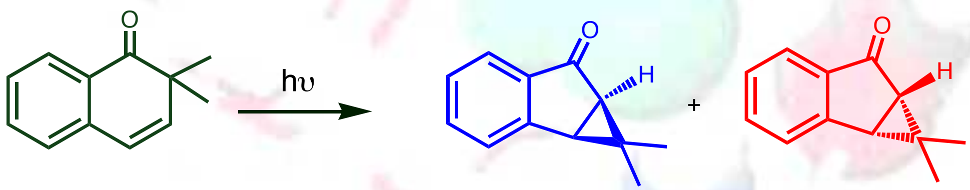
Enantioselectivity in Photoreactions-Generality



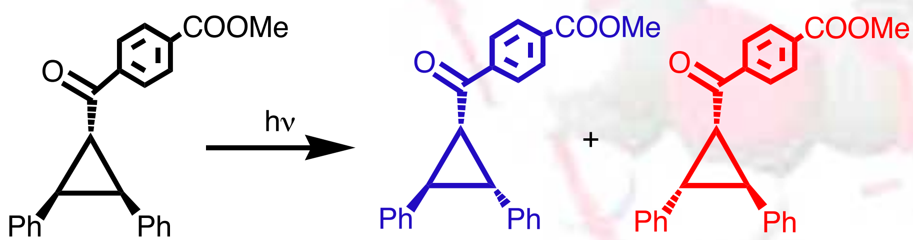
NaY, Norephedrine, RT: 50%ee



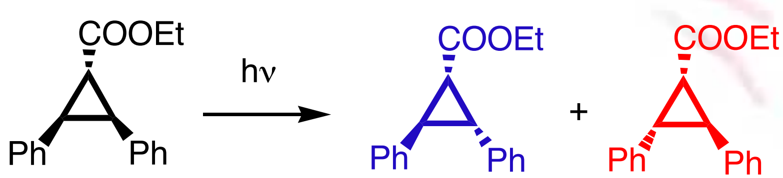
NaY, Ephedrine, -55°C: 50%ee



NaY, Ephedrine: 15%ee

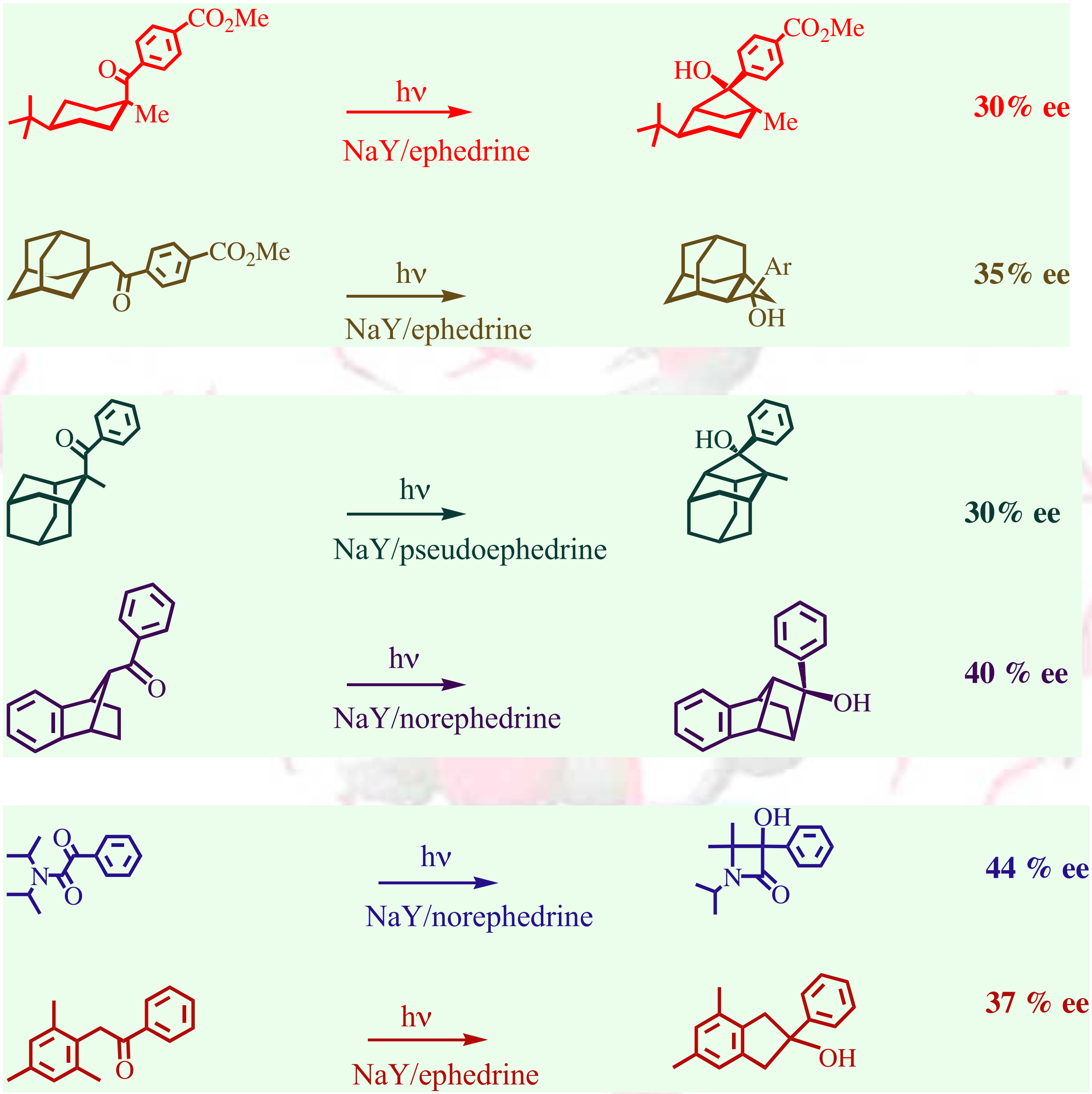


NaY, Norephedrine, RT: 20%ee

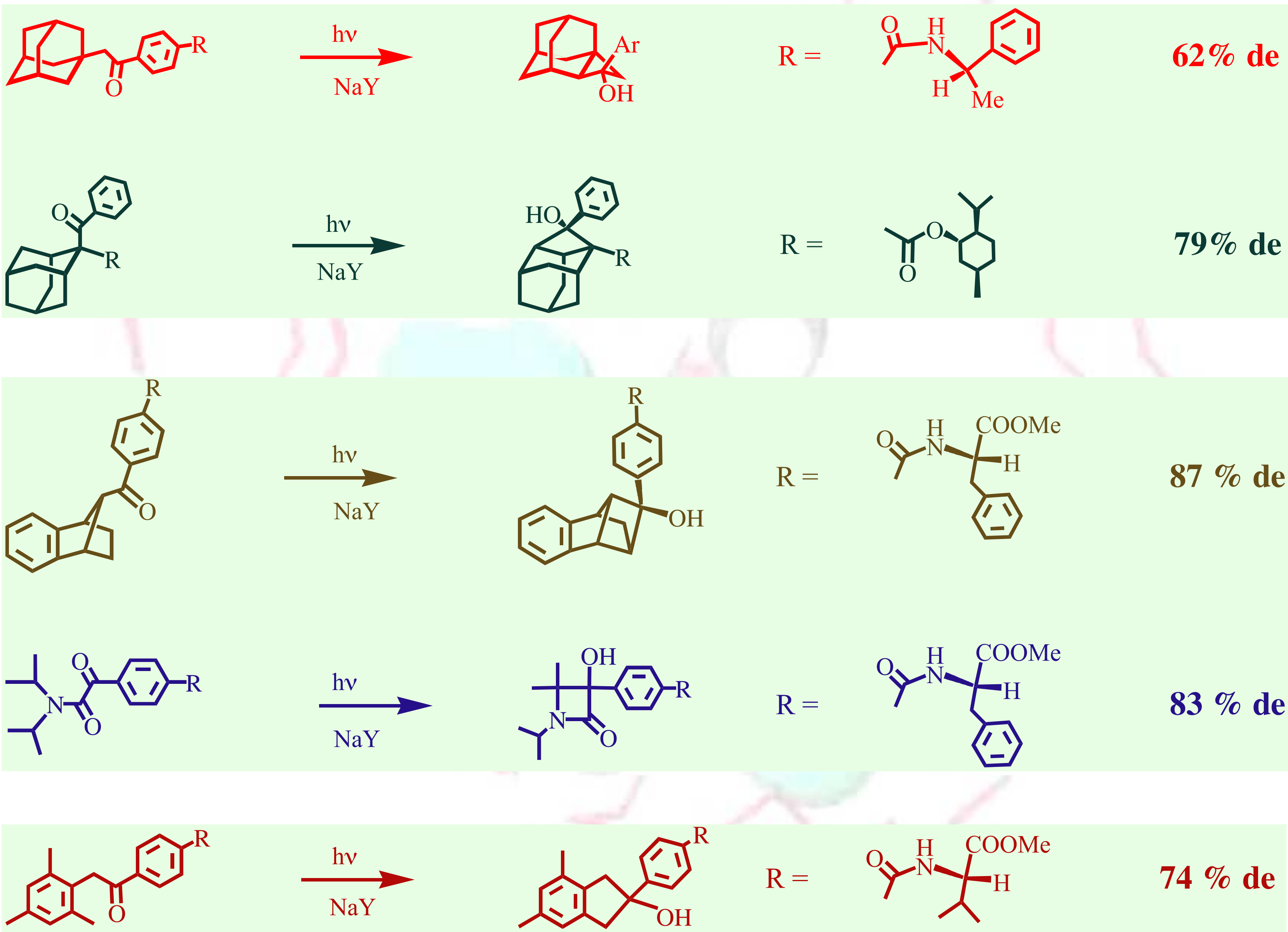


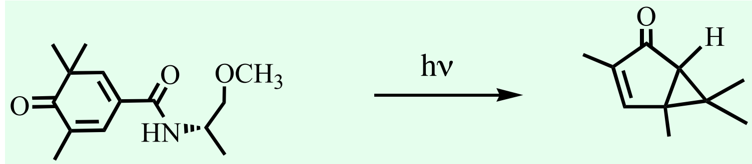
NaY, Cyclohexyl ethyl amine, RT: 17%ee

Solution ee was zero % in all the above cases

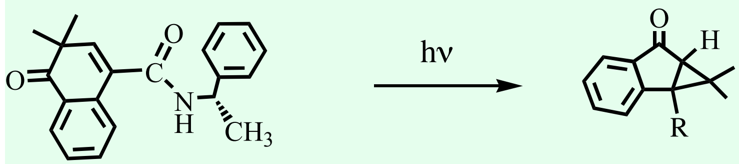


CO2Me
O
Me
hν
NaY/ephedrine
HO
CO2Me
Me
30% ee
CO2Me
O
hν
NaY/ephedrine
Ar
OH
35% ee
O
hν
NaY/pseudoephedrine
HO
30% ee
O
hν
NaY/norephedrine
OH
40 % ee
O
N
O
hν
NaY/norephedrine
OH
N
O
44 % ee
O
hν
NaY/ephedrine
OH
37 % ee

