

5.1 The disconnection approach: language and first principles

Retrosynthesis plans a synthesis backwards. Instead of asking what a starting material can be turned into, it asks what the **target molecule (TM)** could be made from, and repeats the question until the answer is a purchasable starting material. The backward step is a **disconnection**: an imaginary breaking of one bond of the target, corresponding to a real reaction run forwards. Disconnection is written with the retrosynthetic arrow (a double line open arrow, shown here as $\Rightarrow$) and gives **synthons**: the idealised fragments the disconnection implies, charged or radical fragments that may not exist as such. Each synthon is then matched to a **synthetic equivalent**, the real reagent that behaves as that synthon: the acyl cation synthon $R-C+=O$ is matched by the acid chloride $R-COCl$, and the carbanion synthon R^- by the Grignard reagent $RMgX$.

Two auxiliary operations complete the language. **Functional group interconversion (FGI)** changes one functional group into another without touching the skeleton, moving the molecule to a form where a good disconnection exists (oxidise an alcohol to a ketone so that a carbonyl disconnection can be used).

Functional group addition (FGA) deliberately adds a group, often a carboxyl or an activating group, to make a disconnection possible or regioselective, the group being removed later. **Umpolung** names the polarity inversions that supply unusual synthons, such as the dithiane anion as an acyl anion equivalent (Unit 3).

The advantages the syllabus lists are real: working backwards guarantees every step is chosen because the target needs it; it exposes several routes for comparison before any laboratory time is spent; and it concentrates attention on the skeleton forming steps, which decide whether a route is short or long.

5.2 Guidelines for the dissection of molecules

- **Disconnect bonds made by reliable reactions first:** amide, ester and ether bonds, and C-C bonds formed by the named reactions of Unit 2, because the forward reactions are trusted.
- **Disconnect at branch points and near the middle:** two similar sized fragments shorten the longest linear sequence, and convergent routes (fragments made in parallel, joined late) beat long linear ones for overall yield.
- **Use symmetry:** if the target has a plane of symmetry, one disconnection can create both halves from a single fragment.
- **Let functional groups guide the cut:** the C-C bond beside an alcohol is a Grignard disconnection; beside a carbonyl, an enolate disconnection.
- **Prefer disconnections that give stable synthons and cheap equivalents**, and avoid synthons with no real equivalent.
- **Simplify before disconnecting:** FGI the target into the form with the most obvious disconnection, and disconnect the simplified form.
- **Count the cost of protecting groups:** a disconnection demanding extensive protection (Unit 3) is usually inferior to one that avoids the clash.

5.3 C-X disconnections

Heteroatom bonds are the easiest disconnections because the forward reactions are substitutions and acylations of predictable polarity: the heteroatom partner is the nucleophile and the carbon partner is the electrophile (or acyl electrophile).

- **Ethers:** disconnect the C-O bond on either side; choose the side that puts the SN2 displacement on the less hindered carbon, the logic of the Williamson ether synthesis. Aryl alkyl ethers disconnect to phenol plus alkyl halide, never the reverse.
- **Esters and amides:** disconnect at the acyl bond to carboxylic acid (or chloride) plus alcohol or amine. These are one group C-X disconnections: one functional group in the target, one disconnection.
- **Amines:** disconnect a C-N bond to amine plus alkyl halide for simple alkyl groups, but remember overalkylation: for precise work the amine is often better reached by FGI from an amide, a nitrile, an imine reduction (reductive amination) or a Gabriel synthesis, so the apparent C-N disconnection is replaced by a carbonyl level precursor.
- **Sulfides and thiols** follow the same nucleophile-electrophile matching as ethers.

5.4 C-C disconnections: alcohols and carbonyl compounds

Alcohols. The C-C bond next to a carbinol carbon is disconnected so that the carbon bearing OH becomes a carbonyl carbon synthon and the other fragment becomes a carbon nucleophile synthon:

Alcohol disconnection, the 1,1-pattern

R²CH-OH target

=> disconnect the C-C bond beside the OH carbon

=> synthon 1: a carbonyl carbon (equivalent: an aldehyde or ketone)

=> synthon 2: a carbanion at the other fragment (equivalent: a Grignard reagent or organolithium)

Forward: RMgX adds to the carbonyl, work up gives the alcohol.

