1. Medicinal Chemistry and Retrosynthetic Analysis

-Drug = Small molecule that interacts with a macromolecular system to produce a biological response

•Drug targets
1) Proteins
▪Enzymes: inhibitor binds to slow/ prevent natural reaction
-Competitive inhibitor binds in the active site
-Non-competitive inhibitor binds to a different region to change its structure and interrupts enzyme activity

▪Receptors: drug binds to transmit signals across the cell membrane
-Agonist binds to trigger the message
-Antagonist binds to block the site without sending message e.g. antihistamines

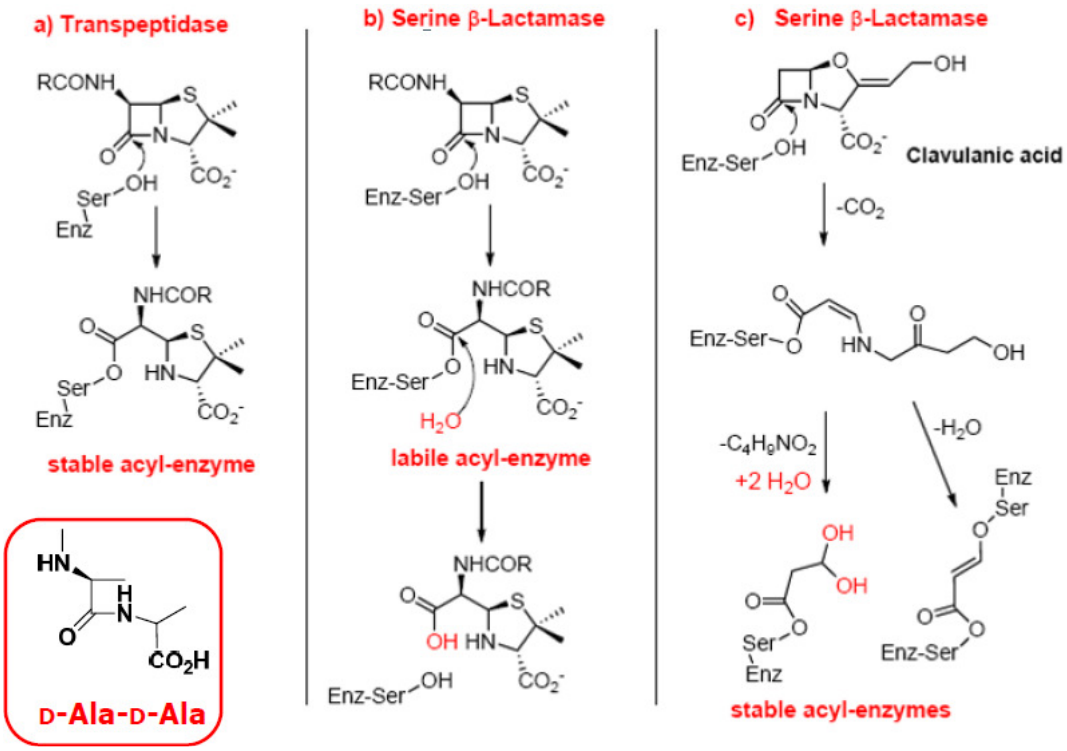
▪Structural proteins: drug binds to disrupt the structure
-Microtubules are required for cell structure, division and the movement of material within a cell during mitosis
-Microtubules are composed of many tubulin stacked together
-Taxol, epothilones bind to tubulin when chromosomes are dividing by H bonding
-Slow down the process of mitosis through H-bonds which stabilise and prolong the intermediate structures
-Cell is frozen mid-division – spindles are not being pulled apart
-Inhibit depolymerisation and block cell replication
-Cancer chemotherapeutic effect

2) Nucleic acids
▪Intercalators: fit between base pairs, distort helix and hinder replication
▪Alkylating agents: react with DNA nucleophiles (base N atoms), forming cross-links and/or distorting the helix
▪Chain cutters: generate reactive species which cleave DNA (e.g. calicheamicin)
▪Antibiotics: bind to ribosomal RNA and inhibit protein synthesis (e.g. streptomycin)

3) Carbohydrates
-Cell surface carbohydrates emerging as potential drug targets

4) Lipids
-Phospholipid membrane is target for hydrophobic molecules
-General anaesthetics increase membrane fluidity
-Some antibiotics create tunnels in membrane
-Vancomycin targets a lipid carrier involved in cell wall building

•Antibiotics evolution
1) β-lactam action and resistance
-β-lactam has an amide in a ring – the lone pair on N cannot access π* orbital of the carbonyl in resonance delocalisation (wrong orbital geometry)
-C-N is significantly weaker
-C becomes more electrophilic and reacts with nucleophile (OH of activate site)

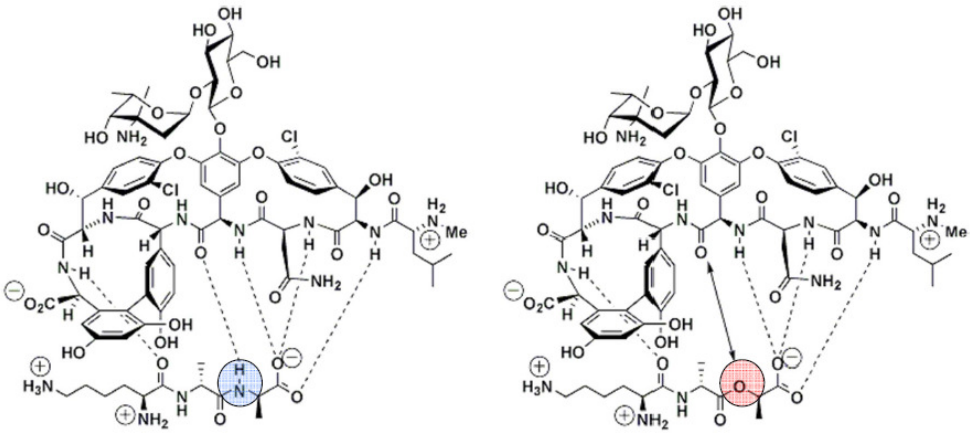


a) Transpeptidase
-β-lactam inhibits the synthesis of peptidoglycan which constitutes the cell wall of bacteria
-Peptidoglycan polymer chains are connected to each other through cross-linking short pentapeptides on terminal D-ala-D-ala
-Transpeptidase (bacterial enzyme) forms an amide bond and cross-links two peptidoglycan chains to form a cell walls
-β-lactam mimics the D-Ala-D-Ala end of the peptide
-Serine OH of the enzyme cleaves the bond on the β-lactam ring in a nucleophilic attack on C=O
-Covalent bond to active site of the enzyme forms a stable acyl-enzyme (inactive)
-Bacteria has weakened cell wall and structural integrity – dilute aqueous solution moves into the cell
-The cell constituents are spewed out and they can no longer replicate

b) Serine β-lactamase
-β-lactamases are enzymes produced by penicillin-resistant bacteria which catalyse the β-lactam ring opening reaction (forms labile acyl-enzyme)
-The enzyme active site has a bit more room which lets water in and hydrolyse the acyl-enzyme intermediate
-Enzyme is regenerated and the open-chain drug is inactive

c) Augmentin
-Clavulanic acid binds to the β-lactamase and forms stable acyl-enzymes
-Antibiotic inhibits transpeptidase