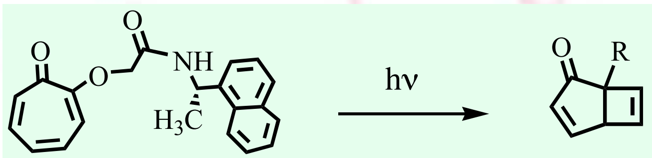

hν
NaY
62% de
hν
NaY
79% de
hν
NaY
87 % de
hν
NaY
83 % de
hν
NaY
74 % de



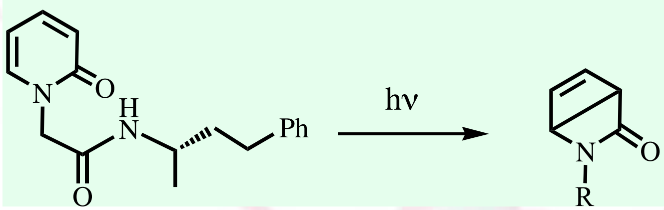
Solution de: 5%
NaY de: 73%



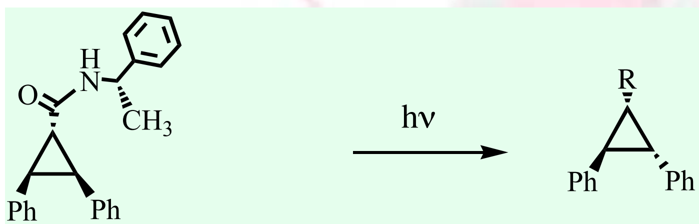
Solution de: 2%
KY de: 81%



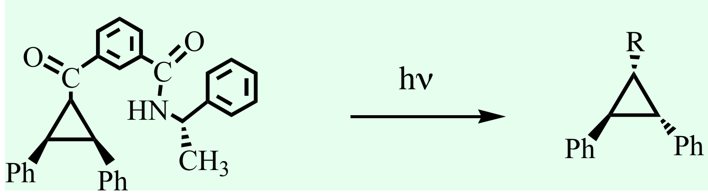
Solution de: 0%
NaY de: 88%



Solution de: 3%
RbY de: 88%



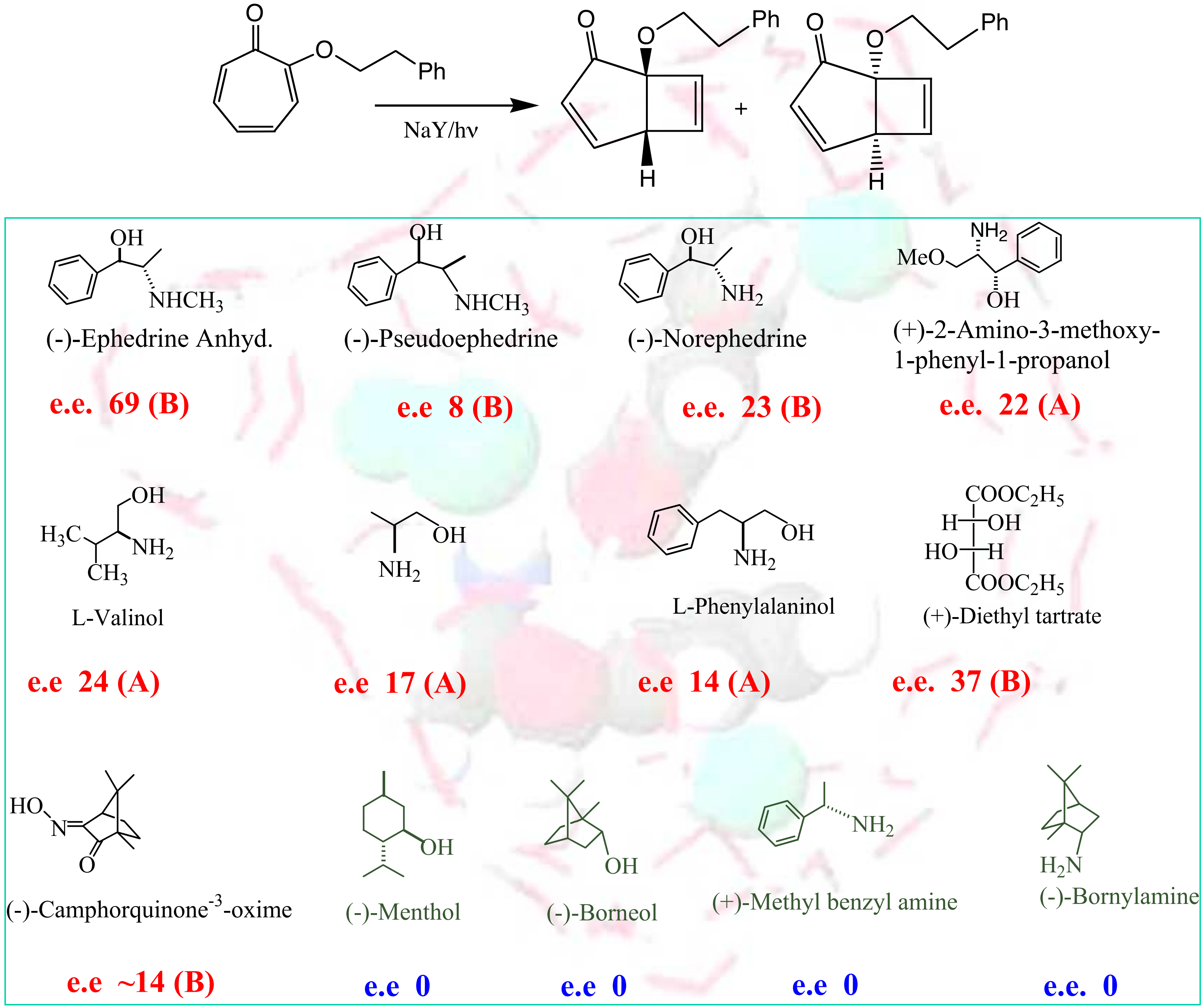
Solution de: 2%
LiY de: 80%



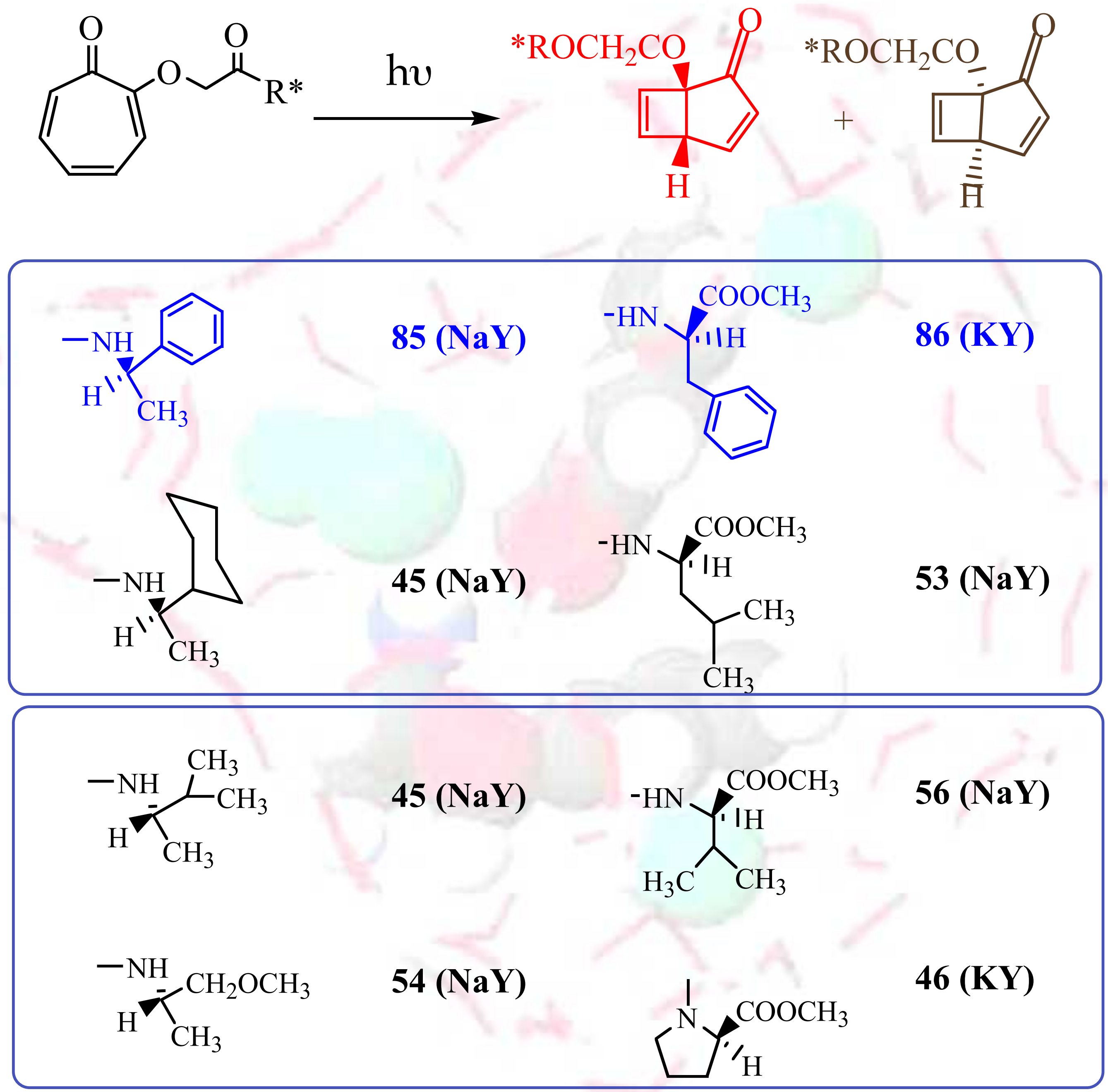
Solution de: 0%
NaY de: 71%

Asymmetric Photoreactions Within Zeolites

- **Modest to Good Chiral Induction**
- **Chiral Induction Depends on**
  - **Reaction and Reactant**
  - Chiral Inductor and Chiral Auxiliary
  - **Nature of the Cation**
  - **Number of Cations (Si/Al ratio)**
  - **Water Content**
  - **Mechanism of the Reaction**
  - **Reactive State (S_1 vs T_1)**



NaY/hν
(-)-Ephedrine Anhyd.
e.e. 69 (B)
(-)-Pseudoephedrine
e.e 8 (B)
(-)-Norephedrine
e.e. 23 (B)
(+)-2-Amino-3-methoxy-1-phenyl-1-propanol
e.e. 22 (A)
L-Valinol
e.e 24 (A)
e.e 17 (A)
L-Phenylalaninol
e.e 14 (A)
(+)-Diethyl tartrate
e.e. 37 (B)
(-)-Camphorquinone-3-oxime
e.e ~14 (B)
(-)-Menthol
e.e 0
(-)-Borneol
e.e 0
(+)-Methyl benzyl amine
e.e 0
(-)-Bornylamine
e.e. 0

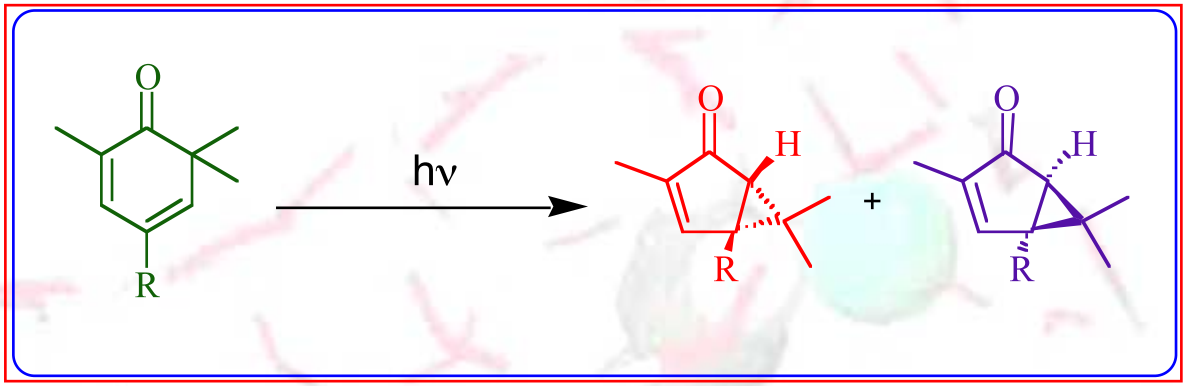


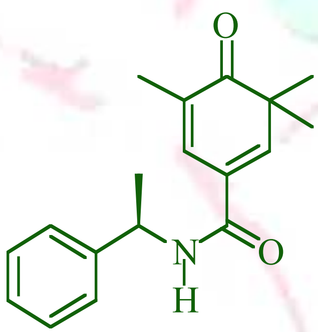
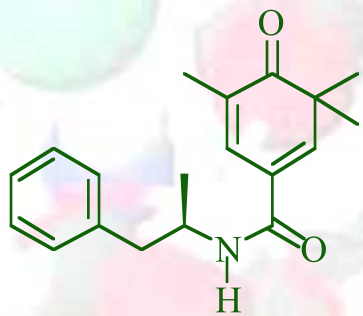
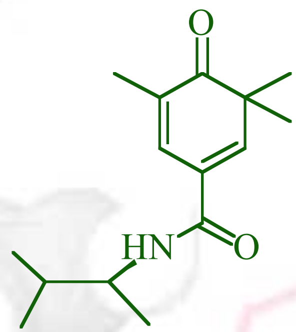
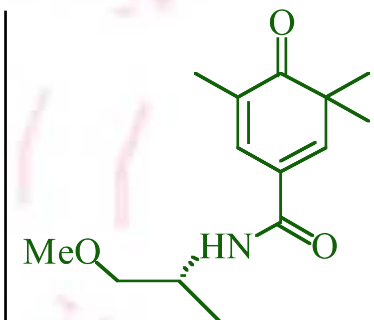
O
O
O
R*
hυ
*ROCH2CO
O
H
+
*ROCH2CO
O
H
—NH
H
CH3
85 (NaY)
-HN
COOCH3
H
86 (KY)
—NH
H
CH3
45 (NaY)
-HN
COOCH3
H
CH3
CH3
53 (NaY)
—NH
CH3
CH3
H
CH3
45 (NaY)
-HN
COOCH3
H
H3C
CH3
56 (NaY)
—NH
CH2OCH3
H
CH3
54 (NaY)
N
COOCH3
H
46 (KY)

Asymmetric Photoreactions Within Zeolites

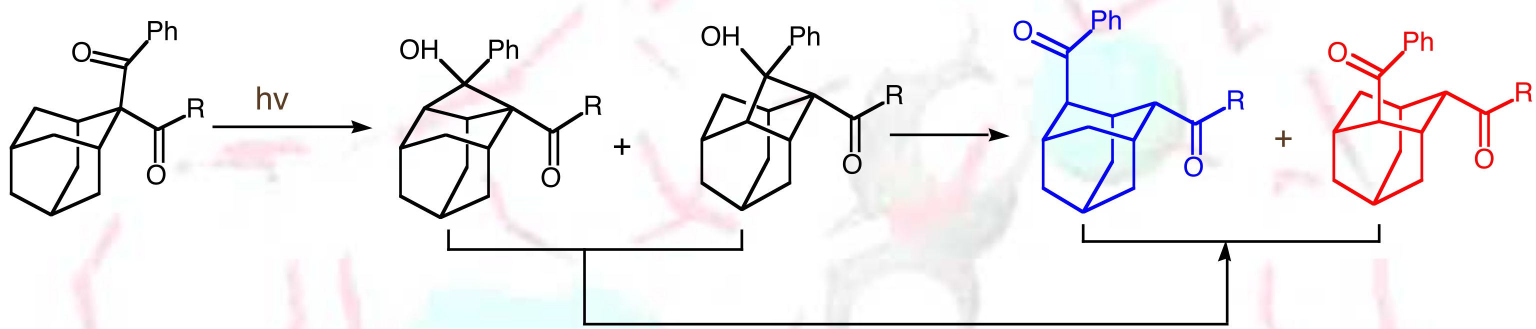
- **Modest to Good Chiral Induction**
- **Chiral Induction Depends on**
  - **Reaction and Reactant**
  - **Chiral Inductor and Chiral Auxiliary**
  - Nature and Number of Cation
  - **Water Content**
  - **Mechanism of the Reaction**
  - **Reactive State (S_1 vs T_1)**

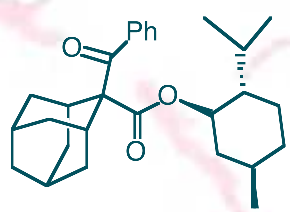
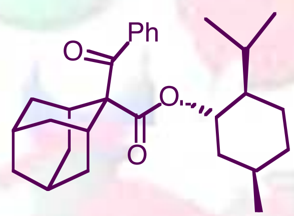
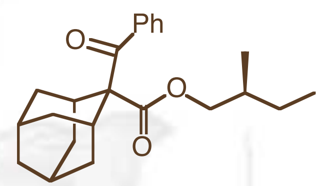
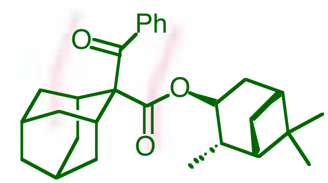
Photochemistry of Chiral Amides of 2,6,6-trimethylcyclohexa-2,4-dienone-4-carboxylic acid