The choice of which group comes from the carbonyl partner and which from the Grignard partner is made on cost, availability and symmetry.

Carbonyl compounds. Ketones and aldehydes disconnect in the same place but with different matched methods: an acyl synthon plus an alkyl synthon (forward: organometallic addition to an acid chloride derivative, a Weinreb amide, or a nitrile), or, for alpha functionalised carbonyls, an enolate synthon plus an electrophile synthon (forward: enolate alkylation and acylation, Unit 1). Carboxylic acids disconnect to the one carbon shorter nucleophile synthon plus carbon dioxide (Grignard carboxylation) or to a nitrile that is hydrolysed. Alpha,beta-unsaturated carbonyls disconnect across the double bond to an enolate donor and an aldehyde, the aldol logic, or are recognised as Michael products.

5.5 Difunctionalised compounds: the 1,n patterns

When two functional groups share a skeleton, the distance between them names the pattern and points to the reaction that makes both relationships at once:

Pattern	Typical target	Disconnection logic	Forward reaction
1,2-Difunctional	Alpha-hydroxy carbonyls, vicinal diols, epoxides	Break the C-C bond between the two functionalised carbons, or simplify by FGI to an alkene	Cyanohydrin and acyloin type couplings; diols by alkene dihydroxylation (OsO ₄ , Unit 3) after FGI
1,3-Difunctional	Beta-hydroxy carbonyls, 1,3-dicarbonyls	Disconnect the C-C bond beside one carbonyl: enolate plus carbonyl	Aldol reaction; Claisen and Dieckmann condensations

Pattern	Typical target	Disconnection logic	Forward reaction
1,4-Difunctional	Gamma-keto esters and acids	Needs one synthon of reversed polarity (umpolung): an acyl anion equivalent or a homoenolate equivalent	Dithiane alkylation then hydrolysis; Stetter reaction
1,5-Difunctional	Delta-keto carbonyls, 1,5-dicarbonyls	Disconnect the bond between the alpha and beta carbons of the enone pattern	Michael addition (Unit 2)
1,6-Difunctional	Hexanedioic (adipic) type chains	Disconnect the central bond and recognise a ring: simplify by FGI to a cyclohexene	Ozonolysis or oxidative cleavage of the ring double bond (Unit 2)

The table is the working core of this unit. The 1,3 and 1,5 patterns arise from ordinary enolate polarity and are easy; the 1,4 pattern is deliberately listed to teach umpolung, because normal polarity cannot join two electrophilic carbons; the 1,6 pattern teaches that a ring can be a synthetic equivalent of a chain.

5.6 Strategies for the synthesis of rings

- **Three membered rings:** carbene and carbenoid addition to alkenes (cyclopropanes, Unit 1), and intramolecular SN2 closures to epoxides and aziridines; in retrosynthesis a cyclopropane disconnects back across one bond to the alkene.
- **Four membered rings:** the hardest common size, because of ring strain and slow cyclisation. Photochemical [2+2] cycloaddition and ketene [2+2] cycloaddition are the reliable entries; a cyclobutanone is read back to a ketene plus an alkene.
- **Five membered rings:** cyclisation is fast and favourable. Dieckmann condensation for carbocycles, Paal-Knorr and Knorr condensations (Unit 4) for pyrroles, furans and thiophenes, 1,3-dipolar cycloadditions for five membered heterocycles, and radical or anionic 5-exo cyclisations.
- **Six membered rings:** the Diels-Alder reaction is the first disconnection to try for a cyclohexene ring (disconnect two bonds back to diene plus dienophile); Robinson annulation builds the ring by Michael addition and aldol closure; Dieckmann and intramolecular aldol reactions close saturated rings; the named quinoline, pyrimidine and purine syntheses of Unit 4 are the heterocyclic equivalents, joining a dinucleophile fragment to a dielectrophile fragment.
- **Heterocyclic rings generally:** read the ring as nucleophile fragment plus electrophile fragment: count the atoms each partner contributes (the 3 plus 2 and 2 plus 3 patterns), place the heteroatom bonds as C-X disconnections (section 5.3) and the remaining C-C bond as the enolate or condensation disconnection.