2) Vancomycin action and resistance
-Vancomycin hugs and smothers D-ala-D-ala end by a network of hydrogen bonding
-Inhibits transpeptidase from accessing the dipeptide
-Bacteria have evolved to replace terminal D-alanine (amine) to D-lactate (alcohol) – removes 1 hydrogen bond and kills the activity of vancomycin

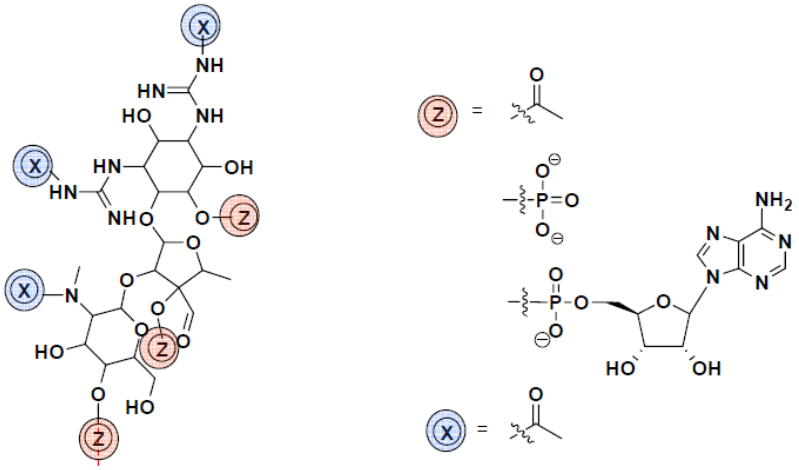


3) Streptomycin action and resistance

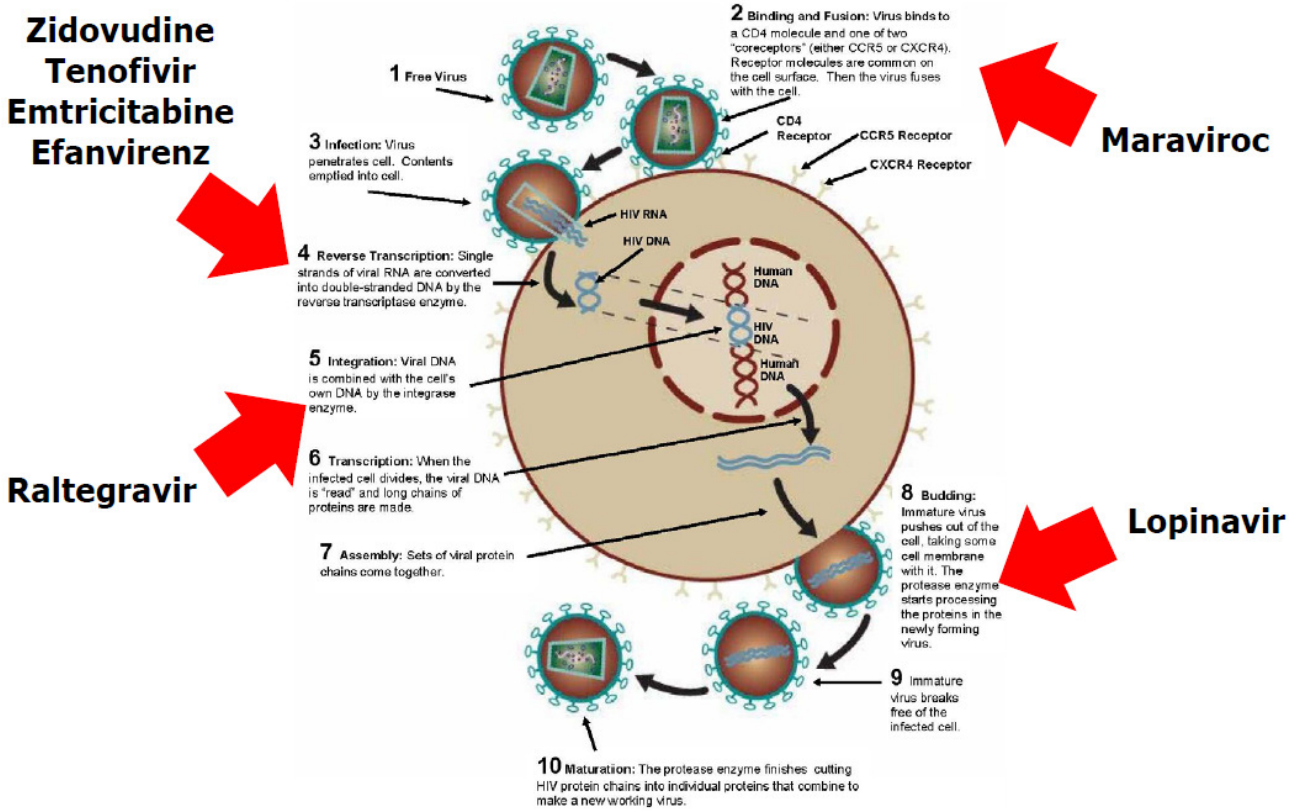
-Streptomycin binds to bacterial ribosome by a network of hydrogen bonding and slows transcription

-Bacteria have evolved and created enzymes that catalyse acetylation, phosphorylation, glycosylation or adenylation of the NH and OH functional groups on the drug to alter reactivity

-Blocks key hydrogen bonding interactions and kills activity



•Modes of action



Pharmacokinetics

▪Pharmacodynamics: how drug interacts with its target to produce biological effects
▪Pharmacokinetics: how it reaches its target
-Absorption = uptake into body
-Distribution = delivery around the body through the blood
-Metabolism = breakdown within body
-Excretion = removal from the body
-Toxicity = unwanted side effects

•Absorption + Distribution
-Oral availability
    -Can be taken as a pill
    -Needs to survive the digestive system (e.g. stomach acid, enzymes)
    -Needs to get across cell membranes
-Solubility
    -Polar enough to dissolve in the blood
    -Hydrophobic enough to pass through fatty membranes
    -Not so fatty that it's lost into fat globules in stomach

•Lipinski's Rule of Five
-Evaluates whether the drug has the right balance between hydrophilicity and hydrophobicity/ right solubility profile → polarity → membrane permeability
-Evaluates oral bioavailability – its suitability to be taken as a pill

1) MW < 500
-Bigger molecule = Less soluble
2) H bond donors < 5
-Excessive H bond donors = Impaired permeability across a membrane bilayer
-Sum of NH bonds and OH bonds = Index of H bond donor character
3) H bond acceptors < 10
-Excessive H bond acceptor = Impaired permeability across a membrane bilayer
-Sum of N and O atoms = H bond accepting ability (not a good model as there is far more variation in hydrogen bond acceptor than donor ability across atom types)
4) LogP < 5
-logP = Partitioning constant between n-octanol and water = a measure of hydrophobicity
-Lipophilicity expressed as a ratio of octanol solubility to aqueous solubility
→ Measure of polarity and hence permeability

(Exam: 5 marks – 4 marks on stating the 4 rules and stating whether the drug fulfils them or not and 1 mark explaining what the rule evaluates)

•Drug discovery
1. Target selection
-Choose a disease
-Choose a drug target (enzyme, receptor, gene …)

