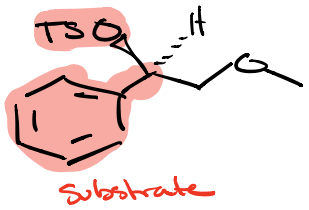
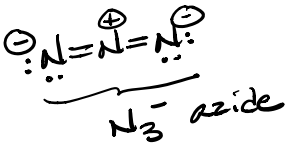


Substrate

NaN_3 ← nuc/base

Acetone ← solvents

30°C ← temp



N_3^- azide

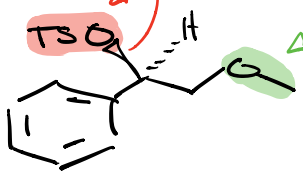
Substrate 2° Benzyl Tosylate

LG -OTs

Base/nucleophile N_3

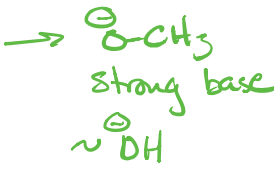
Solvent

Temperature 30°C



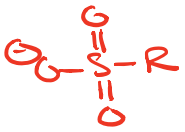
Tosylate

Methoxy

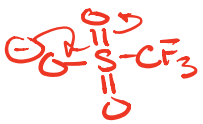


strong base

LG Sulfonates

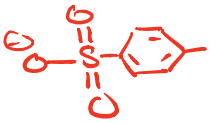


weak Base



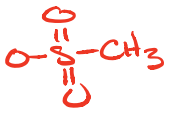
triflate

-OTf



tosylate

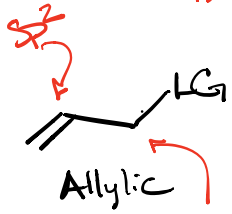
-OTs



mesylate

-OMs

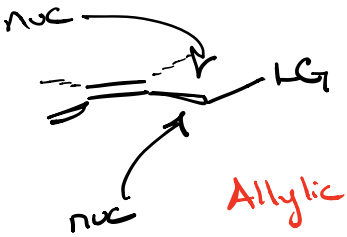
Best



Allylic

Allylic Bromid

Allylic Alcohol



Allylic position = low sterics

= good S_N2 Rxns

low E_A

NUCLEOPHILIC SUBSTITUTION AND ELIMINATION

The question is how do we discern when substitution is favored verse elimination? The answer is found partly in how we should think about reactions of alkyl halides.

> *The characteristic reaction of alkyl halides (or alkyl tosylates) with a Lewis base is **elimination**, special conditions are required to promote substitution.*

Given here is a set of guidelines (not absolutes) that can be used to arrive at the probable solution to nucleophilic substitution/elimination problems.

	Substitution	Elimination
	S_N2	E2
substrate	benzyl = allyl > Me > 1^o > 2^o α-haloketone, α-haloester, α-halonitrile	3^o > 2^o > 1^o
solvent	polar aprotic	polar aprotic
nucleophile	good nuc (weaker base than OH^-)	bulky or strong base >= OH^-
leaving group	sulfonate > I^- > Br^- > Cl^-	sulfonate > I^- > Br^- > Cl^-
Temp	low	high
	S_N1	E1
substrate	3^o > 2^o	3^o > 2^o > 1^o
solvent	polar protic	polar protic
nucleophile	weak nuc (no anions!)	any anionic base
leaving group	sulfonate > I^- > Br^- > Cl^-	sulfonate > I^- > Br^- > Cl^-
Temp	low	high

Classification of Nucleophiles

Very good nucleophile	I^-, HS^-, RS^-
Good nucleophile	Br^-, OH^-, RO^-, CN^-, N_3^-
Fair nucleophile	NH_3, Cl^-, F^-, RCO_2^-
Weak nucleophile	H_2O, ROH
Very weak nucleophile	RCO_2H

Nucleophilic Constants of Various Nucleophiles

Nucleophile	n_{CH_3I}	pK_a of conjugate acid
CH_3OH	0.0	-1.7
F^-	2.7	3.45
$CH_3CO_2^-$	4.3	4.8
Cl^-	4.4	-5.7
NH_3	5.5	9.25
N_3^-	5.8	4.75
$C_6H_5O^-$	5.8	9.89
Br^-	5.8	-7.7
CH_3O^-	6.3	15.7
OH^-	6.5	15.7
$(CH_3CH_2)_3N$	6.7	10.70
CN^-	6.7	9.3
I^-	7.4	-10.7
$(CH_3CH_2)_3P$	8.7	8.69
$C_6H_5S^-$	9.9	6.5