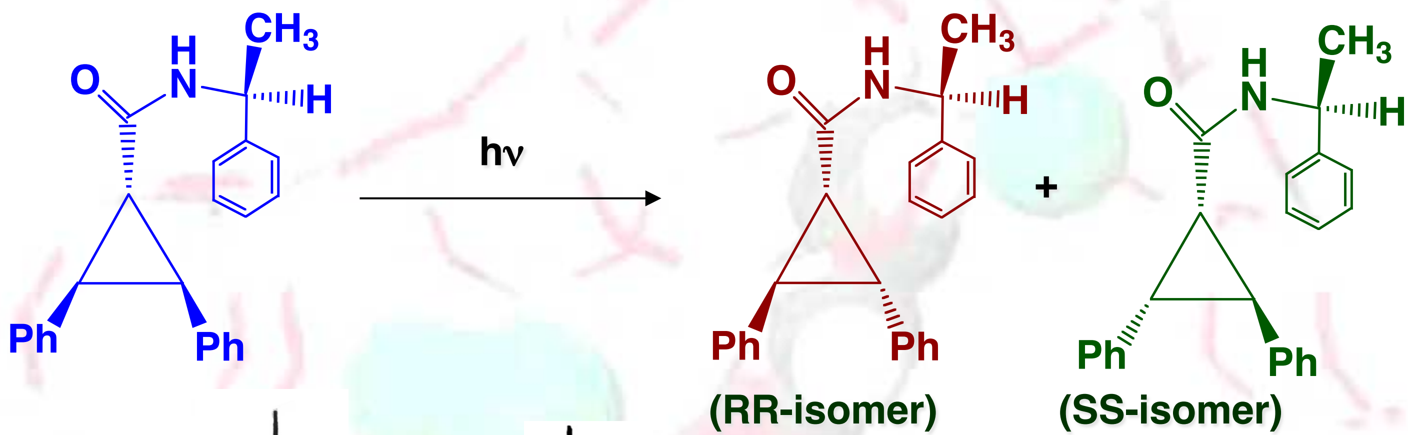
Zeolite				
LiY	17% (A)	34% (A)	4% (A)	40%(A)
NaY	59% (A)	41% (A)	2% (A)	73%(A)
KY	53% (B)	34% (B)	9% (B)	1% (A)
RbY	39% (B)	13% (B)	38% (B)	25%(B)
CsY	9% (B)	8% (A)	31% (B)	20%(B)

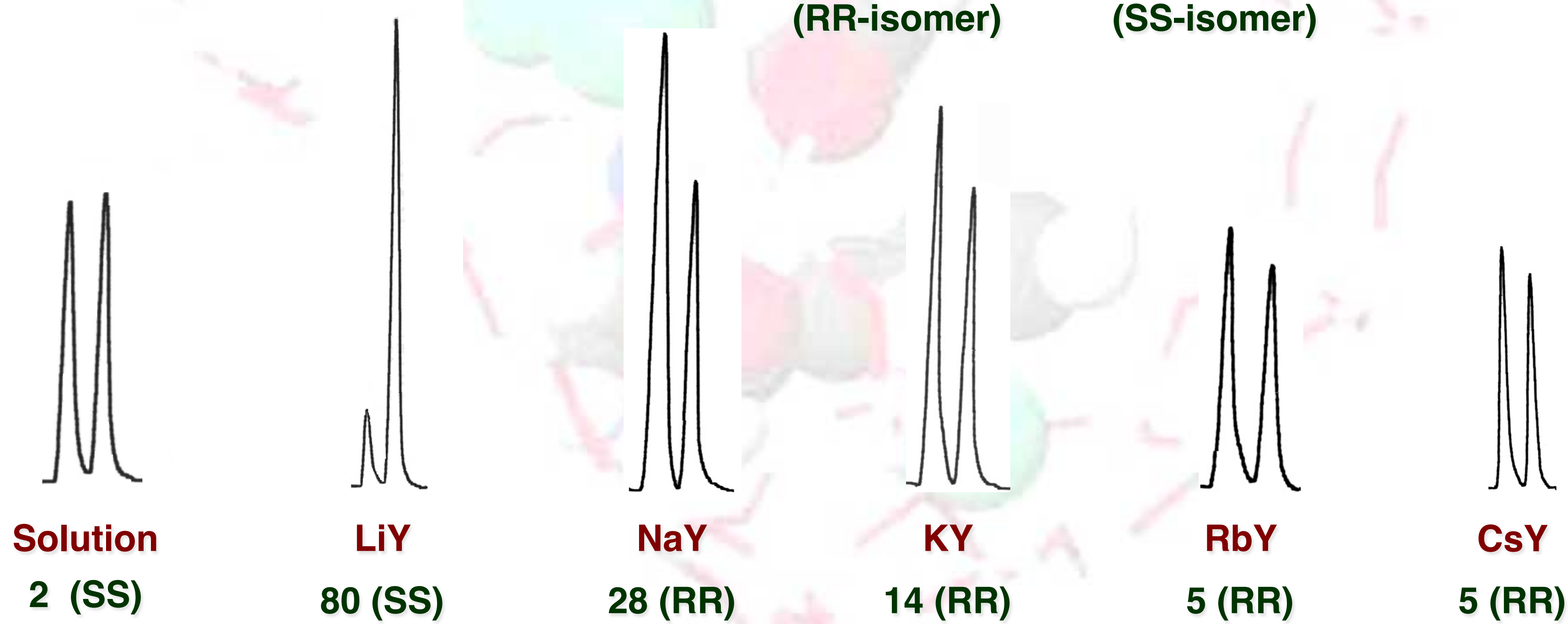
Yang Cyclization of Adamantyl Aryl Ketones within Zeolites



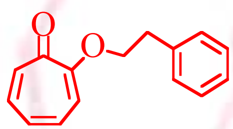
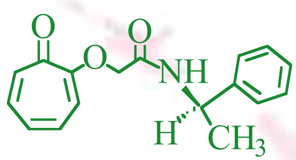
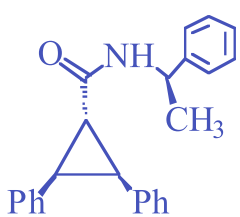
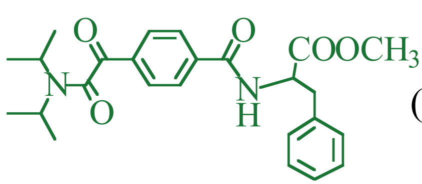
	 (-)menthyl ester	 (+)isomenthyl ester	 S(-)2-methylbutylester	 (+)isopinocampheol ester
CH_3CN	5(A)	14(B)	5(A)	5(B)
LiY	79(B)	65(A)	26(B)	52(B)
NaY	60(B)	79(A)	54(B)	62(B)
KY	31(B)	3(A)	30(B)	4(A)

Chiral Induction Depends on the Alkali Metal Ion



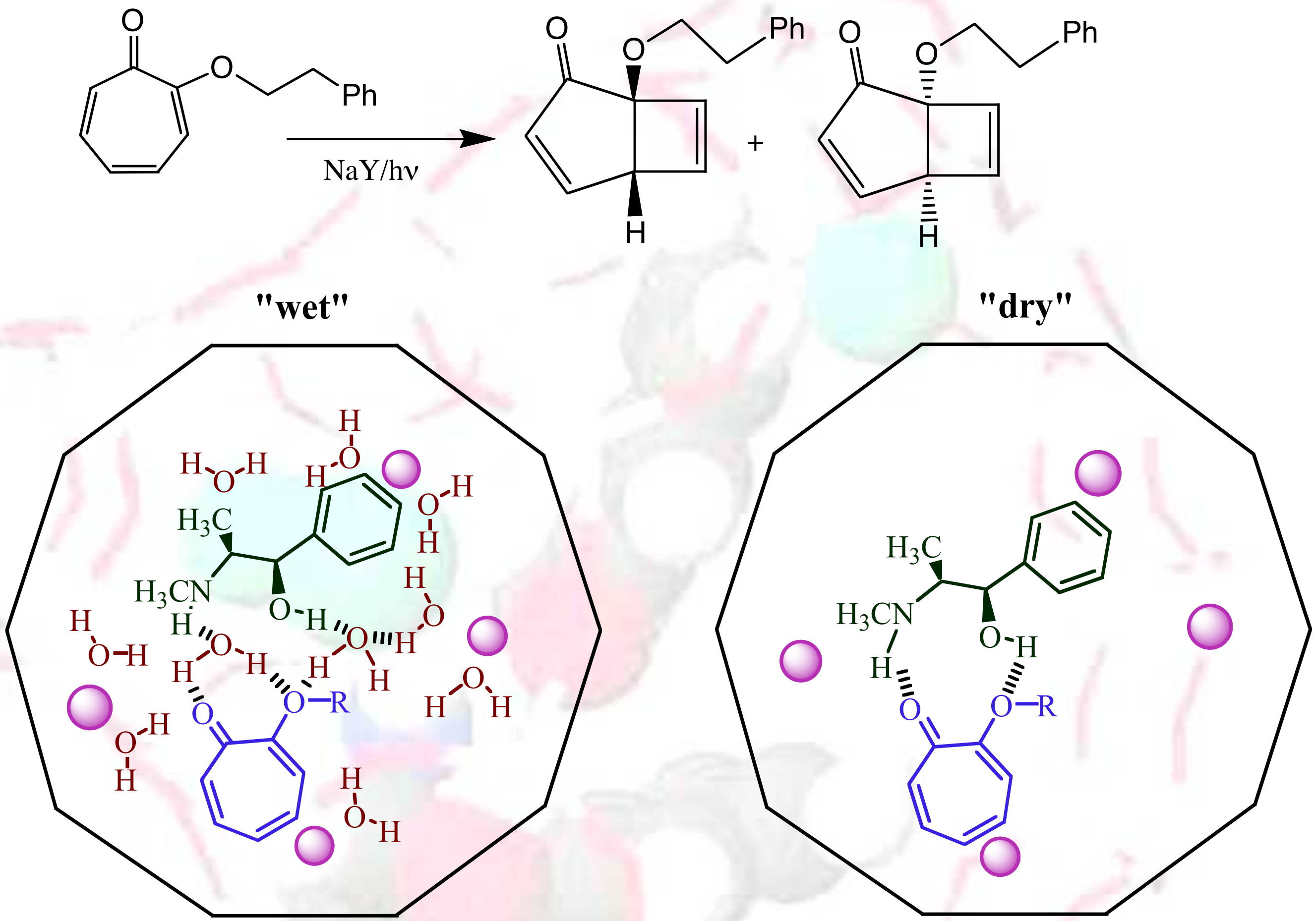


Enantio- and Diastereomeric Excess Depends on the Number of Cations

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

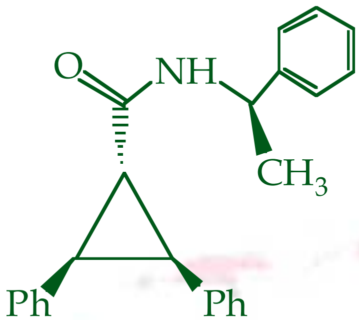
Asymmetric Photoreactions Within Zeolites

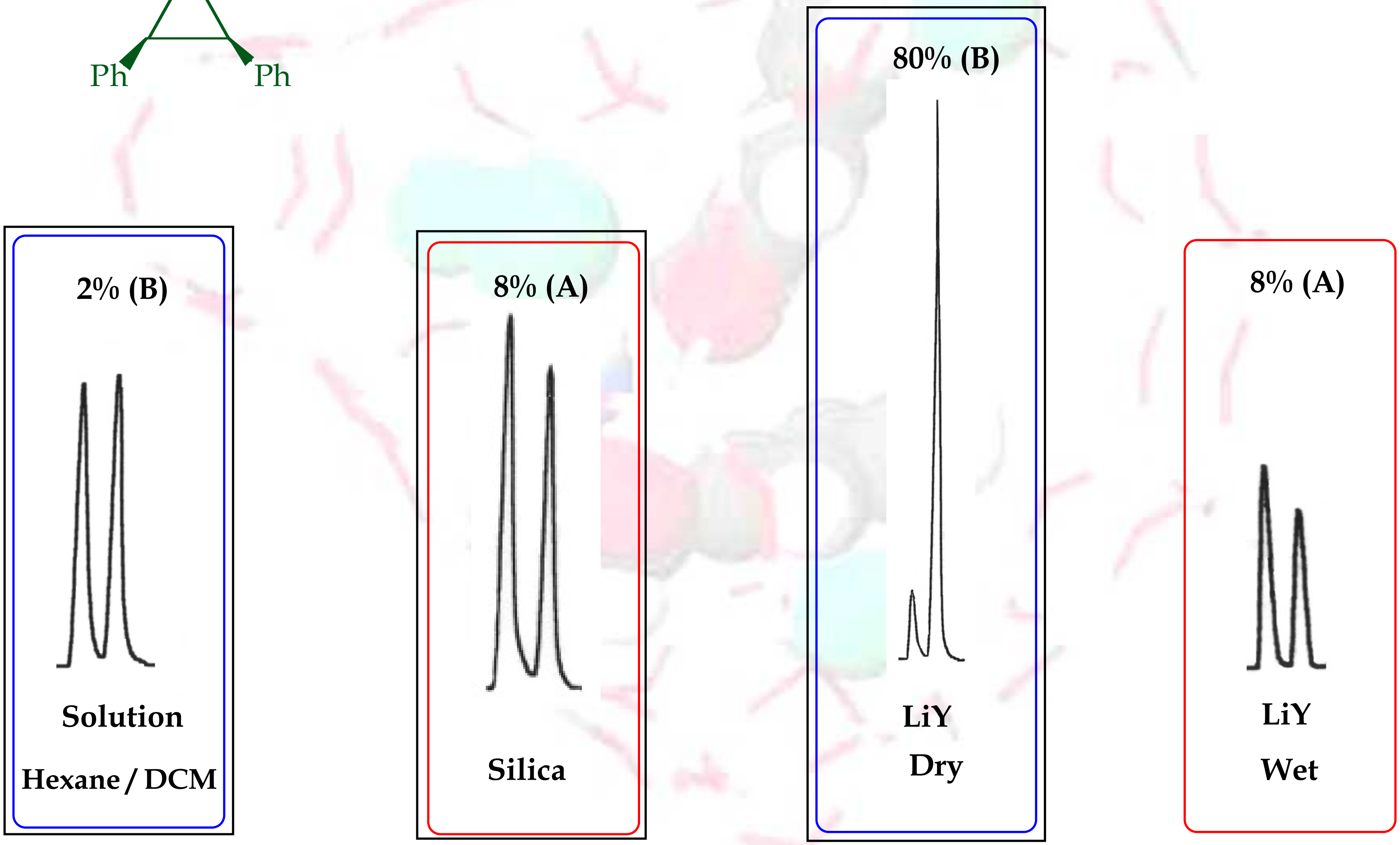
- **Modest to Good Chiral Induction**
- **Chiral Induction Depends on**
  - **Reaction and Reactant**
  - **Chiral Inductor and Chiral Auxiliary**
  - **Nature of the Cation**
  - **Number of Cations (Si/Al ratio)**
  - Water Content
  - **Mechanism of the Reaction**
  - **Reactive State (S_1 vs T_1)**



(-) Ephedrine	17 (B)	68 (A)
(-) Pseudoephedrine	8 (B)	20 (A)
(-) Norephedrine	23 (B)	38 (A)

