

3.1 Aluminium isopropoxide: Meerwein-Ponndorf-Verley reduction and Oppenauer oxidation

Aluminium isopropoxide, $\text{Al}(\text{OCH}(\text{CH}_3)_2)_3$, is the reagent of the **Meerwein-Ponndorf-Verley (MPV) reduction**: in isopropanol solution it reduces aldehydes and ketones to alcohols while leaving carbon-carbon double bonds, nitro groups, halides and other reducible functions untouched. The mechanism is a hydride transfer inside a six membered cyclic transition state in which the carbonyl and an isopropoxide ligand are both bound to aluminium; acetone is formed, and distilling it out drives the equilibrium to product.

Run backwards, the same system is the **Oppenauer oxidation**: a ketone (classically cyclohexanone or acetone) in excess accepts the hydride and an alcohol is oxidised to its carbonyl compound, again with complete selectivity against double bonds. This pair of reactions matters in steroid chemistry, where a single secondary alcohol must be oxidised or a single ketone reduced in a molecule full of other functionality, and the mild, neutral conditions explain their survival in the reagent canon.

3.2 N-Bromosuccinimide (NBS)

N-Bromosuccinimide is the reagent for radical bromination at allylic and benzylic positions (the Wohl-Ziegler bromination). With a radical initiator (light, peroxide or AIBN) in carbon tetrachloride or a substitute solvent, NBS maintains a very low concentration of bromine: the chain carrier bromine radical abstracts the weak allylic or benzylic hydrogen, and the resulting resonance stabilised radical takes bromine from Br_2 as fast as it forms. Keeping Br_2 scarce is the whole trick, because free bromine at high concentration would add across the double bond instead. HBr produced in the chain regenerates Br_2 from NBS, so the cycle sustains itself.

Further uses of NBS: bromination of arenes under ionic conditions in polar solvents, alpha bromination of ketones through their enols, and as a source of electrophilic bromine for bromohydrin formation with water as co-solvent. Allylic bromides from NBS are standard intermediates for introducing amines, ethers and carbon chains at allylic positions in terpene and steroid work.

3.3 Diazomethane

Diazomethane, CH_2N_2 , is a yellow gas used in ether solution, a reagent of unmatched convenience and matched hazard: it is toxic, carcinogenic in concern and explosive, and is generated and used in situ behind screens with ground glass free apparatus.

Reactions:

- **Methylation of carboxylic acids**: instant, quantitative conversion into methyl esters with nitrogen as the only byproduct, because the acid protonates diazomethane to a methyldiazonium ion that the carboxylate displaces in an $\text{S}_\text{N}2$ step. Phenols and enols are methylated more slowly in the same way. Analytical chemists use it (or the safer trimethylsilyldiazomethane substitute) to make methyl esters for gas chromatography.

- **Arndt-Eistert homologation:** an acid chloride reacts with diazomethane to a diazoketone, which undergoes the Wolff rearrangement (Unit 1) to the one carbon longer acid.
- **Cyclopropanation and homologation of ketones:** addition to alkenes with metal catalysis (carbene chemistry, Unit 1), and ring expansion of cyclic ketones.
- **1,3-Dipolar cycloadditions** with alkynes and activated alkenes.

3.4 Diazopropane

Diazopropane (1-diazopropane and 2-diazopropane) is the higher homologue of diazomethane, prepared similarly and handled with the same precautions. It ethylates rather than methylates: carboxylic acids give ethyl esters and phenols give ethyl ethers, and it enters the same cyclopropanation and cycloaddition chemistry with an ethyl group in place of methyl. It is examined mainly as the homologue example and is used far less often, because diazomethane covers most needs at lower risk.

3.5 Dicyclohexylcarbodiimide (DCC)

Dicyclohexylcarbodiimide (DCC) is a dehydrating coupling reagent: it consumes the water of a condensation and is itself converted into dicyclohexylurea (DCU), which precipitates and is filtered off.