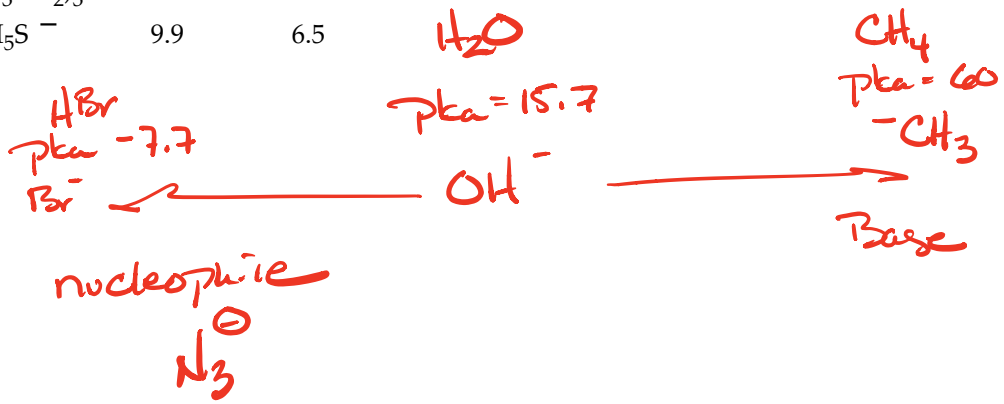
Solvents Which Promote S_N2/E2 (bimolecular)

- Acetone
- Dimethyl sulfoxide (DMSO)
- *N*,*N*-Dimethylformamide (DMF)
- Acetonitrile
- Hexamethylphosphoramide (HMPA)

Solvents Which Promote S_N1/E1 (Unimolecular/Ionizing)

Increasing nucleophilicity (solvolysis)

- Ethanol
- Methanol
- 50% Aqueous Ethanol
- Water
- Acetic Acid
- Formic Acid
- Trifluoroethanol
- Trifluoroacetic acid

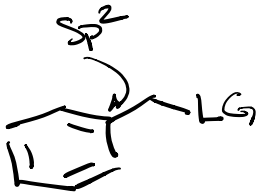


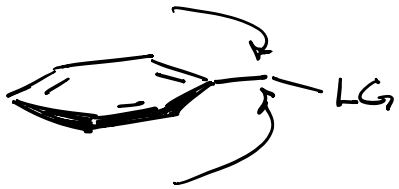
Benzyl

Benzyl bromide

benzyl alcohol

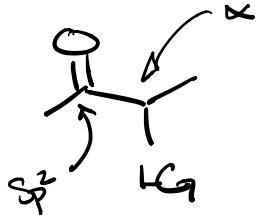
phenyl



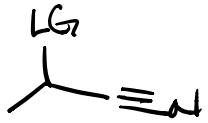


Low sterics

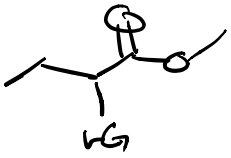
benzyl LG = good S_N2



α-haloketon



α-halonitrile



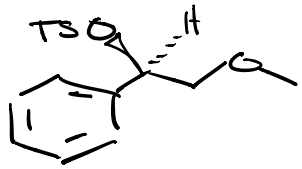
α-haloester

good S_N2

Br^-

I^- Good LG

A good LG = weak base



Substrate

NaN_3 → Acetone, 30°C

Substrate 2° Benzyl Tosylate ⇒ S_N2

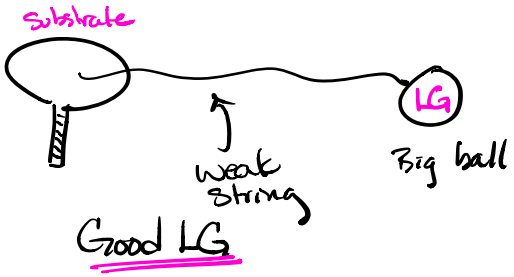
LG -OTs S_N1 / S_N2 / E_1 / E_2 ?