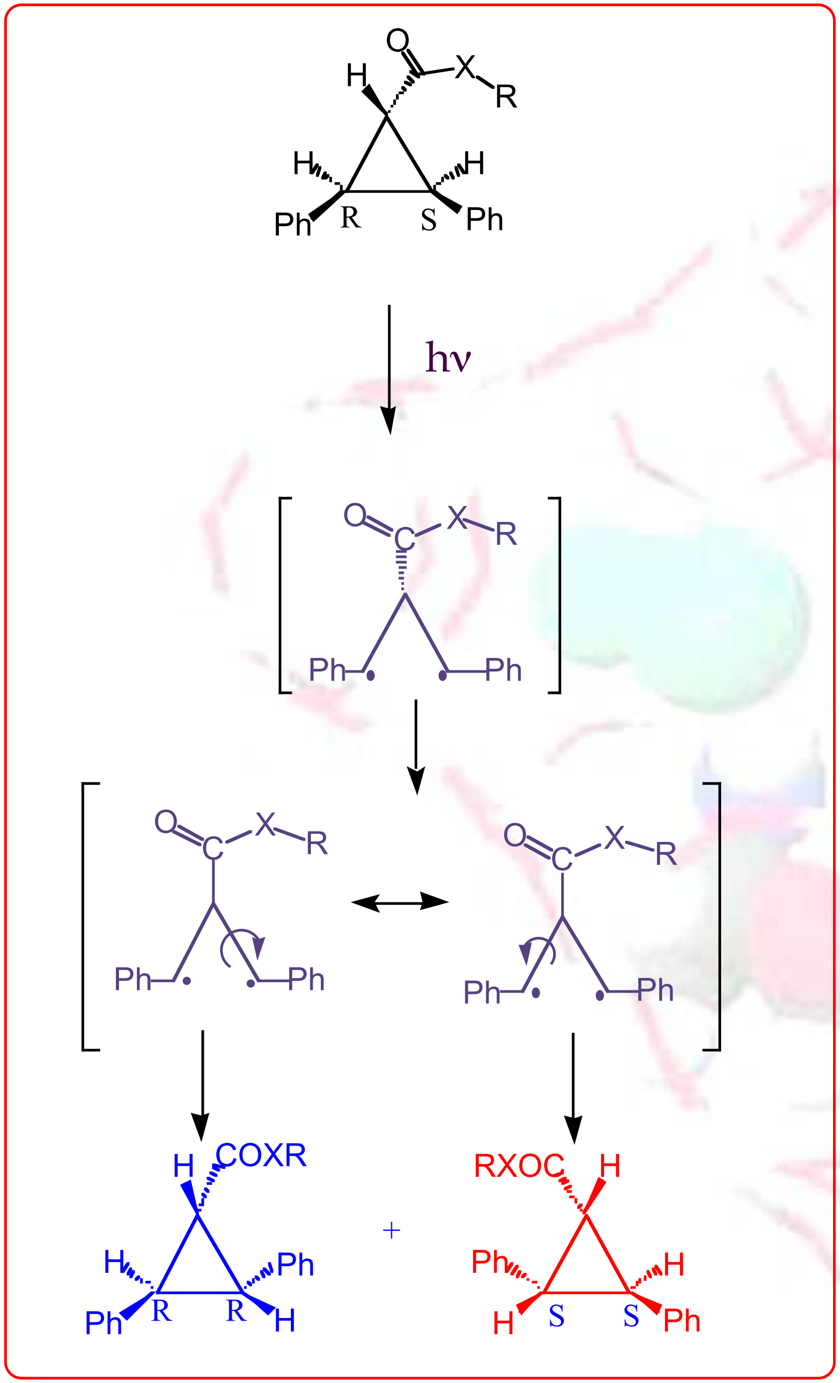
Role of confined space and effect of water



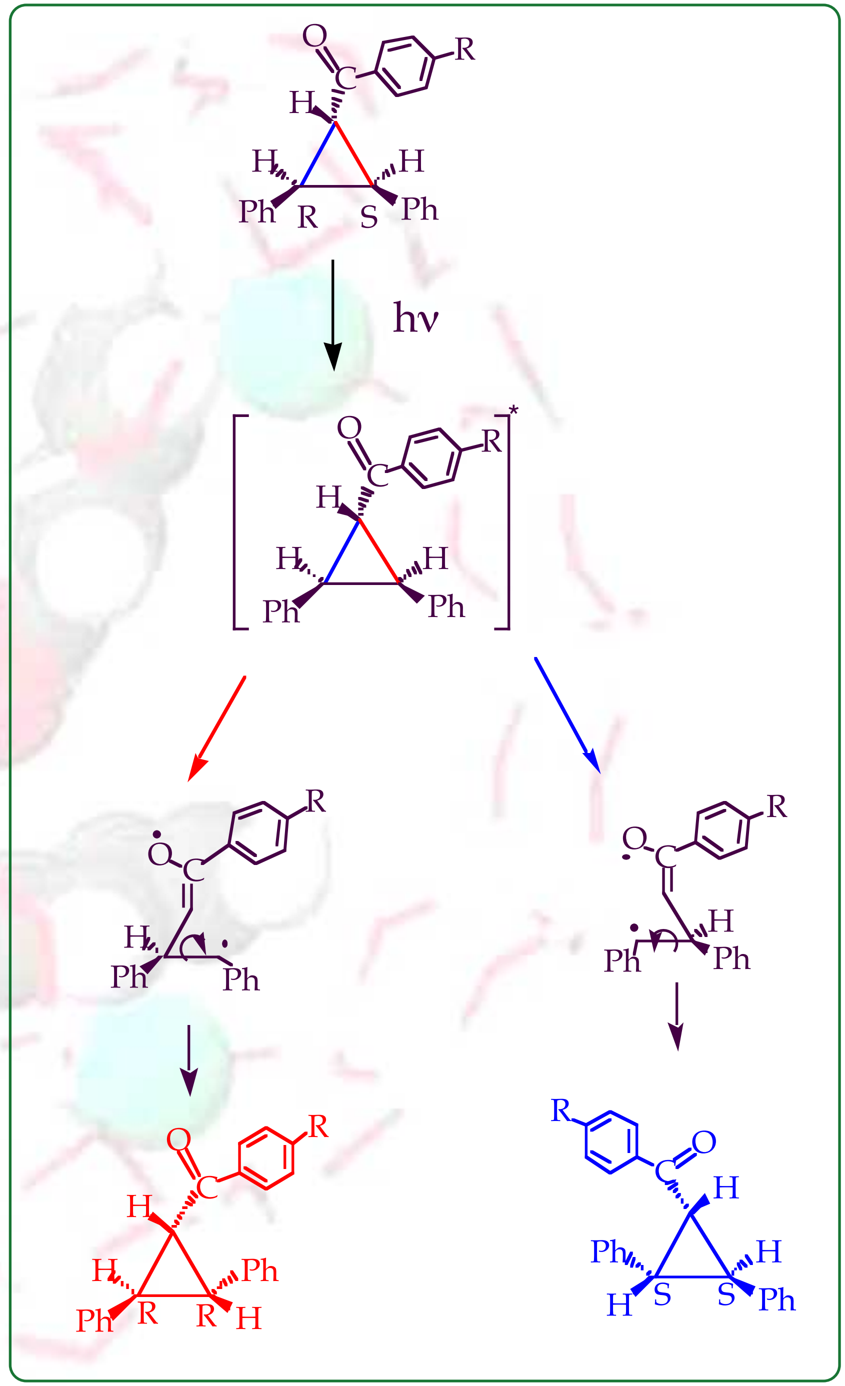


Asymmetric Photoreactions Within Zeolites

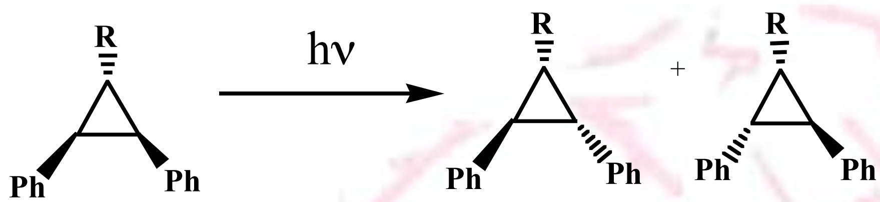
- **Modest to Good Chiral Induction**
- **Chiral Induction Depends on**
  - **Reaction and Reactant**
  - **Chiral Inductor and Chiral Auxiliary**
  - **Nature of the Cation**
  - **Number of Cations (Si/Al ratio)**
  - **Water Content**
  - Mechanism of the Reaction
  - **Reactive State (S_1 vs T_1)**



O
X
R
H
H
H
Ph
R
S
Ph
hν
O
C
X
R
Ph
Ph
COXR
RXOC



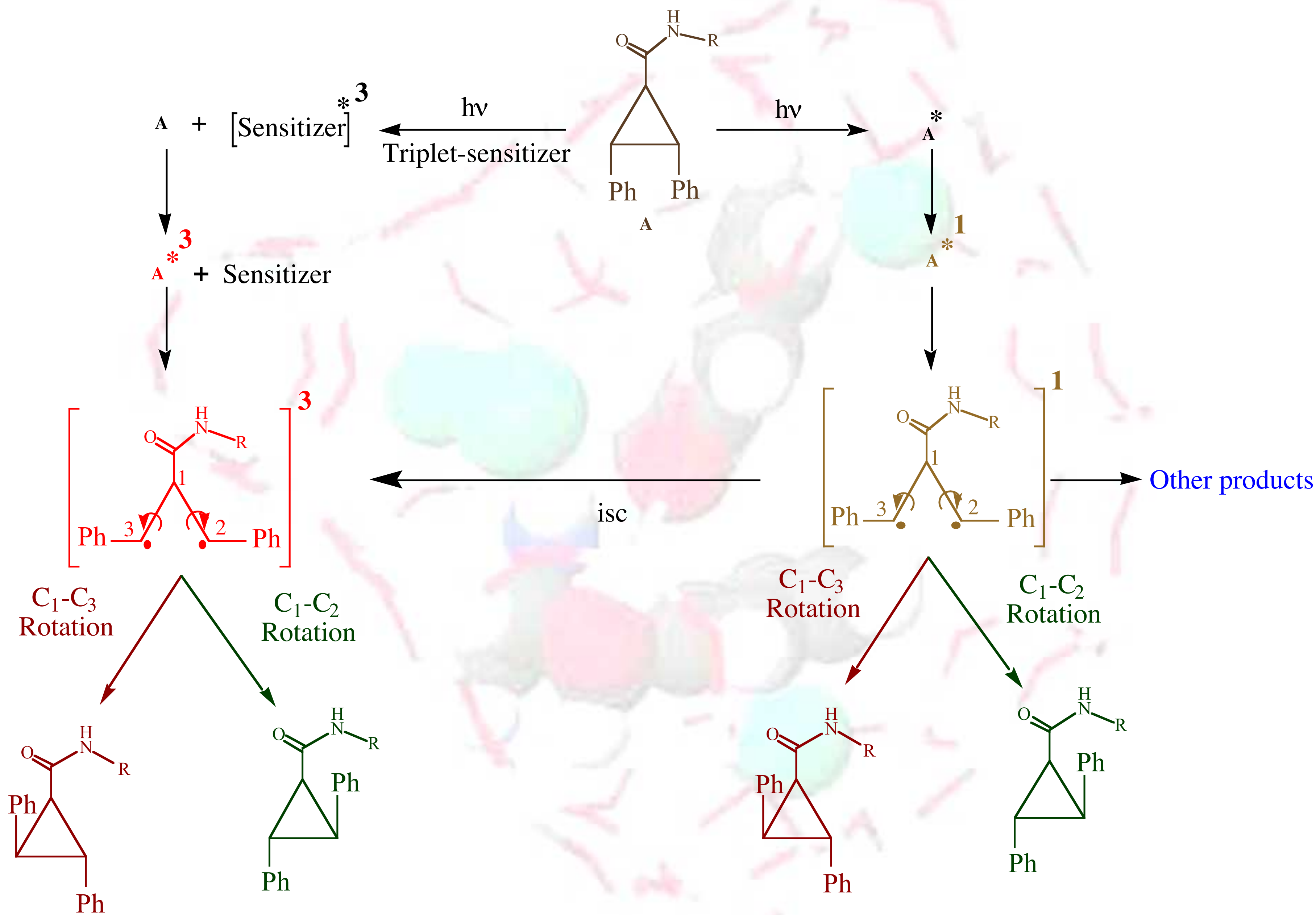
O
C
R
H
Ph
R
S
hν
*



% de	% de	Zeolite	% de	% de
83	15	LiY	10	27
21	25	NaY	32	41
80	52	KY	53	29
47	13	RbY	32	25
5	4	CsY	6	0
2	0	Solution	2	5

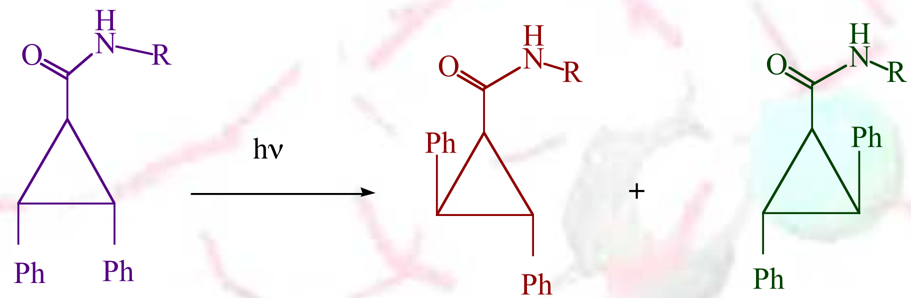
Asymmetric Photoreactions Within Zeolites

- **Modest to Good Chiral Induction**
- **Chiral Induction Depends on**
  - **Reaction and Reactant**
  - **Chiral Inductor and Chiral Auxiliary**
  - **Nature of the Cation**
  - **Number of Cations (Si/Al ratio)**
  - **Water Content**
  - **Mechanism of the Reaction**
  - Reactive State (S_1 vs T_1)

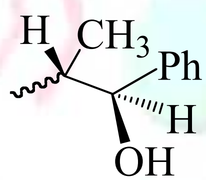


hν
Triplet-sensitizer
hν
Sensitizer
A
isc
Other products
C1-C3
Rotation
C1-C2
Rotation