5.7 Sequence of events in a disconnection analysis

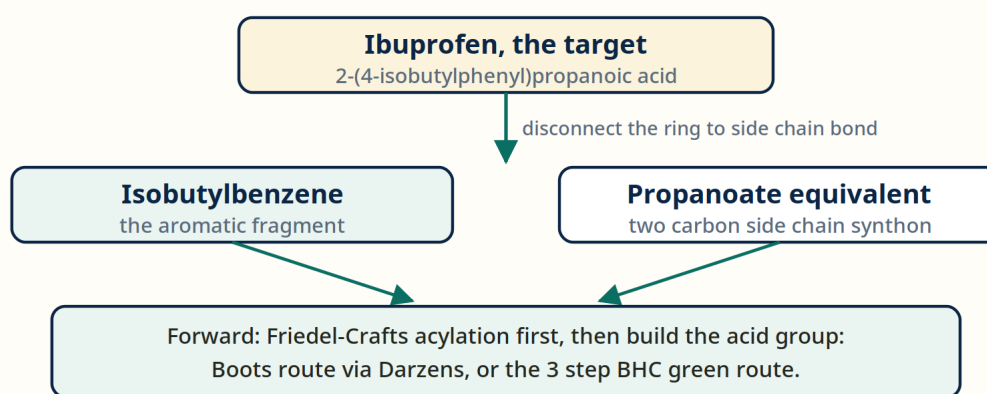
The KBH copy names the working order explicitly, and it is the order used in the worked examples of any textbook treatment:

- 1 **Analyse:** identify every functional group in the target, the ring systems, the stereocentres and any symmetry.
- 2 **Simplify:** apply FGI on paper to reach the form of the target with the most powerful disconnection available.
- 3 **Disconnect:** break one strategic bond, write the synthons, and immediately write the real synthetic equivalents under them; a disconnection without known equivalents is a guess, not a plan.
- 4 **Repeat:** treat each fragment as a new target until every fragment is a known or purchasable compound.

- 5 **Write the forward synthesis:** reverse every arrow, order the steps so that reactive groups are made late or protected (Unit 3), check each step against a named, trusted reaction, and check that no step destroys functionality installed earlier.
- 6 **Compare routes** where more than one analysis succeeded: shortest longest sequence, cheapest starting materials, fewest protections and safest reagents win.

Worked illustration, ibuprofen. The target is 2-(4-isobutylphenyl)propanoic acid: a carboxylic acid one carbon from a benzylic centre, on a para substituted ring. Disconnect the bond between ring and side chain first (a Friedel-Crafts disconnection): the synthons are isobutylbenzene plus a two carbon propanoate electrophile equivalent. Forward, the industrial Boots route acylates isobutylbenzene, then builds the acid through a Darzens glycidic ester sequence, hydrolysis and decarboxylation; the later BHC green route keeps the same acylation disconnection but executes it in three steps (HF catalysed acylation, hydrogenation of the ketone, carbonylation). One good disconnection can support more than one forward execution, and the greener execution wins commercially.

Retrosynthesis of Ibuprofen: One Key Disconnection



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Figure: Ibuprofen dissected. One Friedel-Crafts disconnection supports both the Boots and the BHC forward routes.

Frequently Asked Questions

Q: How does the stability order of carbocations differ from that of carbanions, and why?

Carbocations are stabilised by electron donation, so the order is tertiary > secondary > primary > methyl, with allyl and benzyl cations higher still because the charge is delocalised. Carbanions are stabilised by electron withdrawal and delocalisation of the lone pair, so simple alkyl anions follow the reverse order, and the useful carbanions are resonance stabilised ones such as enolates and the anions of 1,3-dicarbonyl compounds. The same substituent, an alkyl group, stabilises one and destabilises the other because the two species have opposite electron demand.

Q: Which experiments would you use to prove that a reaction goes through a carbocation?

Look for the cation's fingerprints: rearranged products from hydride or alkyl shifts, racemisation at the reacting carbon, a rate law that depends only on the substrate, strong acceleration by ionising solvents, and common ion rate depression. Where direct evidence is wanted, carbocations can be generated in superacid media and observed by NMR, or trapped with azide ion to give alkyl azides among the products.