Base/nucleophile $N_3^{\ominus}$ Good nuc ⇒ S_N2

Solvent polar aprotic S_N2 / E_2

Temperature 30°C High or low ? in between S_N2 / E in middle

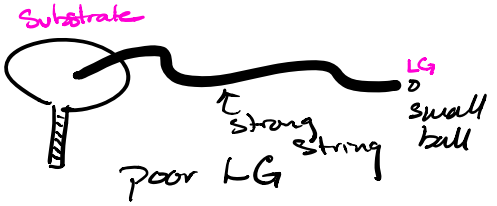
S_N2 major E_2 minor



Good LG

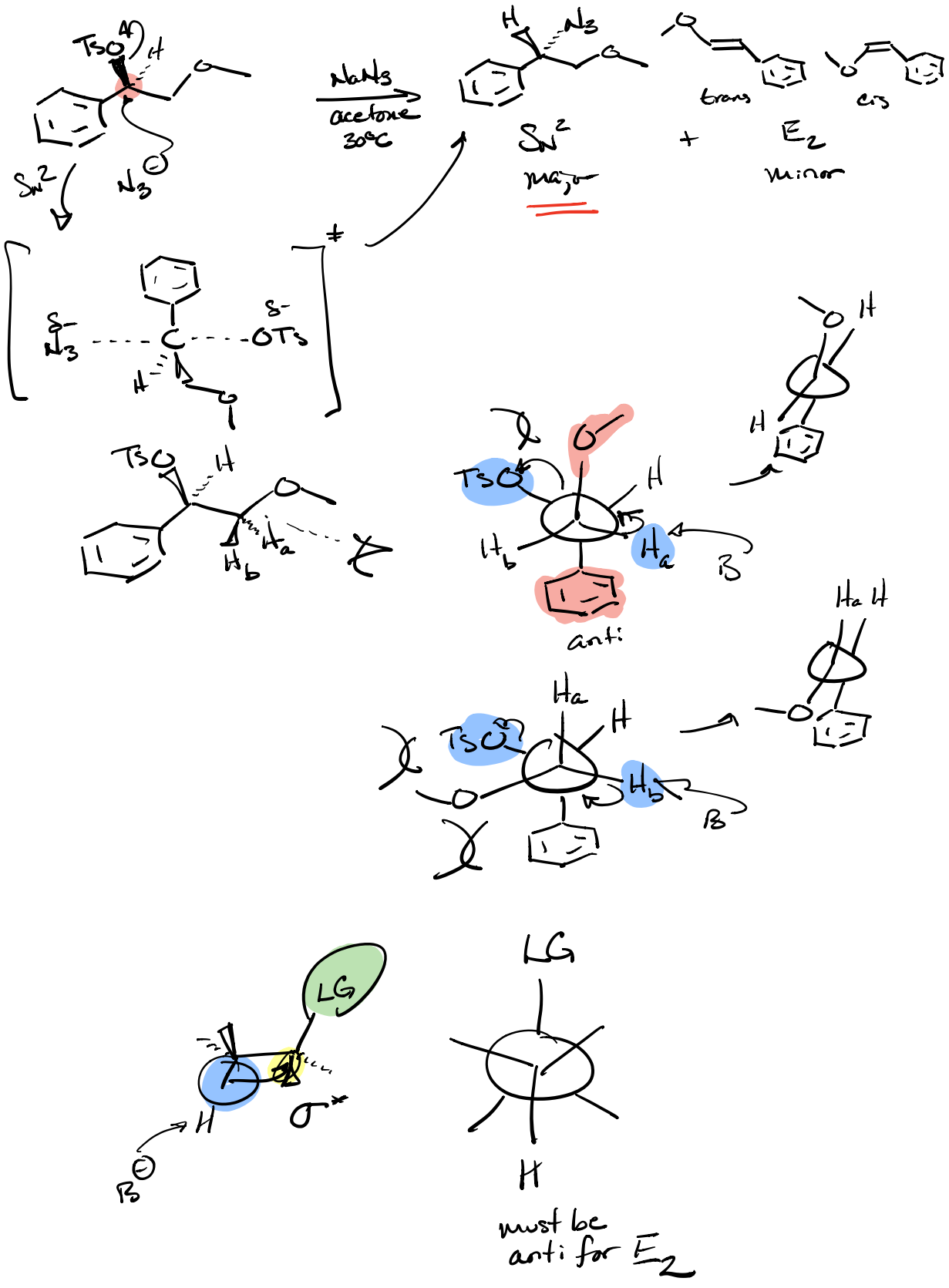
Low temp ~ 25°C might actually be high

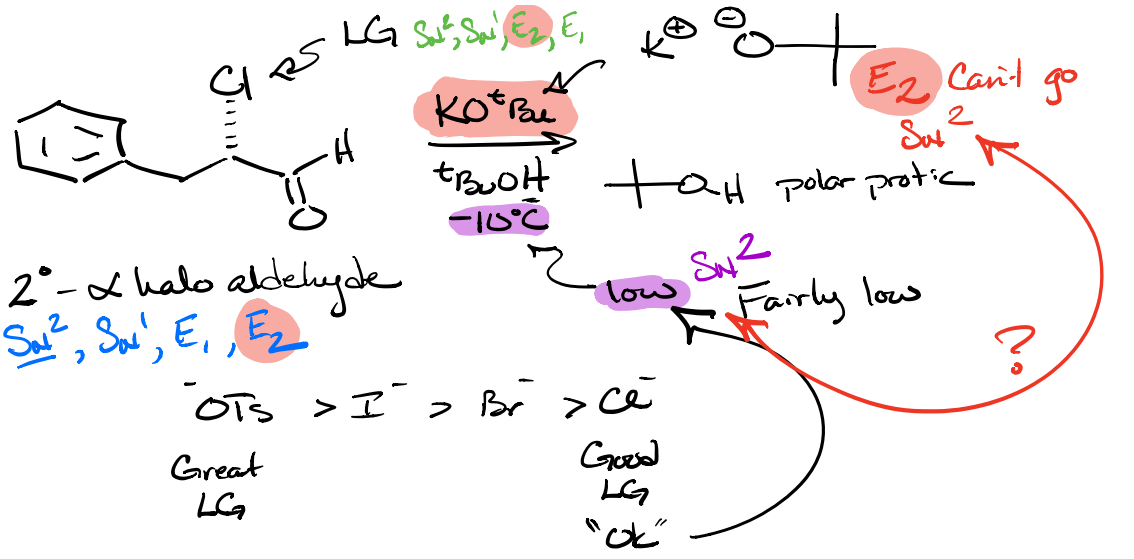
High > 25°C
low < 25°C



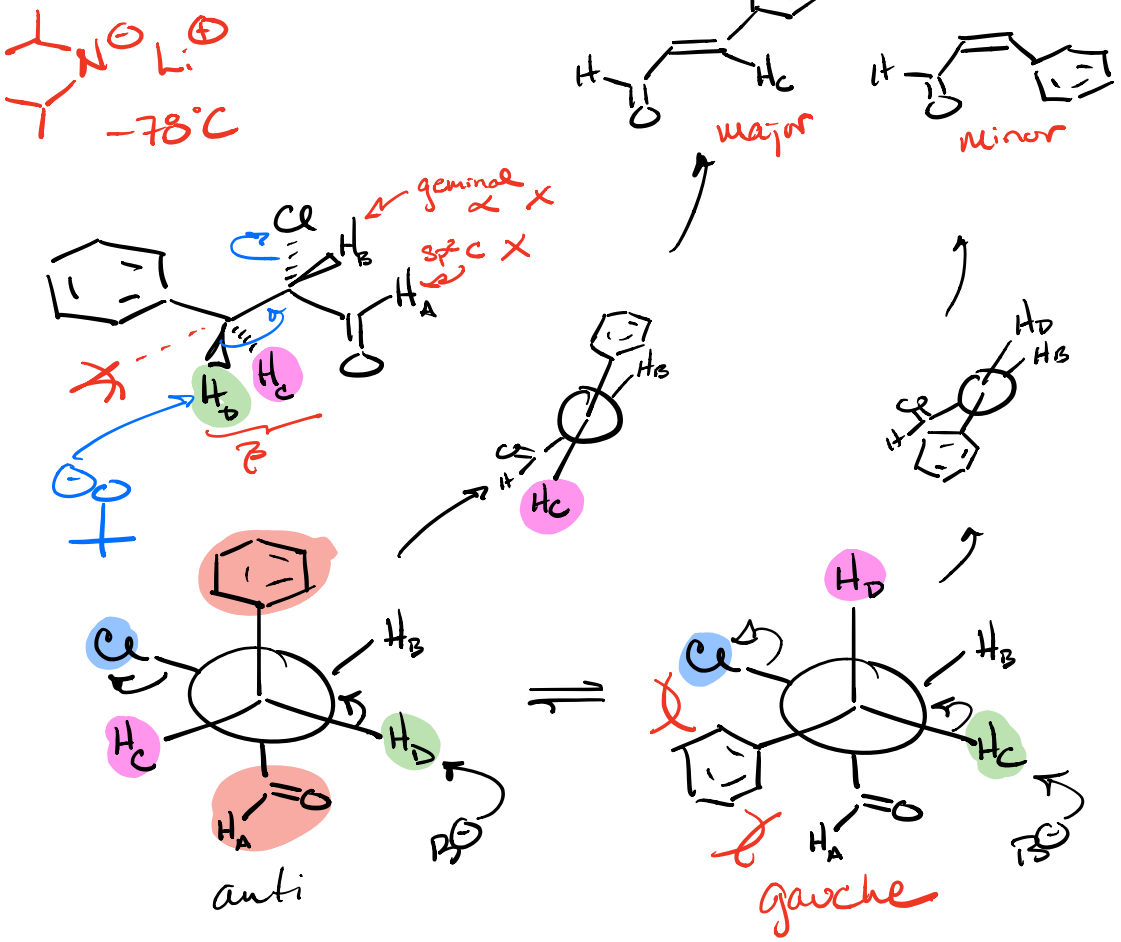
Poor LG

High temp Δ or > 100°C