Diastereoselectivity Dependence on Reactive State



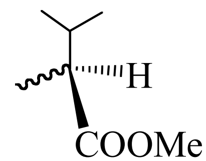
R =



Norephedrine derivative

Method	LiY	NaY
Direct	25-B	60-A
Sens[3] (4-MAP)[*3]	23-B	69-B

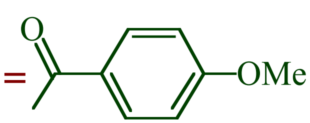
R =



L-Valine Methyl ester derivative

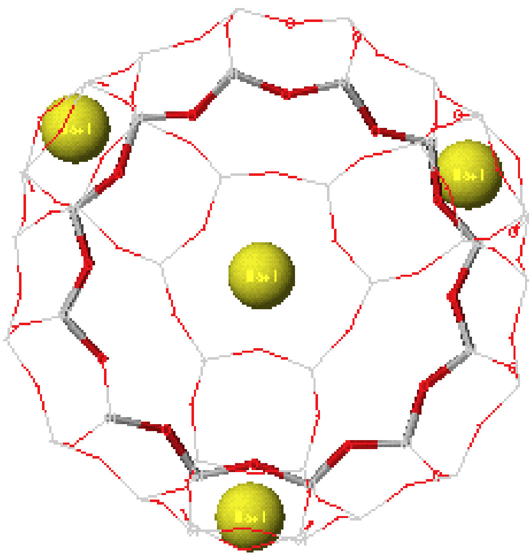
Method	LiY	KY
Direct	83-B	80-A
Sens[3] (4-MAP)[*3]	52-B	81-A

(4-MAP) =



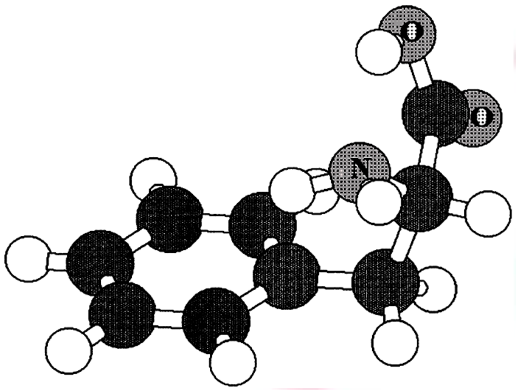
Asymmetric Photoreactions Within Zeolites

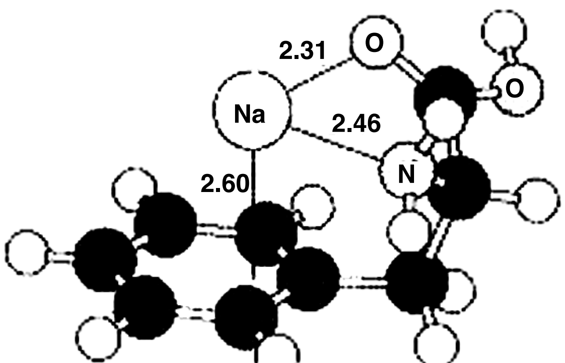
Cation is the Key

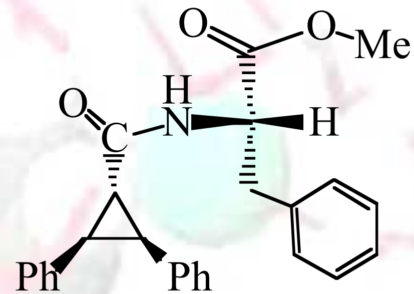


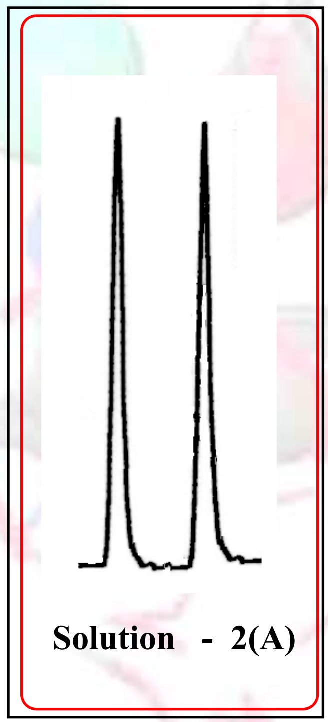
- Chiral Induction Depends on
  - Nature of the Cation
  - Number of Cations (Si/Al ratio)
  - Water Content

Cation binding changes the conformation of the chiral auxiliary

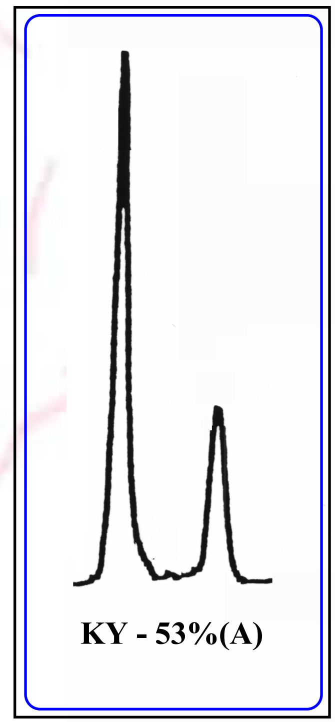






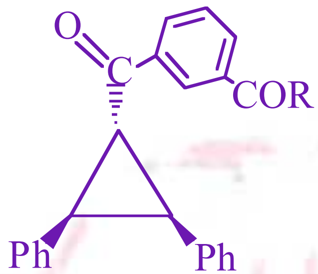
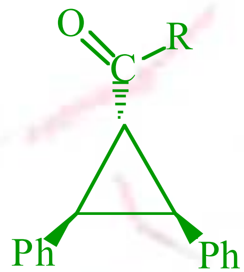
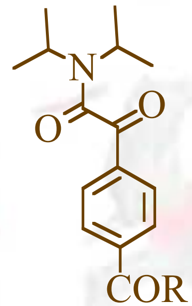
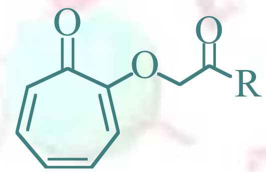
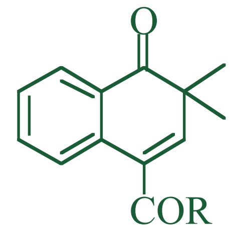
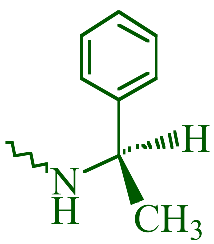
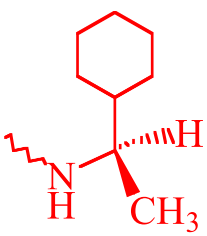


Zeolite	**%de**
LiY	10(A)
NaY	32(A)
KY	53(A)
RbY	32(A)
CsY	6(A)

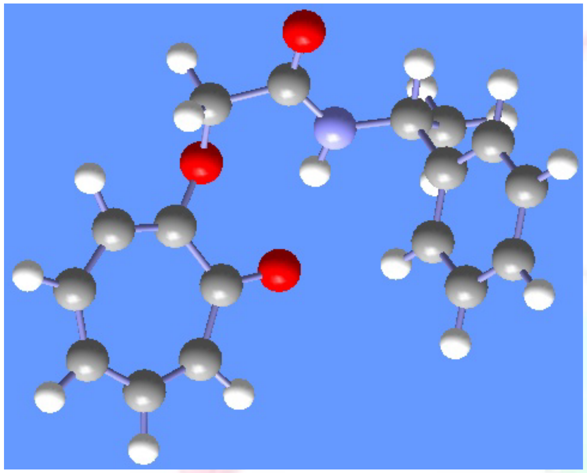


R. C. Dunbar, J. Phys. Chem., 104, 8067 (2000)

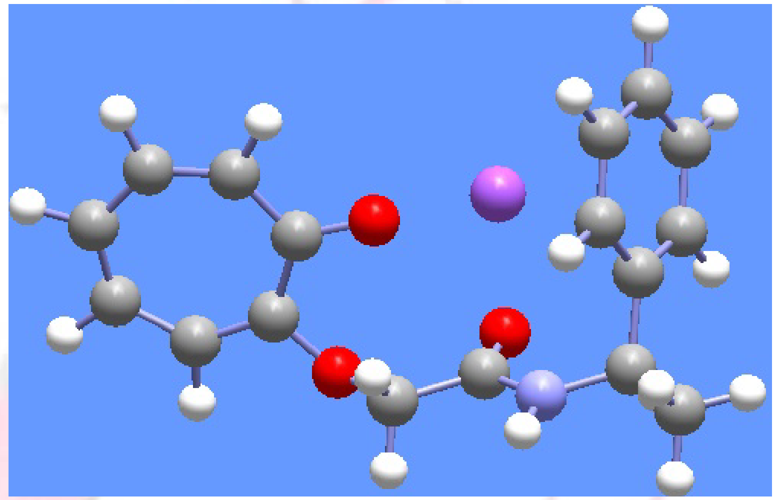
Importance of Cation-Chiral Auxiliary Binding: Phenyl vs Cyclohexyl

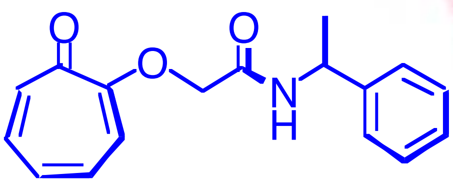
	 **NaY**	 **LiY**	 **NaY**	 **NaY**	 **KY**
	**71**	**80**	**62**	**85**	**81**
	**30**	**29**	**22**	**45**	**45**

Importance of Cation-Chiral Auxiliary Binding: Phenyl vs Cyclohexyl

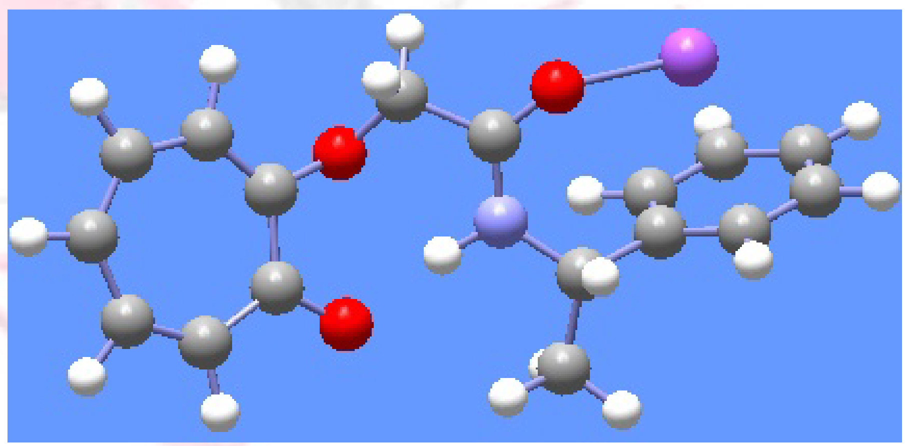


B.E (Na^+ complex) = -96.89 kcal/mol



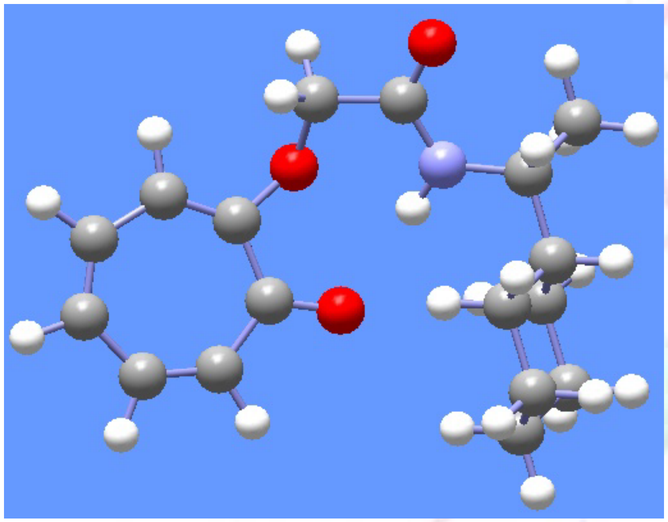


B.E (Na^+ complex) = -85.90 kcal/mol

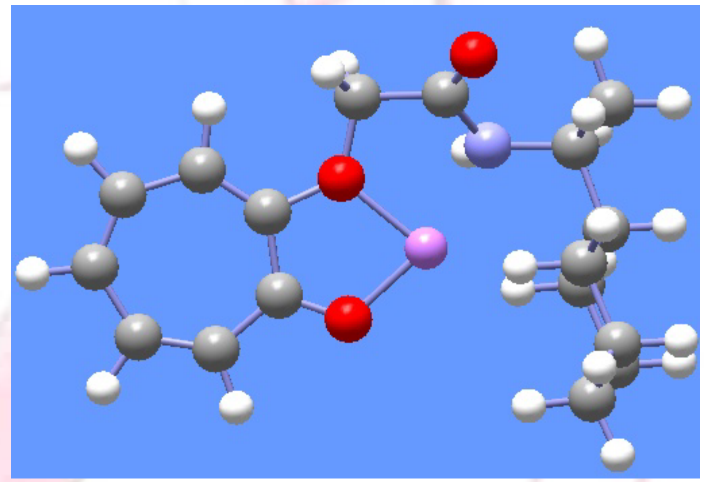


Gaussian 98   HF/ 3-21G *

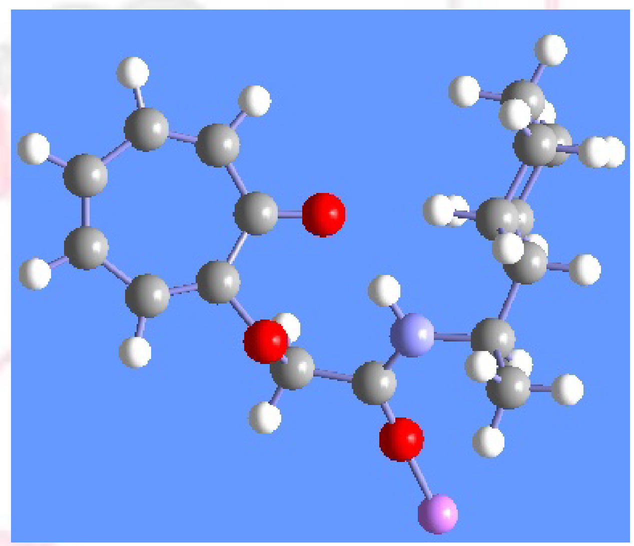
Importance of Cation-Chiral Auxiliary Binding: Phenyl vs Cyclohexyl