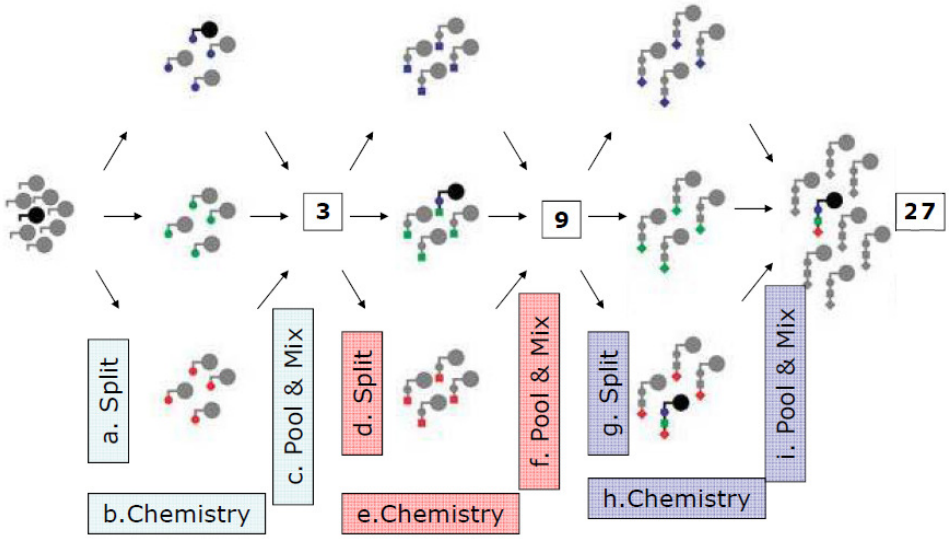
2. Screening = Fire large number of molecules at the target
-Develop a bioassay
-Screen for a lead compound
-'High Throughput' options

3. Characterisation
-Isolate and purify
-Determine drug structure

1. Lead Identification

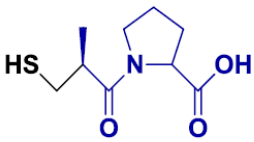
▪High throughput
1. Nature ('natural products')
-Plants, bacteria, sponges, animals

2. Synthetic libraries
-Combinatorial chemistry
-Beads are reacted with different molecules to form new compounds
-The compounds are mixed then separated out
-Another reaction is done
-Limited chemistry and diversity of structures as structurally similar compounds are produced

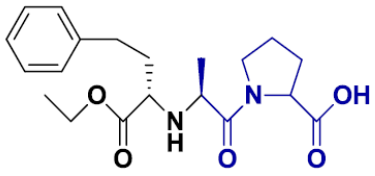


-Diversity Oriented Synthesis
-Structurally diverse compounds are produced
-Cover broader molecular space

▪More focussed
3. Existing drugs
-Changing functional groups on an existing drug to enhance binding affinity and efficacy and to reduce side effect



Captopril
(Bristol-Myers Squib)



Enalapril
(Merck)

-Enhancing a side effect e.g. Viagra

4. The natural substrate
-Salbutamol mimics adrenaline which is a natural substrate for β receptors

5. Rational design
-Use algorithm and 3D molecular shaping to model a target (e.g. protein or nucleic acid)
-Predict a structure for a drug that can bind and have a pharmaceutical effect
-Bottom up designing

2. Lead Optimisation

•Structure-Activity Relationships (SARs)
-Vary functional groups in turn (iterative changes)
-Define which are important for biological activity (or toxicity)
-Hydrogen bond donors and acceptors

-Groups which are salts in vivo
-Hydrophobic groups

-Optimise pharmacodynamics

-Optimise pharmacokinetics

-Getting drug to target

-Optimising access

-Improving absorption

-Allowing targeted delivery

-Keeping drug in one piece

-Increasing resistance to chemical/enzymatic attack

-Reducing side effects

-Lowering resistance to eventual breakdown & excretion

-Reducing/eliminating toxicity

•Isostere

-Isosteres are atoms or groups of atoms with the <u>same valency</u> (steric and electronic features)

-Often similar in size, with some chemical & physical similarities

-Some key differences (reactivity; hydrophilicity/hydrophobicity; H bond donor/acceptor) - place to start changing a molecule to probe SARs

▪Univalent

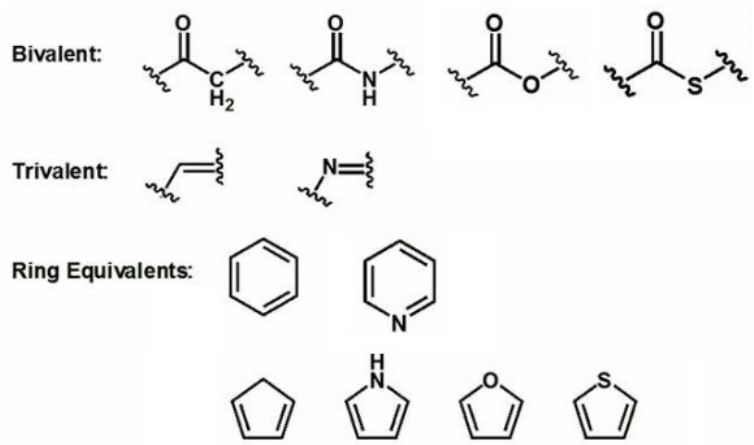
-CH_3, NH_2, OH, SH, F, Cl

-Br, ^{i}Pr

-I, ^{t}Bu

▪Bivalent

-CH_2, NH, O, S



→These studies allow identification of a <u>pharmacophore</u> (minimum representation of key binding groups required for activity)

-Summarises key binding groups required for activity

-Their relative position in space

•Prodrug

-Prodrug is a compound that is inactive but is converted to an active drug in the body

-More membrane permeability/ chemical stability to remain longer in body

-Fewer side effects

•Drug alliances

-Some drugs affect activity or pharmacokinetics of other drugs are administered in combination

-Target different aspects of the same disease profile

-E.g. augmentin = amoxicillin + clavulanic acid

3. Selectivity in Synthesis at sp^2 Centres

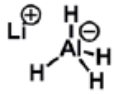
•Selectivity
-Enantioselectivity: Enantiomers are non-superimposable mirror images
-Diastereoselectivity: Diastereomers are stereoisomers that are NOT enantiomers
-Chemoselectivity: One functional group reacts preferentially (in the presence of other functional groups)
-Regioselectivity: One functional group can react in different ways but reacts one way preferentially

-Selectivity implies that there are more than 2 products that CAN be generated (2 transition states)
-There is a preference for one outcome over another outcome

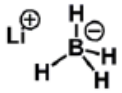
-Specificity: Reactions can be stereospecific (e.g. nucleophile must attack from backside) and the stereochemistry of the starting material dictates the stereochemistry of the product → there is no choice/ preference

<u>Reduction of Carbonyl</u>

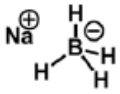
•Hydride reducing agents



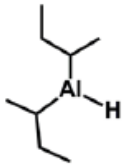
Lithium aluminium hydride
$LiAlH_4$



Lithium borohydride
$LiBH_4$



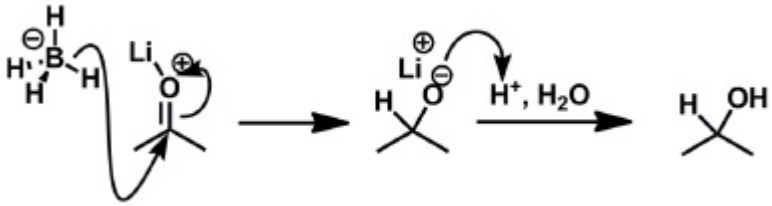
Sodium borohydride
$NaBH_4$



Diisobutyl aluminium hydride
DiBAl-H ®
DiBAl

-Counterion Li, Na = Lewis acid = electron pair acceptor (not stabilising the ate complex)
-Borates, alanates (ate complex) = Hydride (H^-) source