Mechanism in words, for esterification: the carboxylic acid adds to the C=N bond of DCC to give an O-acylisourea, which is an activated ester equivalent; the alcohol attacks it to give the ester and DCU. With a catalytic amount of 4-(dimethylamino)pyridine (the Steglich esterification), even hindered alcohols esterify at room temperature because the acyl group is relayed through a highly reactive acylpyridinium species.

Applications: amide and peptide bond formation (DCC or its more soluble relative DIC with hydroxybenzotriazole additives to suppress racemisation), esterification of sensitive acids, and the Pfitzner-Moffatt oxidation in which DCC with DMSO and acid oxidises alcohols. The drawbacks are the allergenic reagent and the DCU byproduct, which is why modern peptide coupling often uses the reagents of section 3.12 instead.

3.6 Wilkinson's catalyst

Wilkinson's catalyst, chlorotris(triphenylphosphine)rhodium(I), $\text{RhCl}(\text{PPh}_3)_3$, is the classic homogeneous hydrogenation catalyst. In solution it loses one phosphine ligand, oxidatively adds hydrogen to give a rhodium(III) dihydride, binds the alkene, transfers both hydrogens across the double bond in sequence (migratory insertion, then reductive elimination) and releases the alkane.

Because the catalyst is a bulky soluble complex, steric hindrance controls selectivity: less hindered double bonds are hydrogenated fastest, while carbonyls, halides, nitro groups and benzyl ethers survive, so an exposed double bond in a crowded steroid or terpene can be reduced while a buried one is left. It is the standard contrast with heterogeneous catalysts such as palladium on carbon, which are less discriminating, and chiral phosphine versions perform asymmetric hydrogenation, the industrial logic behind L-DOPA manufacture.

3.7 Wittig reagent

The **Wittig reagent** is an alkylidene phosphorane (ylide), $\text{Ph}_3\text{P}=\text{CHR}$, made in two steps: triphenylphosphine displaces halide from an alkyl halide in an $\text{S}_\text{N}2$ step to give a phosphonium salt, and a strong base (butyllithium, sodium hydride or an alkoxide for stabilised cases) removes the alpha proton.

Mechanism in words: the ylide carbon, a stabilised carbanion equivalent, adds to an aldehyde or ketone carbonyl; the betaine closes to a four membered **oxaphosphetane**, which collapses, breaking C-P and C-O

bonds to give the alkene and triphenylphosphine oxide. Formation of the very strong P=O bond drives the whole reaction.

Stereochemistry and scope: non-stabilised ylides (simple alkyl groups) give mainly Z alkenes under salt free conditions; stabilised ylides (bearing an ester or similar group) give mainly E alkenes. The Horner-Wadsworth-Emmons variant, using a phosphonate carbanion, gives E alkenes reliably and a water soluble phosphate byproduct, and is preferred at scale. The Wittig reaction converts a carbonyl into a double bond with the new bond exactly where the carbonyl was, including methylenation ($C=O$ to $C=CH_2$), which few other methods do as cleanly; it is used for exocyclic methylene units and diene construction in vitamin and prostaglandin synthesis. Ketones react more slowly than aldehydes and very hindered ketones may fail.

3.8 Osmium tetroxide

Osmium tetroxide, OsO_4 , is the reagent for syn dihydroxylation of alkenes: it adds across the double bond in a concerted cycloaddition to give a cyclic osmate ester, and hydrolysis releases the cis vicinal diol and osmium in a lower oxidation state.

In practice OsO_4 is expensive and highly toxic (it attacks the eyes and lungs), so it is used catalytically with a co-oxidant that reoxidises the osmium: N-methylmorpholine N-oxide (NMO) in the Upjohn conditions, or potassium ferricyanide in the Sharpless asymmetric dihydroxylation, where cinchona alkaloid ligands on osmium deliver the oxygens to one face and give chiral diols from prochiral alkenes. Alkenes react in the order of their electron richness and accessibility; conjugated and strained systems are fast. The product is always the syn diol, the exact complement of the anti diol obtained by epoxidation followed by acid hydrolysis, a comparison examiners love.