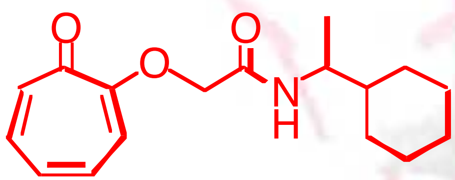


B.E (Na^+ complex) = -75.49 kcal/mol



B.E (Na^+ complex) = -65.32 kcal/mol

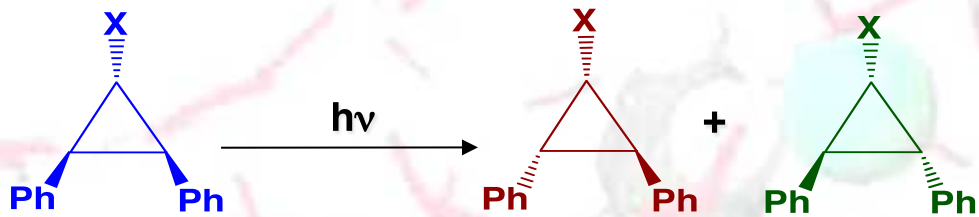


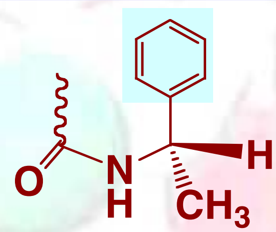


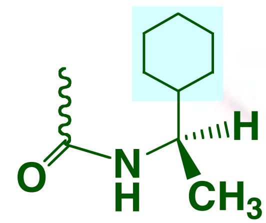
Gaussian 98   HF/3-21G *

Role of Cation-π Quadrupolar Interaction

Phenyl *vs* Cyclohexyl

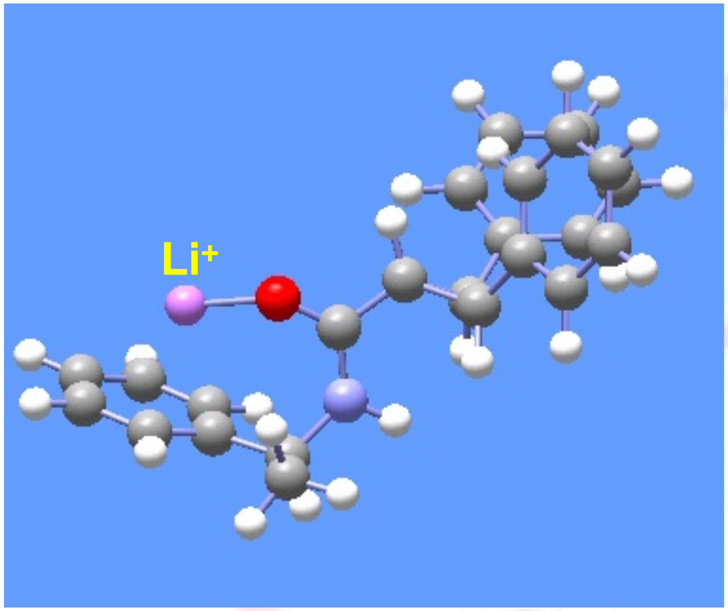




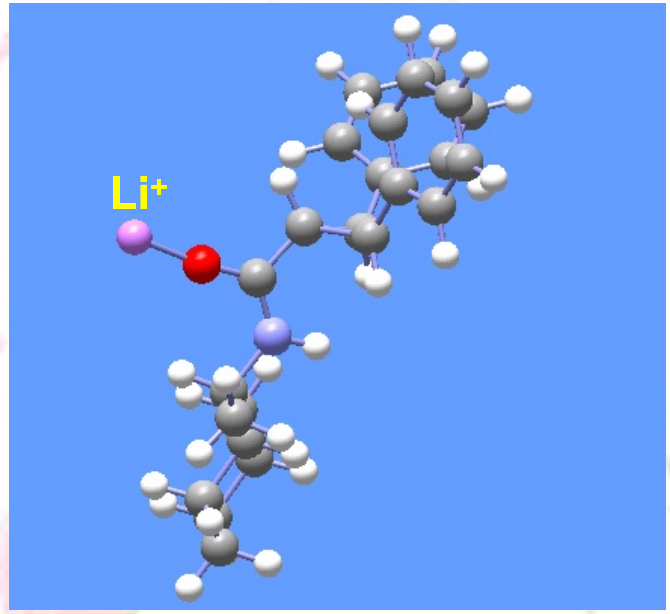


Zeolite	% d.e.	% d.e.
LiY	80-B	29-B
NaY	28-A	24-A
KY	14-A	26-A
RbY	5-A	29-A
CsY	5-A	37-A
Solution	2-B	2-B

Role of Cation-π Quadrupolar Interaction

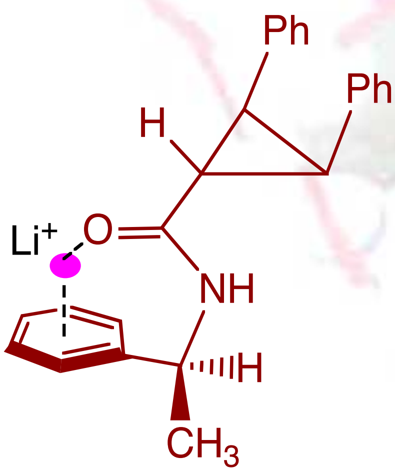


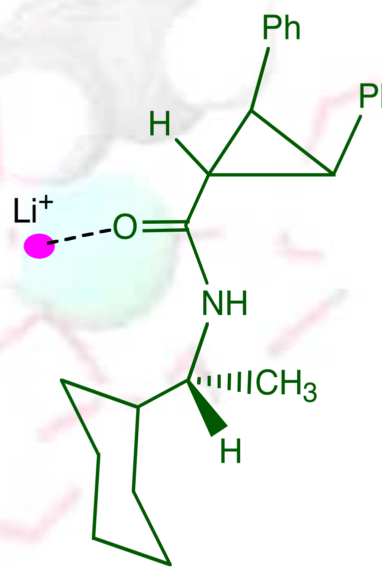
BA = 91.3 kcal/mol

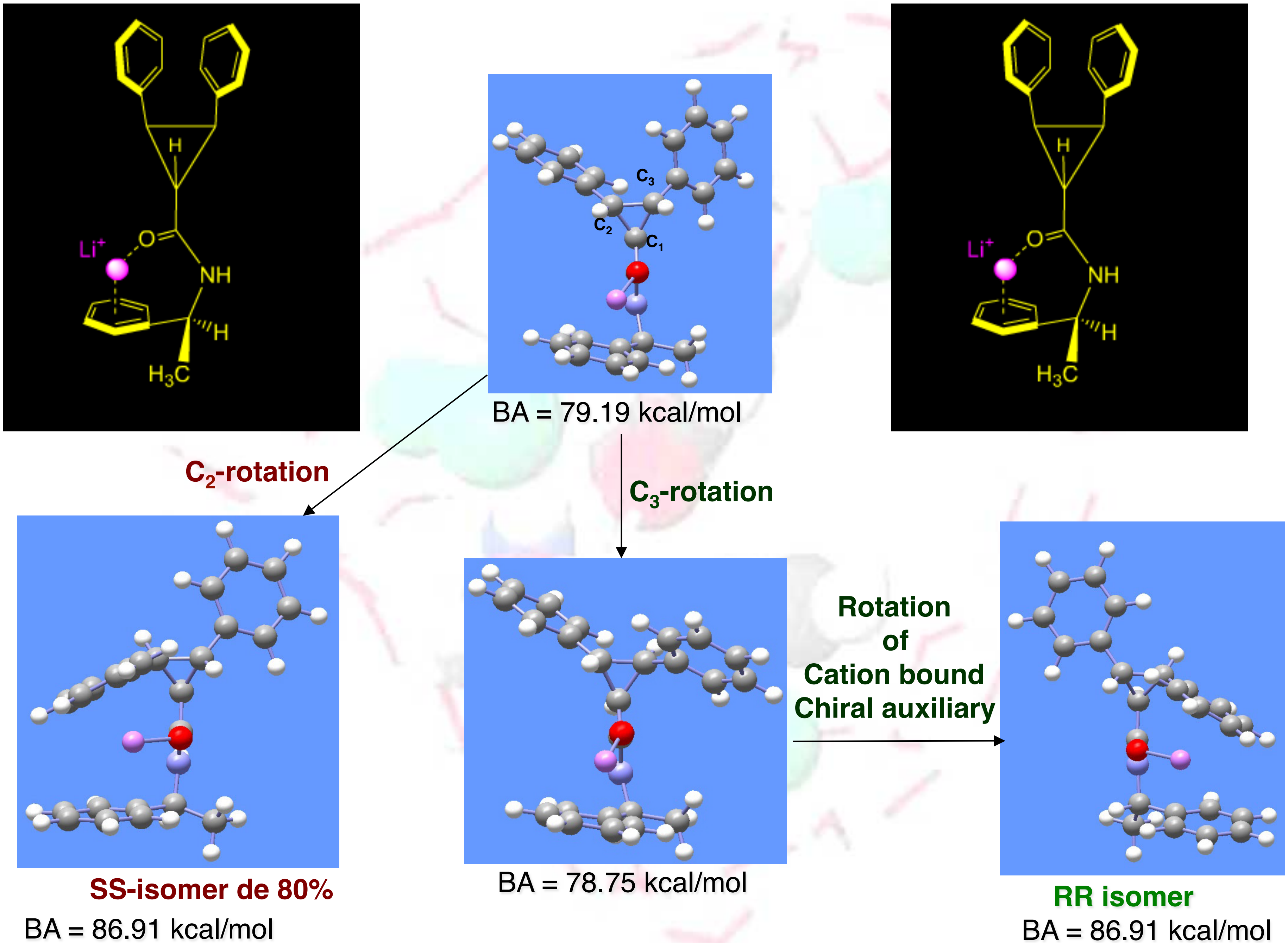


BA = 80.26 kcal/mol

HF / 3-21G



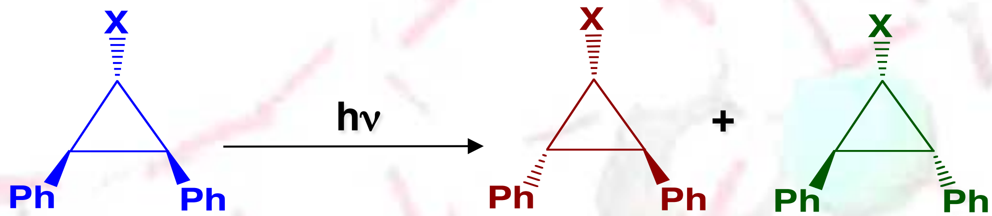


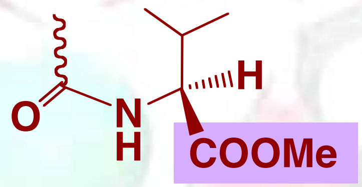


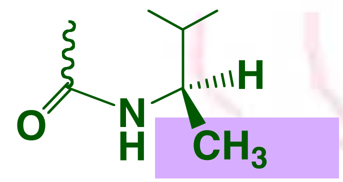
H
Li+
O
NH
H
H3C
C3
C2
C1
BA = 79.19 kcal/mol
C2-rotation
C3-rotation
Rotation
of
Cation bound
Chiral auxiliary
SS-isomer de 80%
BA = 86.91 kcal/mol
BA = 78.75 kcal/mol
RR isomer
BA = 86.91 kcal/mol

Role of Cation-Carbonyl Dipolar Interaction

Carboalkoxy *vs* Alkyl

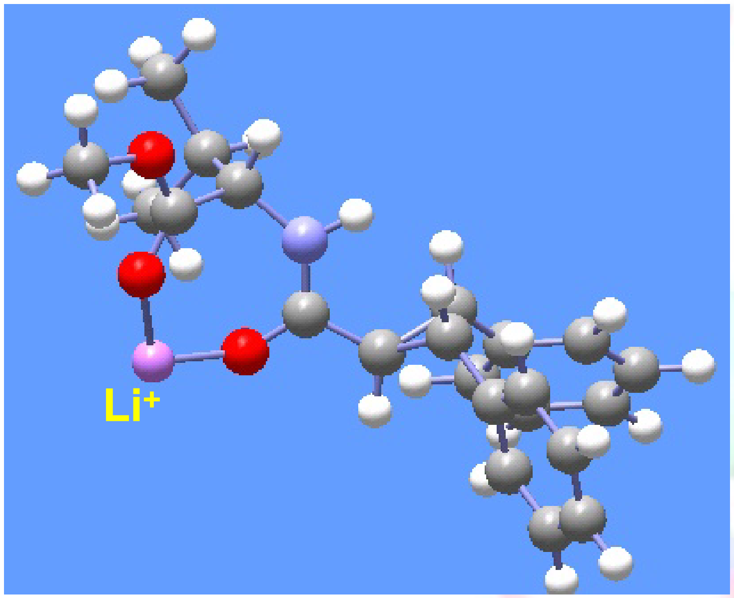




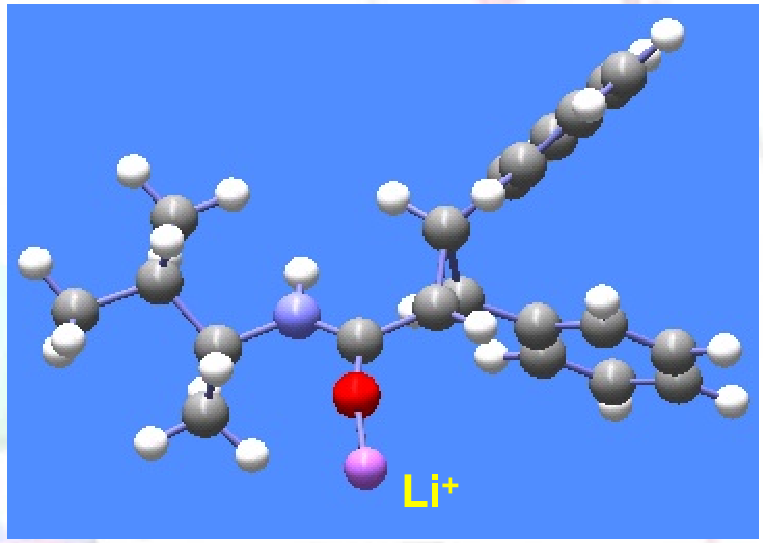


Zeolite	% d.e.	% d.e.
LiY	83-B	7-A
NaY	28-A	7-A
KY	80-A	7-B
RbY	47-A	12-B
Solution	2-B	2-B