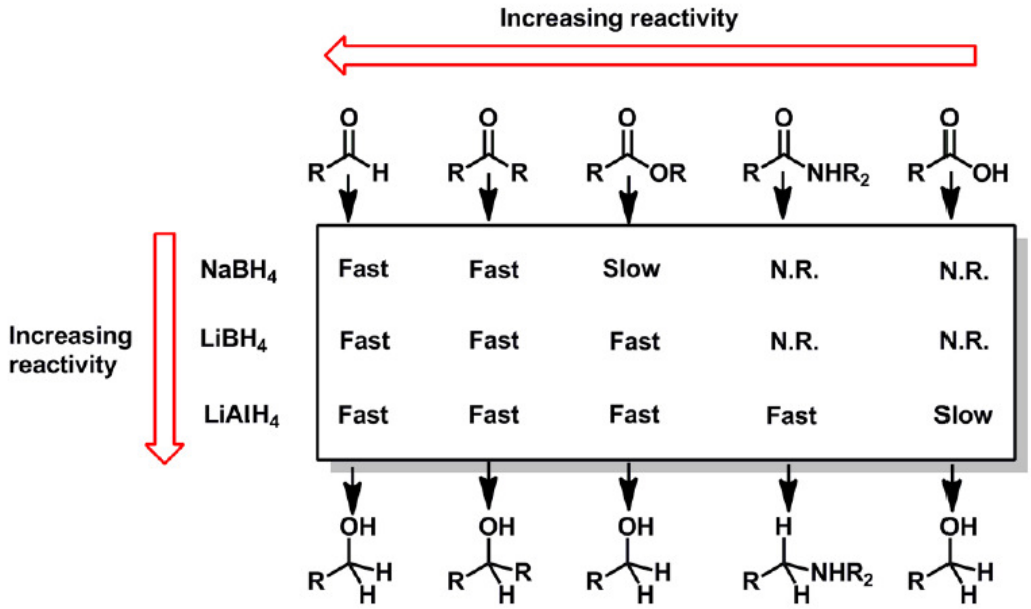
-Borate is more stable than alanate → alanate is a more powerful reducing agent (Al-H bond is weaker/ higher in energy and readily reaches TS by donating electron density out of the Al-H bond)
-Lithium is stronger Lewis acid than sodium → lithium will activate the substrate (increase the electrophilicity of the carbonyl) to a greater extent
-Strength of reducing agent: $LiAl_4 > LiBH_4 > NaBH_4$



-Lewis acid increases the electrophilicity of the carbonyl
-Ate complex donates its electron density

-The reactivity of reducing agents is governed by the stability (nucleophilicity) of hydride reagent and the electrophilicity of carbonyl group

•Chemoselectivity
-Different hydride sources have different levels of reactivity



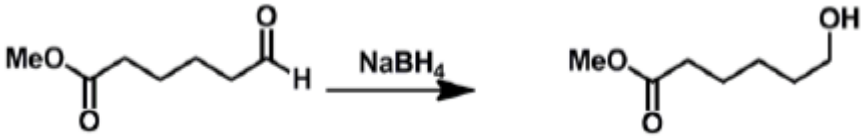
-Reactivity of the carbonyl = Electrophilicity

-Aldehyde > Ketone > Ester > Amide > Acid

-Reactivity of the hydrides = Reducing power

→ Reactivity must be matched

E.g. Aldehyde reacts fast whereas ester reacts very slowly → chemoselective reduction



-To selectively reduce the ester, the aldehyde can be protected with an acetal. Then the ester can be reduced with $LiAl_4$ to alcohol. With THF, water and H^+, the protecting group can be removed.