Q: What is the difference between the Saytzeff and Hofmann products of an elimination?

The Saytzeff product is the more substituted alkene, favoured with small bases because the transition state borrows the stability of the more stable alkene. The Hofmann product is the less substituted alkene, favoured with bulky bases that can only reach the least hindered proton, and in the Hofmann elimination of quaternary ammonium hydroxides where the charged leaving group and statistical proton counts reinforce the same result. Naming the product is not enough in an answer; the reason, alkene stability against steric access, is what earns marks.

Q: Why is fluoride the best leaving group in S_NAr when it is the worst in S_N1 and S_N2?

In S_NAr the rate determining step is addition of the nucleophile to the ring, not breaking of the carbon-halogen bond. Fluorine's powerful electron withdrawal makes the ring carbon more electrophilic and stabilises the Meisenheimer complex, so fluoride substrates react fastest even though the C-F bond is the strongest. In aliphatic substitution the bond must break in or before the rate determining step, so the order reverses and iodide, with the weakest bond, leaves best.

Q: What makes the Mitsunobu reaction give inversion, and when does it fail?

The alcohol oxygen is converted into an alkoxyphosphonium group, turning hydroxide into a leaving group as good as triphenylphosphine oxide, and the nucleophile then performs an ordinary backside S_N2 displacement, which inverts the centre. It fails for tertiary alcohols because the S_N2 step is sterically blocked, and for pronucleophiles too weakly acidic (pK_a above roughly 13) because the DEAD-phosphine betaine cannot deprotonate them.

Q: How do you remember which face the Sharpless epoxidation oxidises?

Draw the allylic alcohol in the standard orientation, double bond horizontal with the CH₂OH group at the lower right. Natural (+)-diethyl tartrate in the titanium complex then delivers oxygen to the bottom face of the double bond and (-)-diethyl tartrate delivers it to the top face. The mnemonic only works quoted with its drawing convention, and the allylic alcohol group is essential because it binds the substrate to the titanium-tartrate catalyst.

Q: What are the three steps of the Suzuki catalytic cycle and what does each do?

Oxidative addition: palladium(0) inserts into the aryl or vinyl halide bond, giving a palladium(II) complex.
Transmetalation: the base activated boronate transfers its organic group from boron to palladium.
Reductive elimination: the two organic groups on palladium join to form the new C-C bond and palladium(0) is regenerated. Each step has a distinct job, bond breaking at the halide, group transfer, and bond making, and the cycle explains both the need for base and the retention of alkene geometry.

Q: What decides which group migrates in the Baeyer-Villiger oxidation?

Geometry first: the migrating group must be anti-periplanar to the O-O bond of the Criegee intermediate. Within that constraint, aptitude follows the ability to carry partial positive charge in the migration transition state, giving the order tertiary alkyl > secondary alkyl and phenyl > primary alkyl > methyl, with electron rich aryl groups migrating faster than electron poor ones. The migrating group retains its configuration because it never detaches from the molecule.

Q: What makes a protecting group orthogonal to another one?

Two protecting groups are orthogonal when each can be removed under conditions that leave the other completely untouched: a benzyl ether (removed by hydrogenolysis) beside a TBDMS ether (removed by fluoride), or a Boc group (acid labile) beside a Cbz group (hydrogenolysis labile). Orthogonality lets a synthesis unmask one functional group at a time, which is the basis of peptide synthesis strategy, where Boc or Fmoc on nitrogen, an ester on the carboxyl and separate side chain masks are all removed in a

planned order.

Q: How do you choose a disconnection for a molecule with two functional groups?

First measure the distance between the groups and name the pattern. A 1,3 relationship disconnects to an enolate plus a carbonyl compound (aldol or Claisen logic), a 1,5 relationship to a Michael addition, a 1,2 relationship is handled by FGI to an alkene or by umpolung couplings, a 1,4 relationship demands one reversed polarity synthon such as a dithiane anion, and a 1,6 relationship is simplified back to a ring alkene that is cleaved oxidatively. The pattern, not the individual groups, makes the choice.

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