3.9 Titanium chlorides

Two titanium chlorides earn their place in the list:

- **Titanium tetrachloride, $TiCl_4$** , is a powerful Lewis acid, stronger and more oxophilic than aluminium chloride in many settings. It promotes Mukaiyama aldol reactions of silyl enol ethers with aldehydes, activates carbonyls toward allylation, and catalyses Diels-Alder reactions at low temperature.
- **Titanium trichloride, $TiCl_3$** , and low valent titanium generated from $TiCl_4$ with zinc, perform the **McMurry coupling**: two carbonyl compounds are reductively joined to an alkene through a pinacolate bound to titanium, which is deoxygenated on heating. The reaction makes hindered and strained alkenes that the Wittig reaction cannot reach, and intramolecularly it closes large rings in natural product synthesis. Titanium reagents also underlie the Kulinkovich cyclopropanol synthesis and the Tebbe methylenation reagent, $Cp_2Ti(Cl)CH_2AlMe_2$, used when a basic Wittig ylide would destroy the substrate.

3.10 Diethyl azodicarboxylate (DEAD)

Diethyl azodicarboxylate is the orange azo ester that partners triphenylphosphine in the Mitsunobu reaction (Unit 2): it accepts the elements of hydrogen as it is reduced to the hydrazine dicarboxylate, the stoichiometric waste of that process. The same oxidising appetite makes DEAD a dehydrogenation reagent in its own right (converting 1,4-dihydropyridines to pyridines, for example) and the aza component in alpha amination of enolates. It is shock sensitive and toxic; diisopropyl azodicarboxylate (DIAD) is the common safer substitute.

3.11 Triphenylphosphine

Triphenylphosphine, PPh₃, is the phosphorus workhorse behind three Unit 2 reactions: it is the backbone of the Wittig reagent, the activator of alcohols in the Mitsunobu reaction, and hydrogen acceptor chemistry elsewhere. Its recurring role is explained by one fact: phosphorus forms an exceptionally strong bond to oxygen, so any process ending in triphenylphosphine oxide has a built in driving force.

Other standard uses: the **Appel conditions** (PPh₃ with carbon tetrachloride or tetrabromide) convert alcohols into alkyl chlorides or bromides with inversion, through the same alkoxyphosphonium intermediate as the Mitsunobu reaction; the **Staudinger reaction** reduces azides to amines through an iminophosphorane hydrolysed by water, a mild alternative to catalytic hydrogenation that preserves other reducible groups; and PPh₃ is the standard ligand in the palladium and rhodium catalysis of Units 2 and 3 (Suzuki, Wilkinson).

3.12 BOP reagent

BOP, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, is a peptide coupling reagent. The carboxylate attacks phosphorus and displaces benzotriazolyloxy (the OBt anion), giving an active benzotriazolyl ester in situ; the amine partner then aminolyses it to the amide. Because the active ester forms quickly and the OBt group suppresses racemisation at the activated residue, BOP made solid phase peptide synthesis of long sequences practical and remains a standard coupling reagent for amide bond formation generally, including the amide bonds of drug candidates in medicinal chemistry.

Two practical points are examinable: BOP produces hexamethylphosphoramide (HMPA) as byproduct, a suspect carcinogen, which led to the safer analogue PyBOP in which pyrrolidine replaces dimethylamine; and coupling reagents of this family (BOP, PyBOP, HBTU, HATU) all work by the same logic of converting a poor leaving group, OH, into a good one under conditions mild enough for amino acid stereochemistry to survive.