low < 100°C


NaN3
acetone
30°C
SN2
major
trans
cis
+
E2
minor
anti
must be
anti for E2


LG SN1, SN1', E2, E1
KO^tBu
tBuOH
-10°C
E2
Can't go SN2
polar protic
low
SN2
Fairly low
2° - α halo aldehyde
SN2, SN1, E1, E2
OTs > I > Br > Cl
Great LG
Good LG "ok"
?


-10°C


-78°C
major
minor
geminal α X
sp2 C X
β
anti
gauche

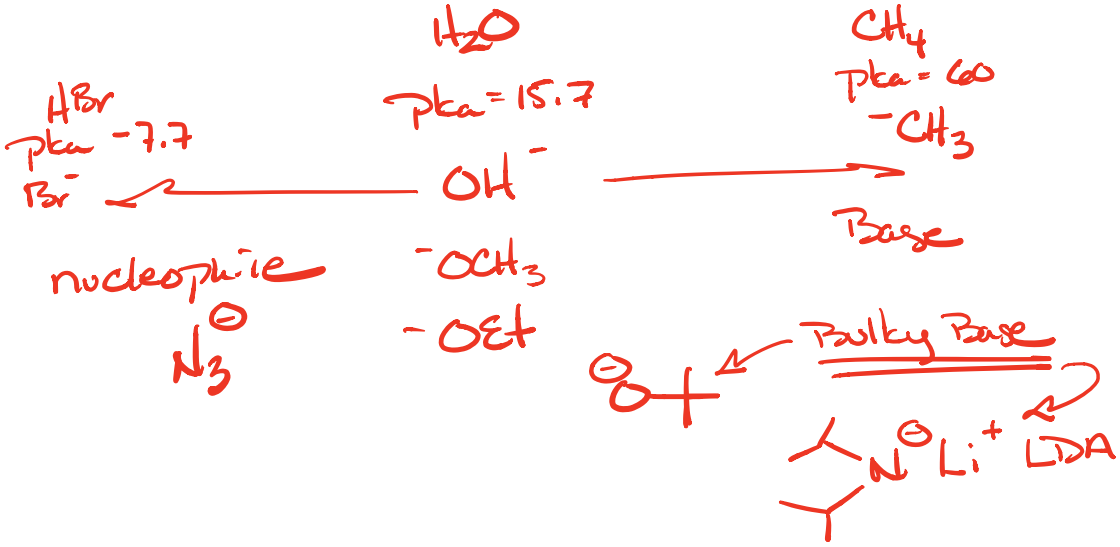
NUCLEOPHILIC SUBSTITUTION AND ELIMINATION

The question is how do we discern when substitution is favored verse elimination? The answer is found partly in how we should think about reactions of alkyl halides.

> *The characteristic reaction of alkyl halides (or alkyl tosylates) with a Lewis base is **elimination**, special conditions are required to promote substitution.*

Given here is a set of guidelines (not absolutes) that can be used to arrive at the probable solution to nucleophilic substitution/elimination problems.