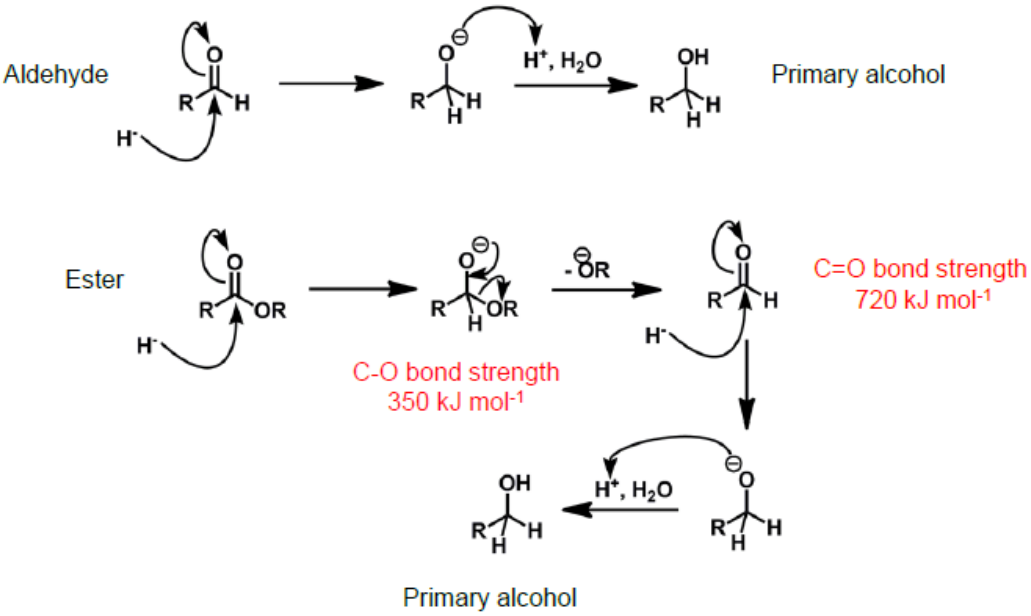
•Mechanistic considerations

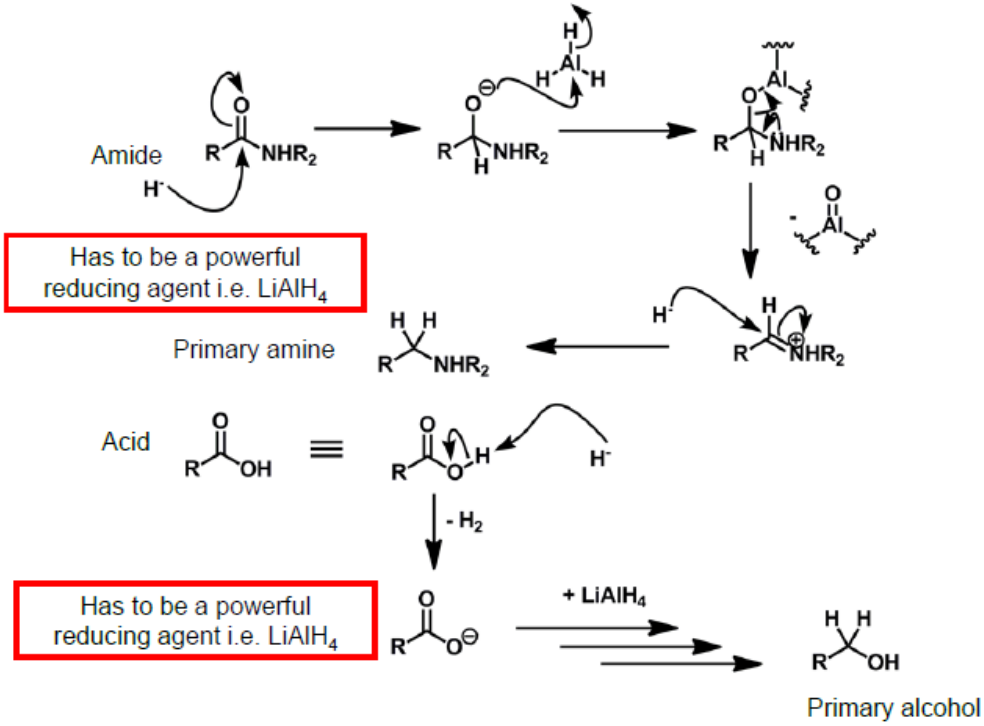
-Reduce the carbonyl

-Generate alkoxide species

-Protonate alkoxide to generate the product

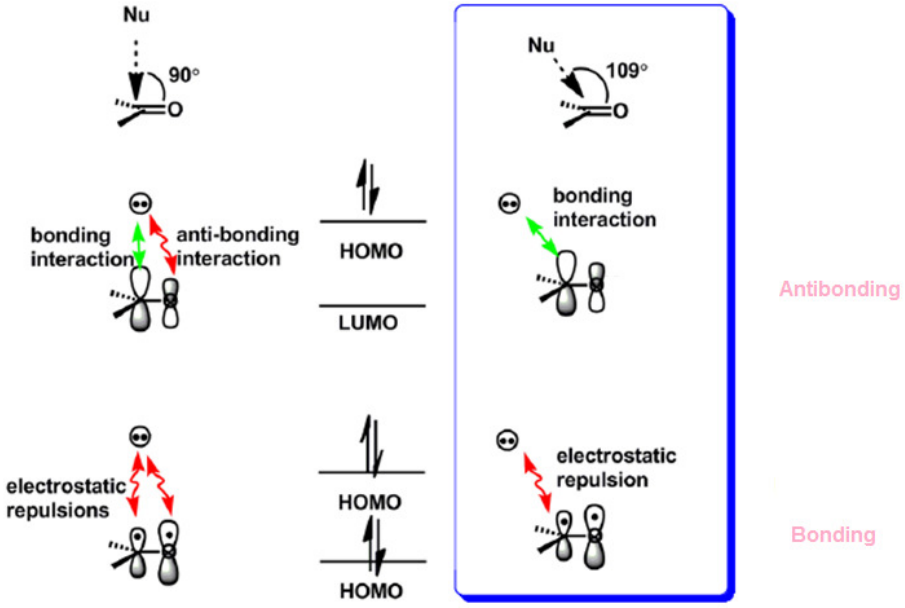
-For esters, the alkoxide collapses and reforms a carbonyl by kicking off another alkoxide because there is a thermodynamic driving force (C=O bond strength is double the C-O bond strength)





-Alkoxide is bound to alanate
-Al-O bond is so strong = Great leaving group
-Lone pair on N pushes off the Al-O species
-Generates an imine – the carbonyl becomes highly electrophilic

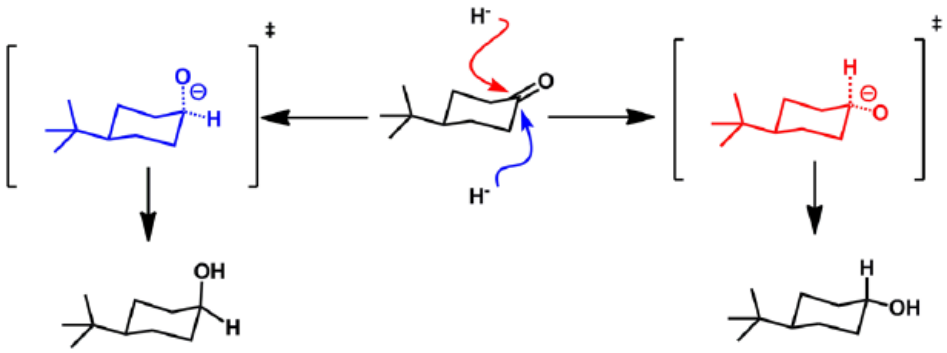
•Diastereoselectivity



-Antibonding: out of phase and larger orbital coefficient on C than O
-Bonding: in phase and larger orbital coefficient on O than C (e^- spends more time on O)
-2 electrons are in π bond
-When a nucleophile comes in, hydride has 2 electrons
-The 2 electrons have to go into antibonding orbital – HOMO of the nucleophile will react with LUMO of the carbonyl
-But bonding orbital is also present – HOMO of the nucleophile will react with HOMO of the carbonyl
-To get maximal overlap, Nu can come in 90° - the electrons will be involved in anti-bonding interaction with the lobe on O and experience electrostatic repulsion with the 2 electrons already in the π bond → unfavourable
-Nu comes in at 107° to maximise the bonding interaction with the antibonding orbital and minimise the electrostatic repulsion with the bonding orbital

▪Burgi-Dunitz trajectory: Nucleophiles attack the carbon atom of the carbonyl group at an angle of 107° which maximises bonding interactions whilst minimising anti-bonding and undesirable electrostatic interactions.

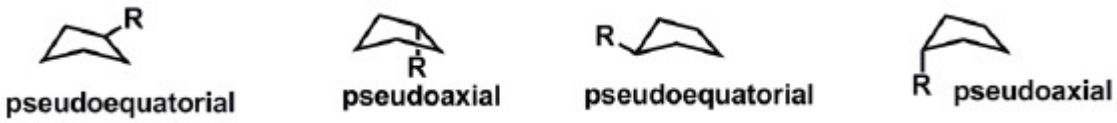
▪Diastereoselective reductions of cyclic compounds:
1) Cyclic compounds
a) 6 membered rings
-Small nucleophiles approach from axial position
-Large nucleophiles approach from equatorial position



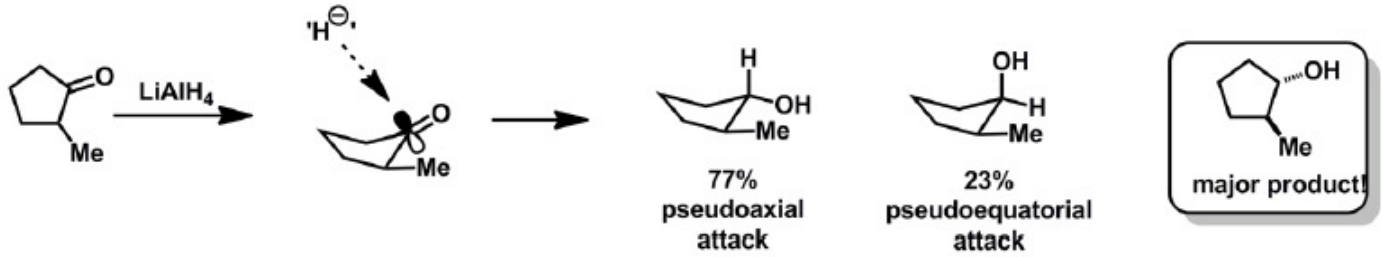
-When H^- approaches from the axial position, the transition state will have O^- on the equatorial position (red). O^- is more stabilised in equatorial position (no 1,3 diaxial clash). So the transition state is lower in energy.
-Irreversible reaction under kinetic control

-Ring flipping is slow as the transition state, the boat form, is high in energy due to flagpole interaction. Therefore, there is preference for one chair position → Specific product

b) 5-membered rings
-5-membered rings have an 'envelope' conformation
-Ring flipping is rapid as there is no transition state (boat form) with high energy
-Substituents can be in pseudoaxial or pseudoequatorial positions or on the point position.