3.13 Grignard reagent

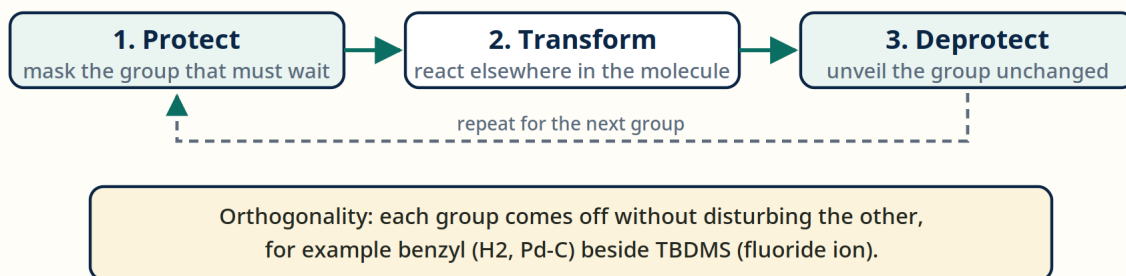
The KBH syllabus copy adds the **Grignard reagent**, RMgX, formed by inserting magnesium into a carbon-halogen bond in dry ether or THF. Its carbon-magnesium bond is polarised towards carbon, so the reagent is a carbanion equivalent and a strong base at once. It adds to carbonyl compounds (aldehydes to secondary alcohols, ketones to tertiary alcohols, esters twice to tertiary alcohols), opens epoxides, and adds to carbon dioxide to give carboxylic acids after work up. The same basicity is its limitation: any acidic proton (water, alcohols, terminal alkynes, amines) destroys the reagent, and substrates carrying both a halogen and an acidic or carbonyl function usually cannot form Grignards directly, which is one of the problems protecting groups exist to solve.

3.14 Protecting groups: the role of protection in synthesis

A **protecting group** is a temporary disguise put on a functional group so that it survives reactions aimed elsewhere in the molecule, and removed when its turn comes. Protection costs two steps, so it is used only when chemoselectivity cannot be achieved directly: the classic situation is a molecule with two groups of similar reactivity, such as an amino alcohol to be acylated on nitrogen only.

A good protecting group must: go on in high yield under mild conditions; be stable to every reagent used while it is in place; come off in high yield under conditions that damage nothing else; and ideally make the intermediate easy to purify. The strategic idea of **orthogonality** completes the concept: two protecting groups are orthogonal if each can be removed in the presence of the other (for example a benzyl ether, removed by hydrogenolysis, beside a silyl ether, removed by fluoride), allowing several groups to be unveiled one at a time in a long synthesis.

The Protect, Transform, Deprotect Cycle



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Figure: Protect, transform, deprotect. Orthogonal groups let several masks be removed one at a time.

3.15 Protection of the hydroxyl group and of diols

- **Ethers:** the **benzyl ether** (from benzyl chloride and base) is stable to acid, base and organometallics and is removed by catalytic hydrogenolysis. The **methoxymethyl (MOM)** and **tetrahydropyranyl (THP)** ethers are acetals in disguise: acid labile, base stable. **Silyl ethers**, above all tert-butyldimethylsilyl (TBDMS, from TBDMSCl and imidazole), are bulky, robust and removed uniquely by fluoride ion (tetrabutylammonium fluoride), the orthogonality exploited throughout polyol synthesis.
- **Esters:** acetyl and benzoyl groups protect alcohols as acetates and benzoates; they are base labile and removed by mild hydrolysis or transesterification (K₂CO₃ in methanol), pairing orthogonally with acid labile groups.
- **Carbonates:** benzyl and tert-butyl carbonates protect hydroxyls in some sequences and are more often met on nitrogen (section 3.18).
- **Cyclic acetals and ketals for 1,2- and 1,3-diols:** a vicinal or 1,3-diol reacts with acetone under acid catalysis to give a cyclic acetonide (a five membered 1,3-dioxolane from a 1,2-diol, a six membered 1,3-dioxane from a 1,3-diol), with benzylidene acetals from benzaldehyde as the alternative. This protects both oxygens at once while leaving other hydroxyls free, the standard manoeuvre in carbohydrate chemistry.