	Substitution	Elimination
	S_N2	E2
substrate	benzyl = allyl > Me > 1^o > 2^o α-haloketone, α-haloester, α-halonitrile	3^o > 2^o > 1^o
solvent	polar aprotic	polar aprotic
nucleophile	good nuc (weaker base than OH^-)	bulky or strong base >= OH^-
leaving group	sulfonate > I^- > Br^- > Cl^-	sulfonate > I^- > Br^- > Cl^-
Temp	low	high
	S_N1	E1
substrate	3^o > 2^o	3^o > 2^o > 1^o
solvent	polar protic	polar protic
nucleophile	weak nuc (no anions!)	any anionic base
leaving group	sulfonate > I^- > Br^- > Cl^-	sulfonate > I^- > Br^- > Cl^-
Temp	low	high



Classification of Nucleophiles

Very good nucleophile	I^-, HS^-, RS^-
Good nucleophile	Br^-, OH^-, RO^-, CN^-, N_3^-
Fair nucleophile	NH_3, Cl^-, F^-, RCO_2^-
Weak nucleophile	H_2O, ROH
Very weak nucleophile	RCO_2H

Nucleophilic Constants of Various Nucleophiles

Nucleophile	n_{CH_3I}	pK_a of conjugate acid
CH_3OH	0.0	-1.7
F^-	2.7	3.45
$CH_3CO_2^-$	4.3	4.8
Cl^-	4.4	-5.7
NH_3	5.5	9.25
N_3^-	5.8	4.75
$C_6H_5O^-$	5.8	9.89
Br^-	5.8	-7.7
CH_3O^-	6.3	15.7
OH^-	6.5	15.7
$(CH_3CH_2)_3N$	6.7	10.70
CN^-	6.7	9.3
I^-	7.4	-10.7
$(CH_3CH_2)_3P$	8.7	8.69
$C_6H_5S^-$	9.9	6.5

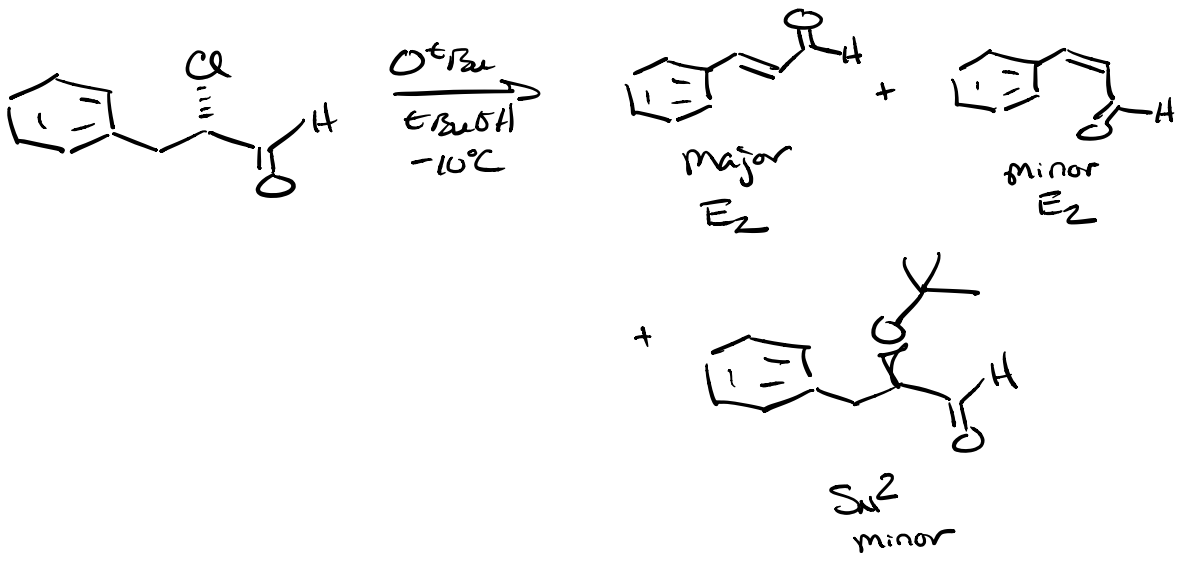
Solvents Which Promote S_N2/E2 (bimolecular)

Acetone
Dimethyl sulfoxide (DMSO)
N,*N*-Dimethylformamide (DMF)
Acetonitrile
Hexamethylphosphoramide (HMPA)

Solvents Which Promote S_N1/E1 (Unimolecular/Ionizing)

Increasing nucleophilicity (solvolysis) ↑

Ethanol
Methanol
50% Aqueous Ethanol
Water
Acetic Acid
Formic Acid
Trifluoroethanol
Trifluoroacetic acid


Cl
H
O
OtBu
tBuOH
−10°C
H
major
E2
+
H
minor
E2
+
H
O
SN2
minor