Role of Cation-Carbonyl Dipolar Interaction

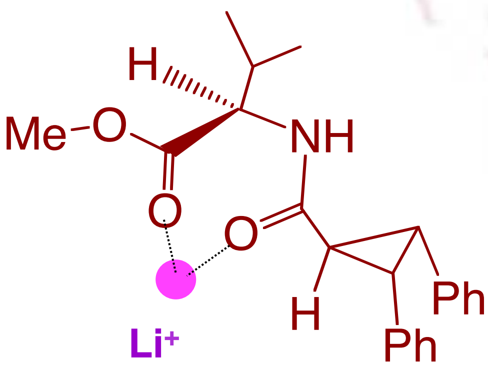


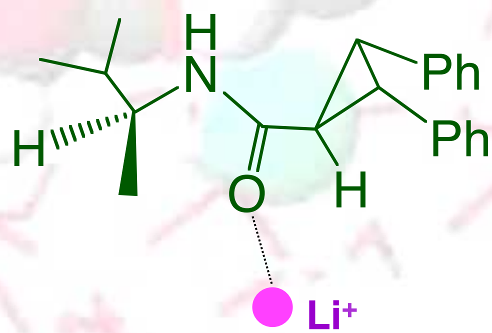
BA = 104.10 kcal/mol



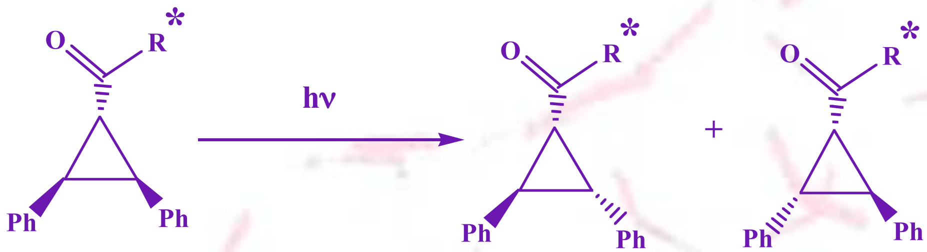
BA = 79.63 kcal/mol

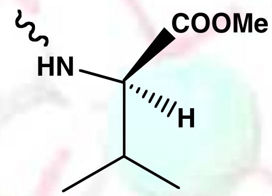
HF / 3-21G





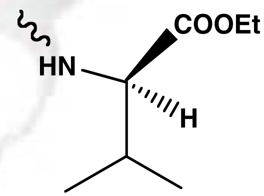
Amino acids as chiral auxiliaries : Cation dependent isomer switch





L-Valine methyl ester

Solution - 2% (A)
LiY - 83% (B)
KY - 80% (A)

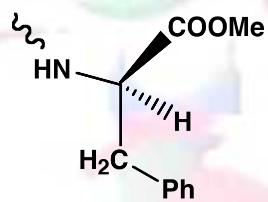


L-Valine ethyl ester

Solution - 20% (A)
LiY - 39% (B)
KY - 61% (A)

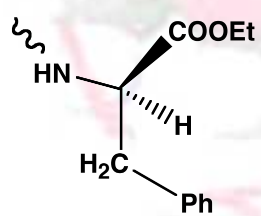
L-Phenylalanine methyl ester

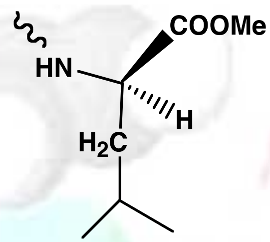
Solution - 2% (A)
LiY - 10% (A)
KY - 53% (A)



L-Phenylalanine ethyl ester

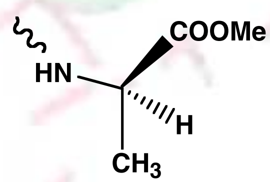
Solution - 1% (A)
LiY - 21% (A)
KY - 44% (A)





L-Leucine methyl ester

Solution - 3% (A)
LiY - 26% (B)
KY - 46% (A)

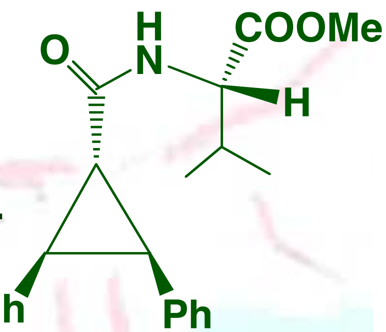


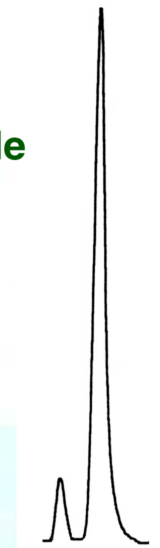
L-Alanine methyl ester

Solution - 5% (B)
LiY - 34% (B)
KY - 31% (A)

Cation Dependent Diastereomer Switch

Amide of
L-Valine methyl ester

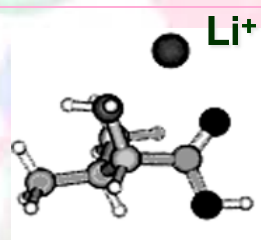




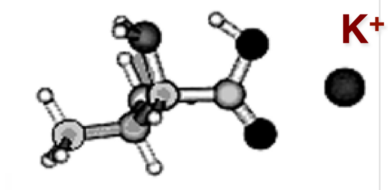
LiY
83 (SS)

KY
80 (RR)