3.16 Protection of the carbonyl group

Aldehydes and ketones are protected as **acetals and ketals**: treatment with an alcohol and acid catalyst, with water removed, converts C=O into C(OR)₂. Ethylene glycol gives cyclic 1,3-dioxolanes, preferred because ring formation is favourable and the ring hydrolyses cleanly. The acetal is stable to base, hydride reducing agents, Grignard reagents and organolithiums, everything that would attack a carbonyl, and is removed by dilute aqueous acid. The standard demonstration: to reduce an ester in a molecule that also contains a ketone, protect the ketone as its ketal, reduce the ester with lithium aluminium hydride, then hydrolyse the ketal back. The related 1,3-dithiane protects the carbonyl and inverts its polarity (umpolung): the dithiane proton is acidic, so the masked aldehyde becomes a nucleophilic acyl anion equivalent, hydrolysed back with mercury(II) salts.

3.17 Protection of the carboxyl group

A carboxylic acid is usually protected as an **ester**: methyl and ethyl esters for simple masking (removed by hydrolysis, which may be too harsh for sensitive molecules), **benzyl esters** removed by hydrogenolysis under neutral conditions, and **tert-butyl esters** removed by acid (trifluoroacetic acid). The syllabus also

names **amides and hydrazides** as carboxyl protection: converting the acid into a robust amide (for example a Weinreb amide, which additionally controls Grignard addition to stop at the ketone) or a hydrazide masks the acidic proton and the carbonyl electrophilicity during steps elsewhere, with hydrolysis restoring the acid. Choice among these follows the usual logic: pick the mask whose removal conditions the rest of the molecule can survive.

3.18 Protection of the amino group and amino acids

- **Carbamates:** the **Boc group** (tert-butyloxycarbonyl, from di-tert-butyl dicarbonate) is stable to base, hydrogenolysis and nucleophiles and is removed by acid (TFA or HCl), releasing isobutene and carbon dioxide. The **Cbz group** (benzyloxycarbonyl, from benzyl chloroformate) is removed by catalytic hydrogenolysis and survives acid that would remove Boc, so Boc and Cbz are mutually orthogonal. **Fmoc** (9-fluorenylmethoxycarbonyl) is removed by mild base (piperidine) through an E1cB mechanism and is the standard N-protection of solid phase peptide synthesis.
- **Amides:** simple acylation (acetyl, benzoyl) protects an amine as an amide, strongly deactivating it (the acetanilide of aniline chemistry), and the phthalimide of the Gabriel synthesis protects nitrogen through alkylations until hydrazine releases the primary amine.
- **Amino acid strategy:** peptide synthesis combines these: the amino group of one residue is masked (Boc or Fmoc), the carboxyl of the other as an ester, side chain groups carry their own orthogonal masks, the coupling reagent (DCC or BOP, sections 3.5 and 3.12) forms the bond, and the terminal mask is removed for the next cycle. Orthogonality is not a refinement here; it is the entire technology.

Group protected	Protecting group	Put on with	Taken off by
Hydroxyl	Benzyl ether	Benzyl chloride, base	H ₂ , Pd-C hydrogenolysis
Hydroxyl	TBDMS silyl ether	TBDMSCl, imidazole	Fluoride (TBAF)
Hydroxyl	Acetate ester	Acetic anhydride, pyridine	K ₂ CO ₃ , methanol
1,2- or 1,3-Diol	Acetonide (cyclic ketal)	Acetone, acid catalyst	Dilute aqueous acid
Carbonyl	Cyclic acetal or ketal	Ethylene glycol, acid	Dilute aqueous acid
Carboxyl	Benzyl ester	Benzyl alcohol coupling, or BnBr on the salt	H ₂ , Pd-C
Carboxyl	tert-Butyl ester	Isobutene, acid	Trifluoroacetic acid
Amino	Boc carbamate	Boc anhydride	Acid (TFA)
Amino	Cbz carbamate	Benzyl chloroformate	H ₂ , Pd-C
Amino	Fmoc carbamate	Fmoc chloride or Fmoc-OSu	Piperidine (base)

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