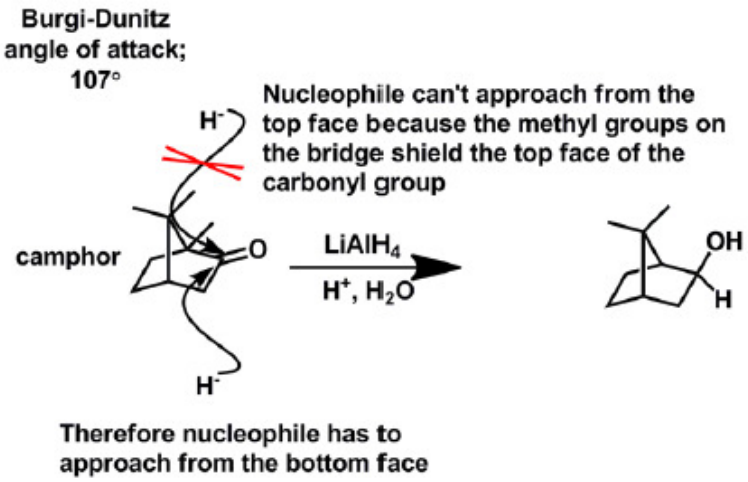
-The result is a very flexible system that gives moderately stereoselective reactions



-The two faces of the ketone are very similar
-Me-substituent prefers a pseudoequatorial position
-Small nucleophiles approach from pseudoaxial position
-However, the ring can flip before the nucleophile can bind (23% product made from pseudoequatorial attack)

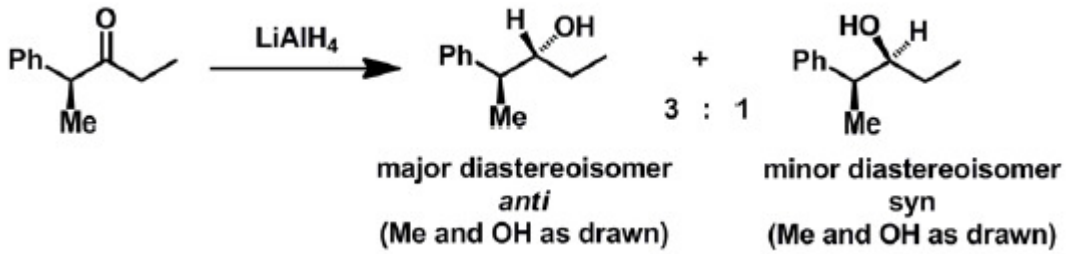
-Large nucleophiles approach from the least hindered face and give the expected cis-alcohol product

c) Bridged cyclic compounds
-Nucleophiles approach from the least hindered face (equatorial attack)
-Steric argument overriding electronic argument



→It is easy to control the level of diastereoselectivity of reactions that occur on cyclic substrates. To achieve a good stereocontrol during a total synthesis, a ring is adopted.

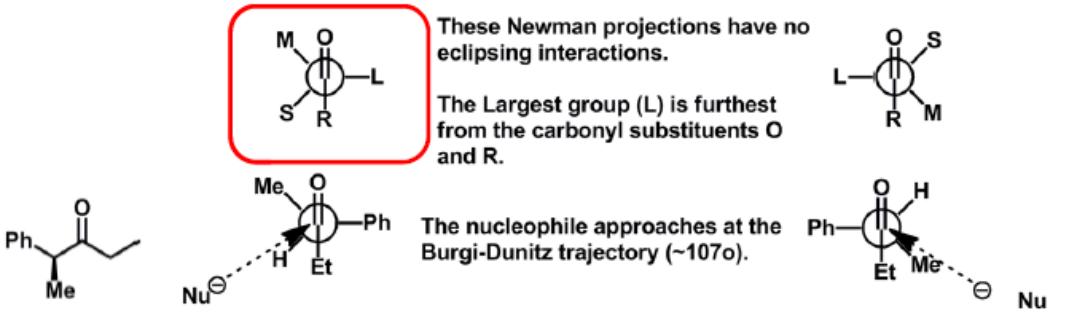
2) Acyclic compounds



-The ketone has an α-stereogenic centre
-Bonds around the carbonyl can rotate freely
-H^- makes a 109° attack on the front or back face but anti predominates (3:1)

-Although the starting ketone has an infinite number of accessible conformations at the reaction temperature, one leads to a lower energy transition state
-Hammond postulate guides this stereoselectivity: Features which stabilise the starting material may stabilise the transition state as well

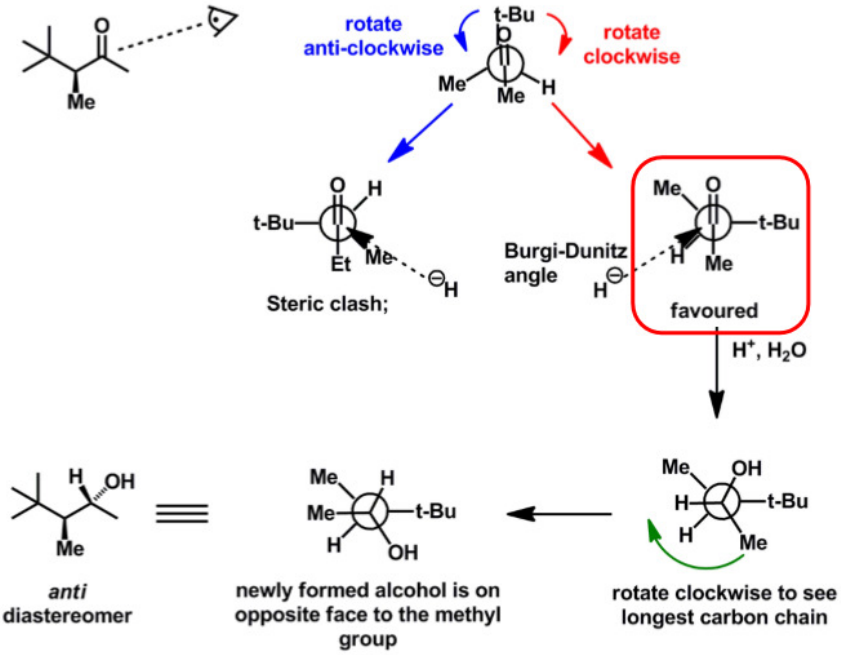
▪<u>Felkin-Anh model</u>
If there is a stereogenic centre α to the carbonyl then:
-Draw the Newman projection with the stereogenic centre at the rear of the diagram
-Rotate the group at the rear so that the large group is perpendicular to the carbonyl group (there will be two possible conformations)
-The nucleophile will approach at the Burgi-Dunitz trajectory (107°) over the small group (i.e. one conformation will react preferentially)
-Draw the product Newman projection
-Draw the product in the standard fashion along the longest carbon chain