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



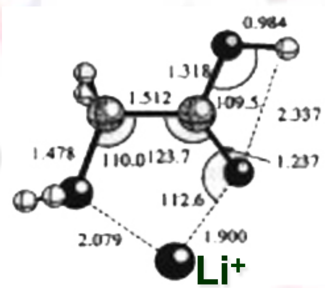
Valine



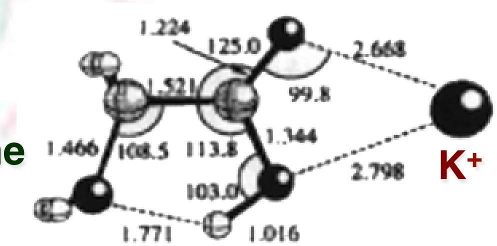
NO - Co-ordination

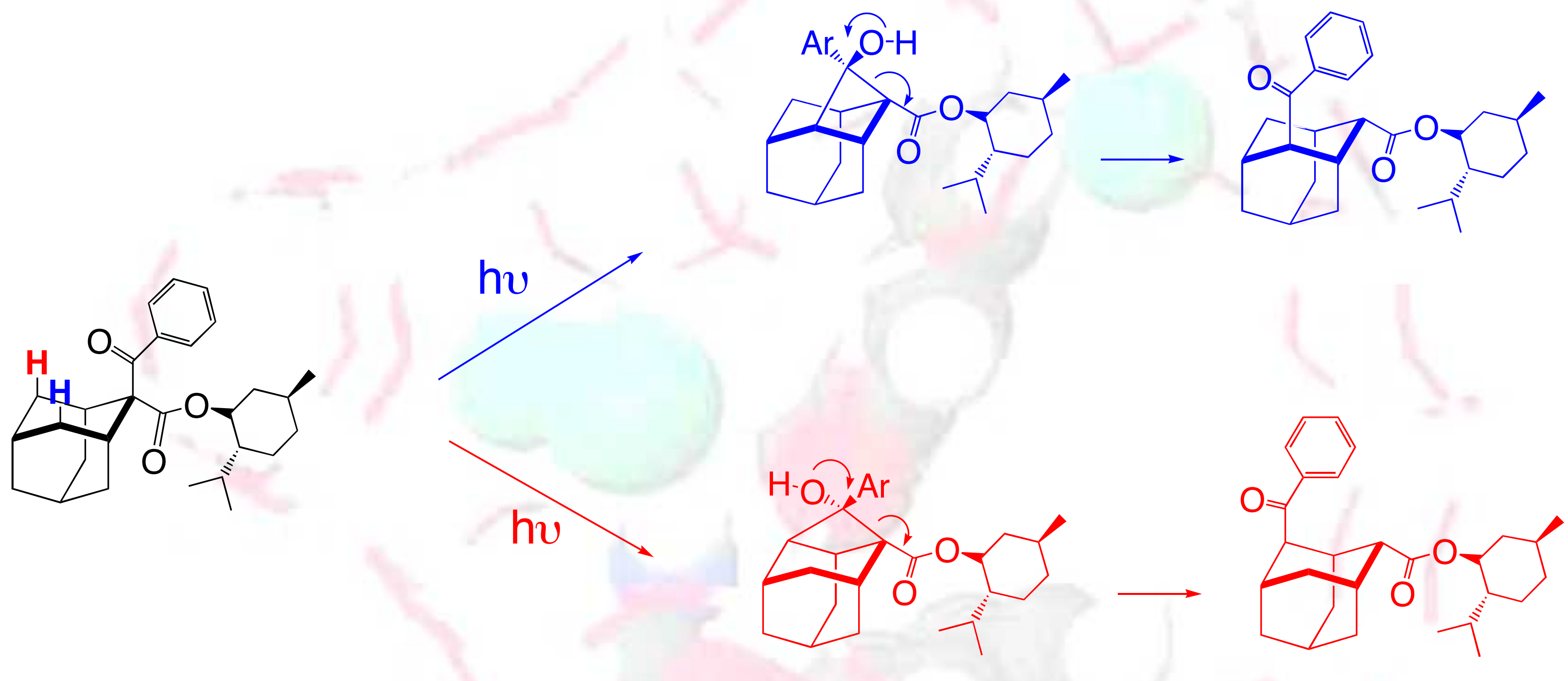
OO - Co-ordination

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

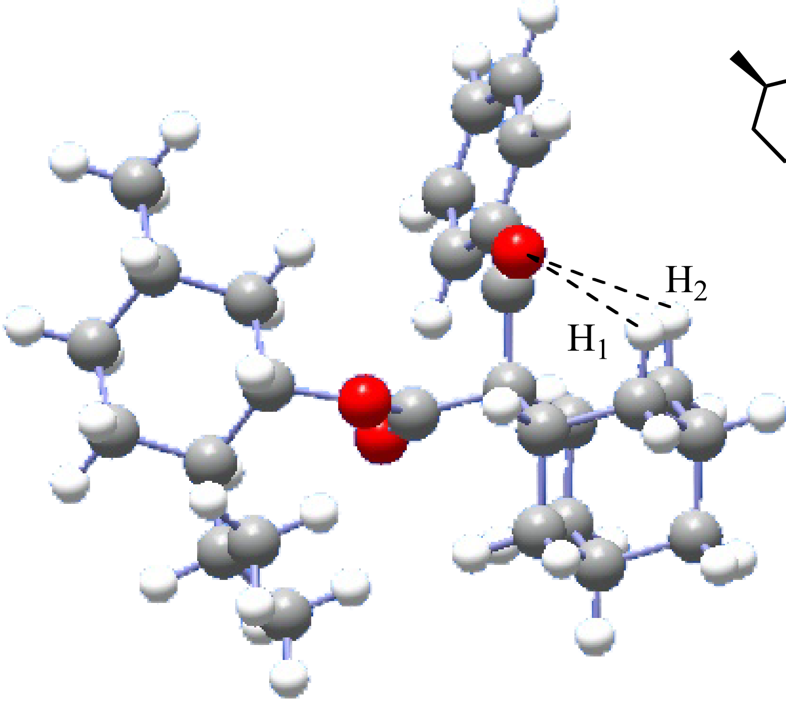


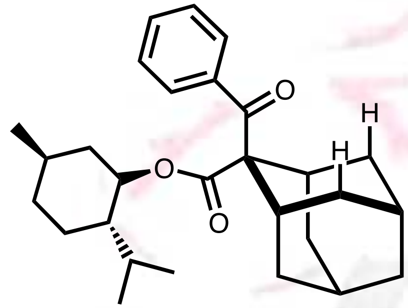
Glycine

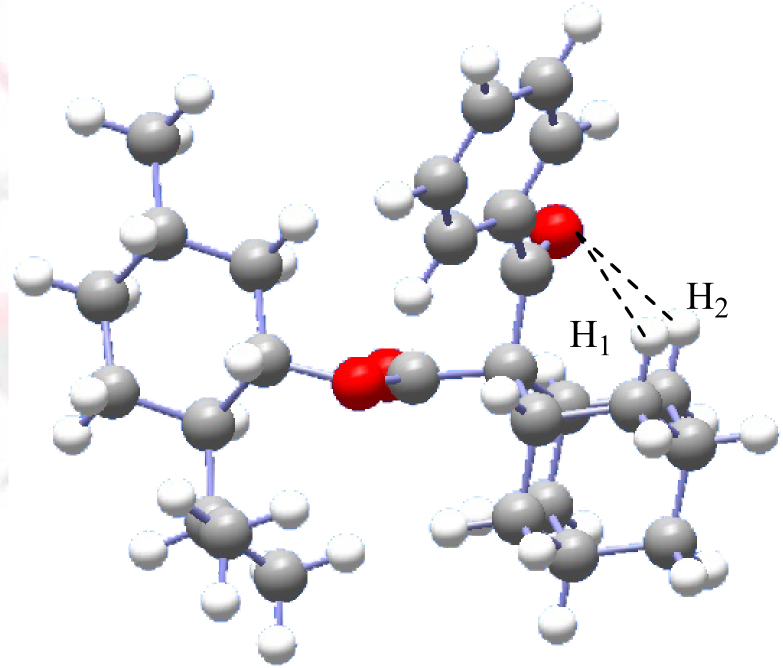




de in CH_3CN: 5% LiY: 79% NaY: 60% KY: 31%







Difference in Energy is 2.3 kcal/mol

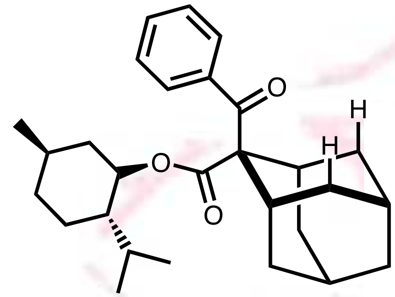
C=O----H$_1$ 2.49 A^0

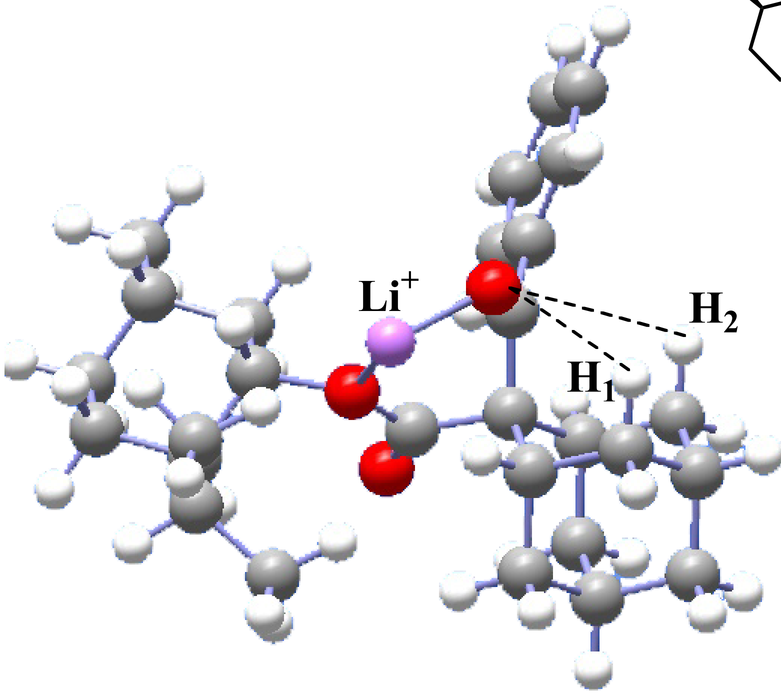
C=O---H$_2$ 3.48 A^0

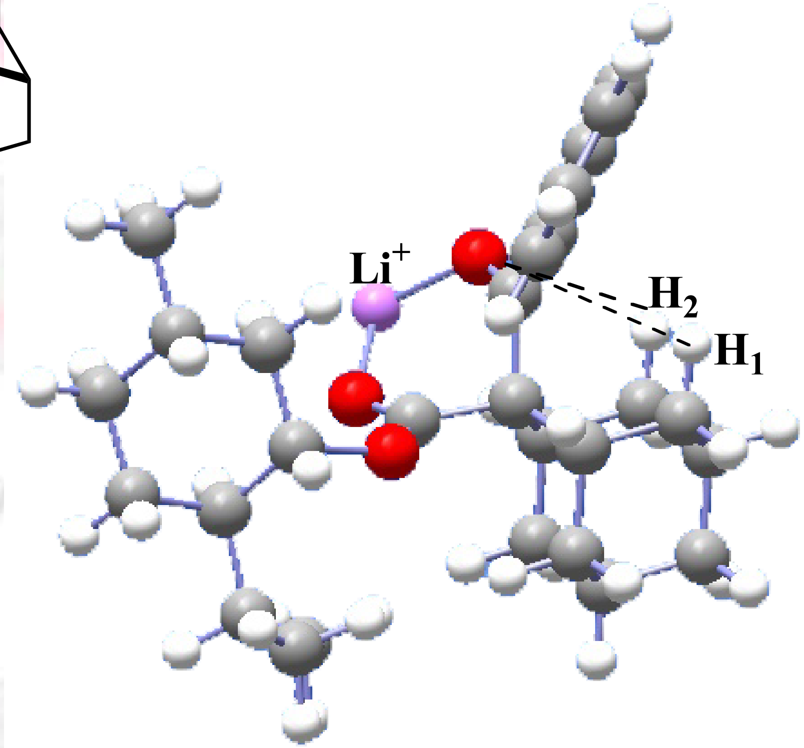
C=O----H$_1$ 3.65 A^0

C=O----H$_2$ 2.65 A^0

B3LYP/6-31G*







Difference in Energy is 10.4 kcal/mol

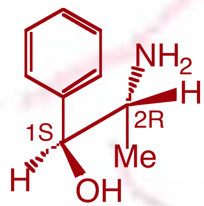
C=O-----H_1 2.55 A^0

C=O----H_2 3.51 A^0

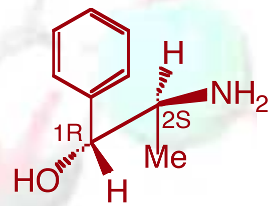
−C=O----H_1 3.79 A^0

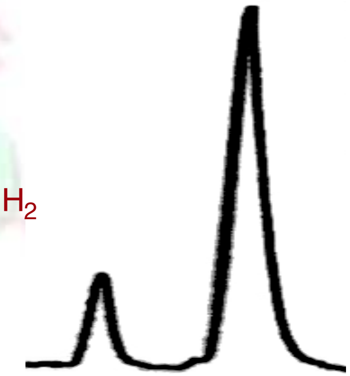
−C=O----H_2 2.78 A^0

Cyclohexyl phenyl ketone with norephedrine in dry NaY zeolite



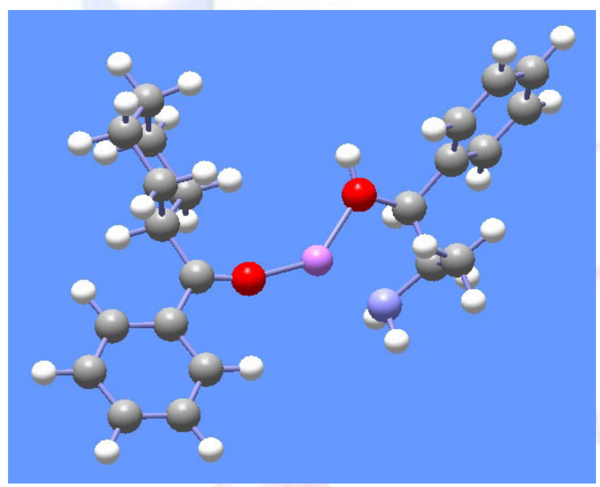
(+) Norephedrine 68% R
R(+)Cyclohexyl benzyl alcohol





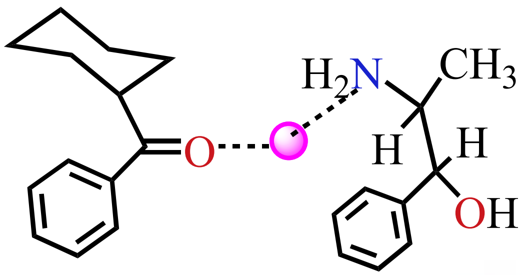
(-) Norephedrine 67% S
S(-)-Cyclohexyl benzyl alcohol

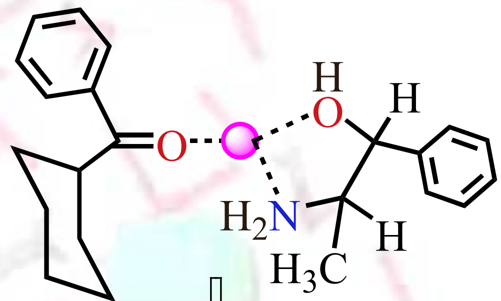
Reaction inside wet NaY with norephedrine as chiral inductor gives only 2%ee.

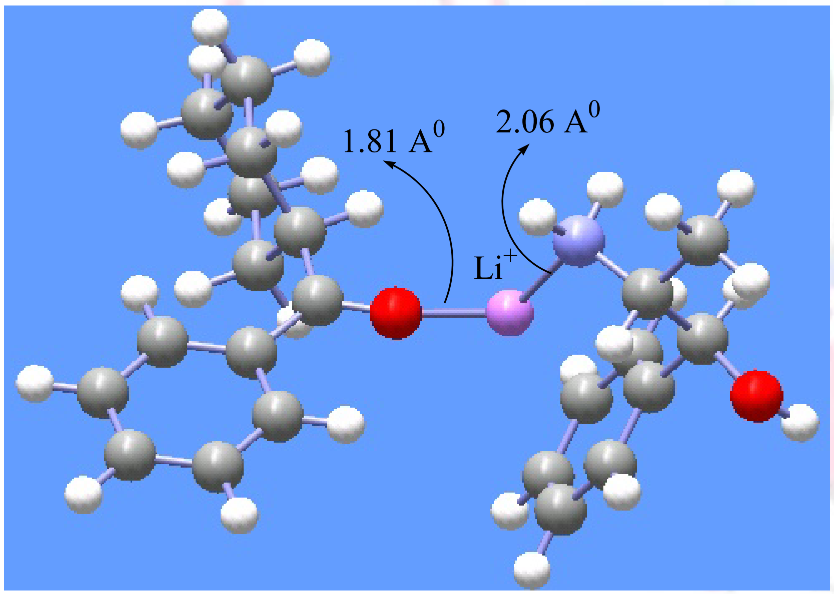


Gaussian 98 B3LYP/6-31 G*

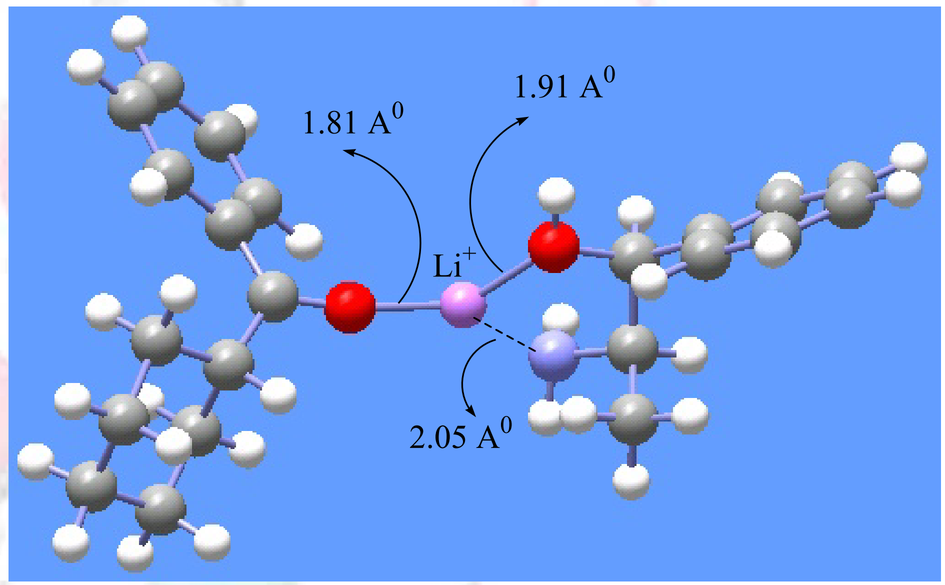
Interaction between the ketone, lithium cation and the chiral inductor.







Energy = -1068.4535 a.u.



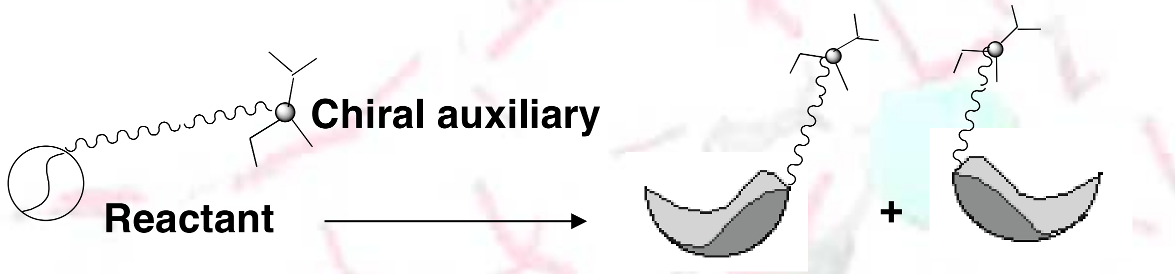
Energy = -1068.4663 a.u.

Difference in Energy: 8.03 k cal/mol

Gaussian 98 B3LYP/6-31G(d)

A Model

Isotropic media

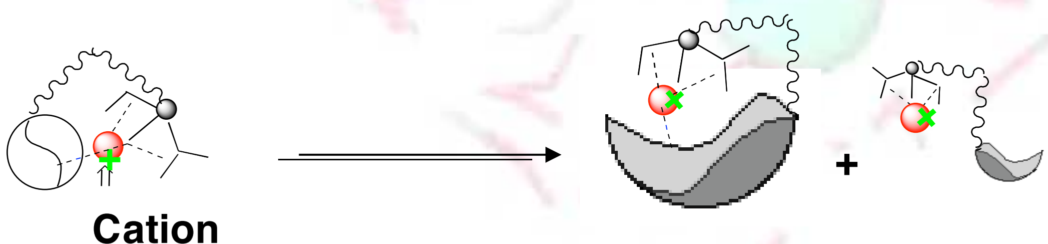


Diastereomeric products 1:1

Confined space (Role of confinement)

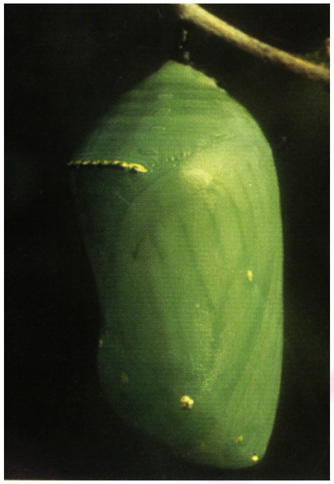
Slight diastereomeric excess

Inside zeolites (Role of cations and confinement)



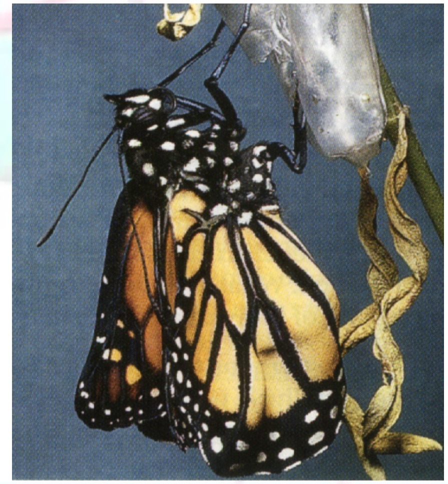
Large diastereomeric excess

Asymmetric Induction within Zeolites



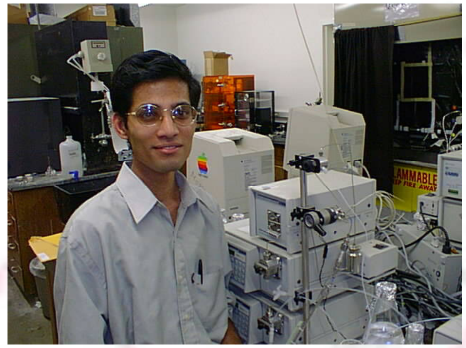
Chemistry in a

Confined Space

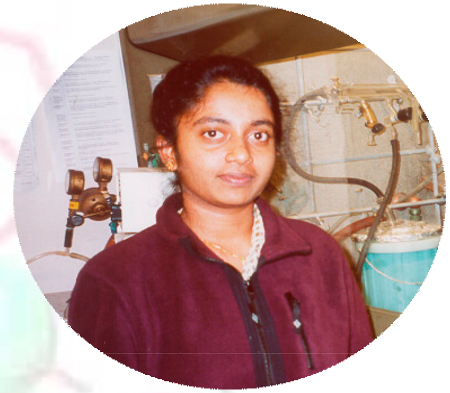


- Chiral inductor
- Chiral auxiliary
- Chiral auxiliary and Chiral inductor
- Chiral inductor as a reagent (or as a sensitizer)

J. Shailaja

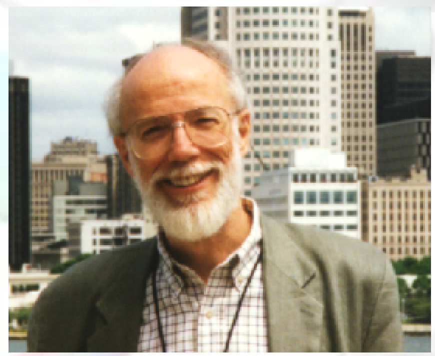


J. Sivaguru



Sireesha

S. Uppili



J. R. Scheffer

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A. Joy

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K. Ponchot

T. Shichi

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WHERE DISCOVERIES BEGIN

SCIENCE THAT MATTERS

U.S. Department of Energy

Science for America's Future