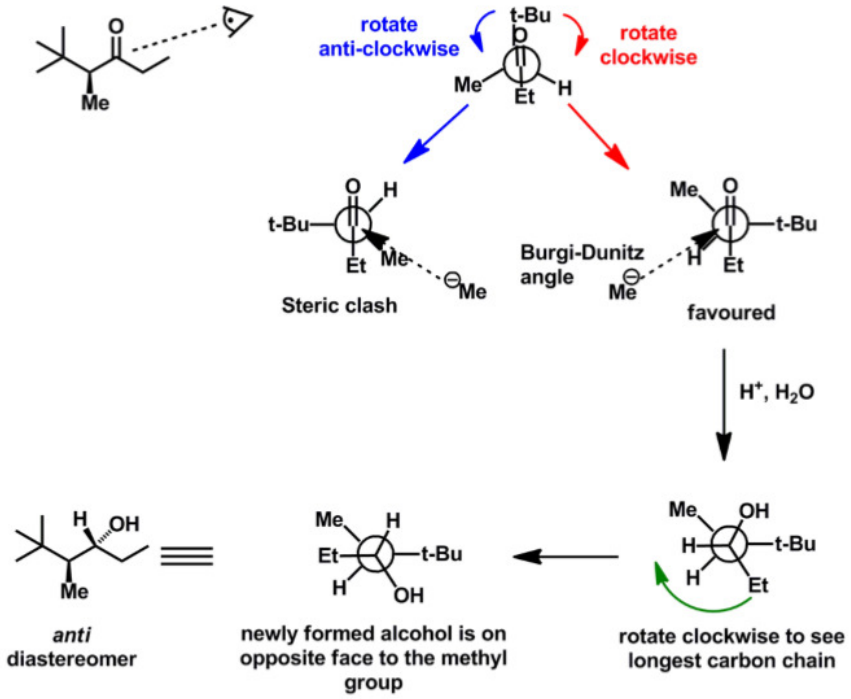
-Nu^- has to go on top of H or Me – attacking over H is least sterically hindered than Me → favoured conformation

-Ph takes all the place so there can be no approach (between largest group and carbonyl)

-Example Question



-Mention: Nucleophile attacks the carbonyl from Burgi-Dunitz trajectory
-Hydride coming over methyl group provides steric clash – Hydride coming over a hydrogen minimises steric clash
-Write favoured and draw a box around the most likely transition state
-Longest carbon chain is formed (longest carbon chain at the front is antiperiplanar from the longest carbon chain at the back)
-Redraw
-Write which diastereomer

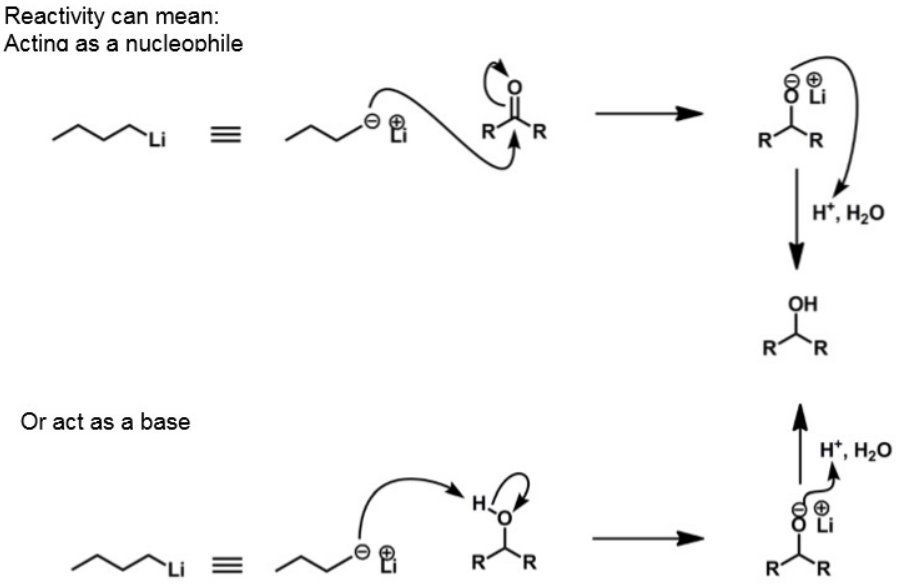


Organometallics

-Another nucleophile capable of reacting with carbonyl groups: organometallic species
-RMgX = Organomagnesium = Grignard reagents
-R_2CuLi = Organocuprate = Gilman reagents
-RLi = Organolithium reagents

-All organometallic species have polar covalent bond (canonical resonance between covalent and ionic forms)

-Reactivity is determined by nature of organometallic species
-Base attacks acidic H and nucleophile attacks everything but proton

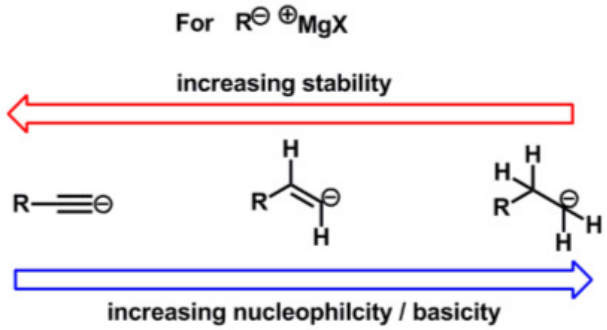


-Both carbanion and metal parts contribute to reactivity

1) Carbanion
-More reactive organometallic species = Less stable carbanion

-For organometallics with the same metal component:

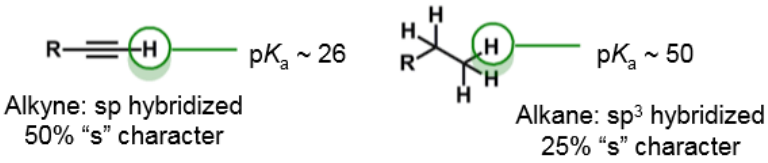
a) Reactivity increases with decreasing “s” character



-$sp < sp^2 < sp^3$

-If the orbital containing the lone pair (negative charge) has a lot of “s” character, then the negative charge is held closer to the positively charged nucleus (in a sphere) and is thus stabilised by the nucleus charge

-If the orbital has a more “p” character, then the negative charge is held further away from the nucleus – the lone pair is available to move to the electrophilic centre on carbonyl (antibonding orbital)

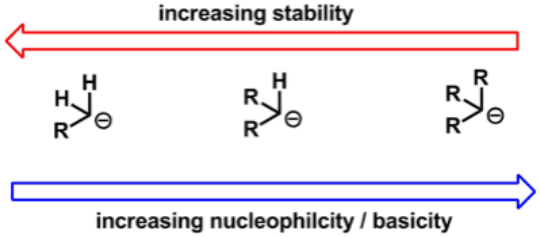


Alkyne: sp hybridized
50% “s” character

Alkane: sp^3 hybridized
25% “s” character

-Alkyne is easier to deprotonate as the carbanion (conjugate base) is very stable

b) Reactivity increases with substitution of EDG

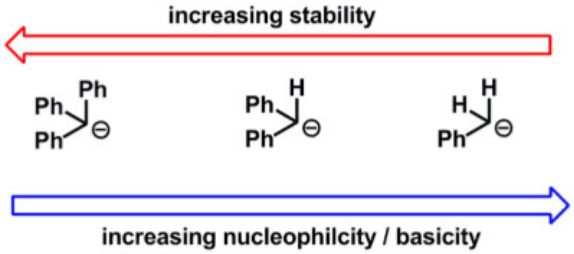


-Primary < Secondary < Tertiary

-Alkyl groups are slightly electron donating (negative hyperconjugation) as C-H/C-C bond eclipses with sp^3 hybridised orbital that contains the 2 electrons and repels them → Destabilise the carbanion → Increase reactivity

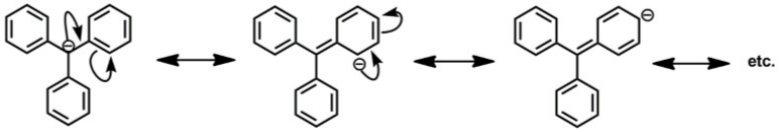
-Tert-butyllithium is a stronger base than *n*-butyllithium

c) Reactivity decreases with substitution of EWG

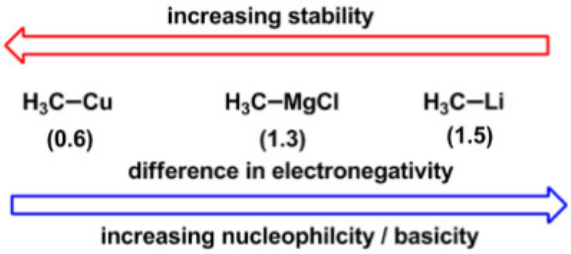


-More resonance stabilised < Less resonance stabilised

-Electron withdrawing groups help to stabilise the negative charge (no e^- density on C) therefore decrease reactivity



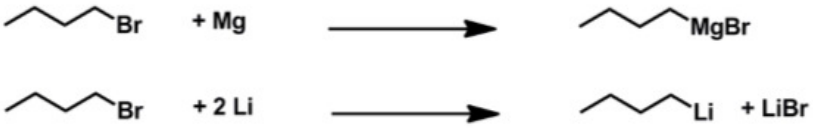
2) Metal – Reactivity increases with larger EN difference



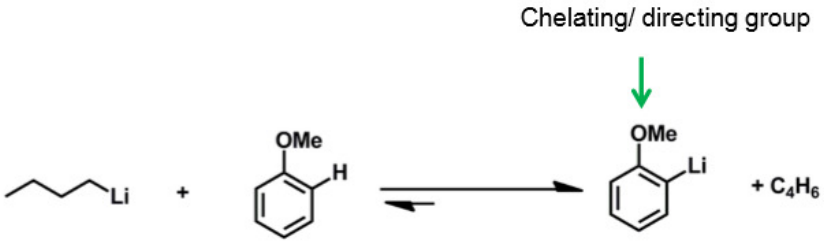
-Cu < Mg < Li
-The larger the difference in electronegativity between the metal and the organic parts, then the more ionic/ less covalent is the bond and the greater the reactivity
-More covalency = Electrons not as available to act as a nucleophile

-Example:

•Formation
1) Reductive replacement (Grignard synthesis)
-Oxidative addition of the metal into C-Br bond



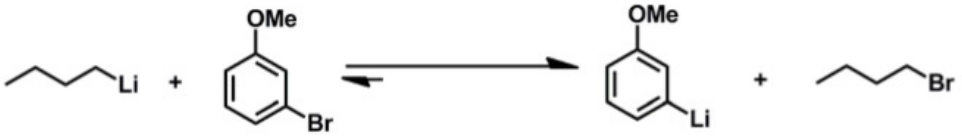
2) Metal – hydrogen exchange
-Deprotonation



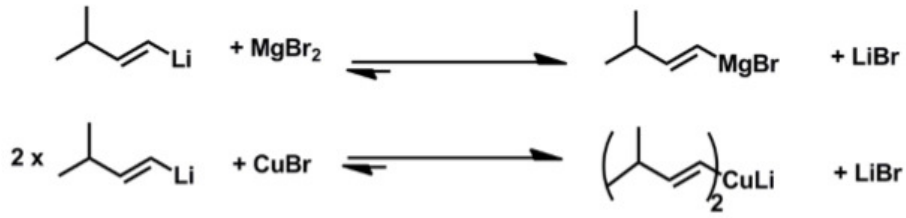
ortho lithiation

-Li is a Lewis acid and is attracted to the lone pair on O of anisole (coordination to any lone pair on directing group)
-Carbanion fragment is placed right over the ortho position and deprotonates there
-This reaction works as the carbanion C is going from sp^3 to sp^2 = increased stability = thermodynamic driving force

3) Metal – halogen exchange
-Reaction preferential for Li
-Alkyl bromide + low temperature (-78°C)
-Carbanion from organometallic takes Br and carbanion from the ring takes the Li
-C-Br bond strength is smaller than C-H bond → Meta lithiation

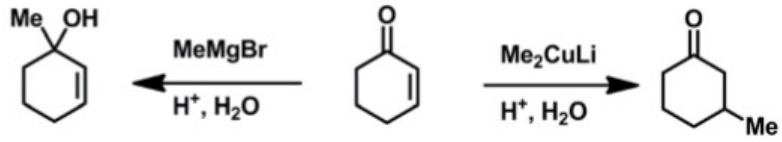


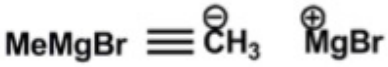
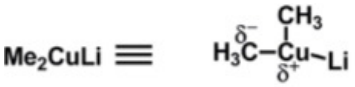
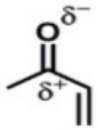
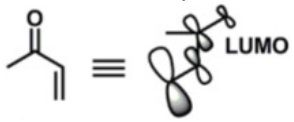
4) Metal – metal exchange (transmetallation)



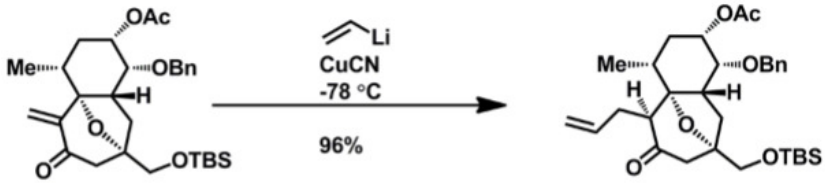
-More reactive metal to less reactive metal (thermodynamic drive)

•Regioselectivity



Li, Mg organometallics (hard metals)	Cu organometallics (soft metal)
Highly polarised/ ionic bond 	Covalent bond 
React by electrostatic interactions	React by frontier molecular orbitals bonding interactions
-Electron pair (negative charge) is held close to the carbon atom → carbanion is a hard nucleophile -Highest partial positive charge on carbon atom of carbonyl: hard electrophile 	-Electron pair is shared between carbon and Cu atoms, only a slight partial charge on carbon atom → carbanion is a soft nucleophile  -β-carbon has the largest orbital co-efficient which is most likely to bump into orbital with a lone pair
Hard species: carries a charge or a high partial charge Hard nucleophiles react fastest with hard electrophiles	Soft species: carries a low partial charge Soft nucleophiles react fastest with soft electrophiles
1,2 addition	1, 4 addition

-Example: Resiniferatoxin (potent analgesic)



-Bridged bicyclic system → Nucleophile attacks the least hindered face = Top face
-Organocuprate is generated from adding organolithium and CuCN
-Highly covalent, more stabilised C-Cu bond is formed
-1,4 reaction

•Diastereoselectivity